

Remedies Containing Asteraceae Extracts

A Prospective Observational Study of Prescribing Patterns and Adverse Drug Reactions in German Primary Care

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Abstract

Background: The use of complementary therapies by patients has increased over the past 20 years, both in terms of self-medication and physician prescriptions. Among herbal medicines, those containing extracts of Asteraceae (Compositae), such as *Echinacea spp.*, *Arnica montana*, *Matricaria recutita* and *Calendula officinalis*, are especially popular in the primary-care setting. However, there remains a gap between the growing acceptance of these remedies and the lack of data on their safety.

Objective: The aim of this study was to analyse prescribing patterns and adverse drug reactions (ADRs) for Asteraceae-containing remedies in Germany.

Methods: Primary-care physicians, all of whom were members of the German National Association of Anthroposophic Physicians were invited to participate in this prospective, multicentre, observational study. During the study period (September 2004 to September 2006), all prescriptions and suspected ADRs for both conventional and complementary therapies were documented using a web-based system. The study centre monitored all ADR reports and conducted a causality assessment according to Uppsala Monitoring Centre guidelines. Relative risks (RRs) and proportional reporting ratios (PRRs) were calculated.

Results: Thirty-eight physicians, 55% of whom were general practitioners and 45% were specialists, fulfilled the technical requirements and were included in the investigation. Because documenting all ADRs (i.e. serious and non-serious) was time consuming, only a subgroup consisting of seven physicians agreed to report nonserious in addition to serious ADRs. During the study period, a total of 50 115 patients were evaluated and 344 ADRs for conventional and complementary remedies were reported. Altogether, 18 830 patients (58.0% female, 60.3% children) received 42 378 Asteraceae-containing remedies. The most frequently prescribed Asteraceae was *Matricaria recutita*

(23%), followed by *Calendula officinalis* (20%) and *Arnica montana* (20%). No serious ADRs for Asteraceae-containing remedies were reported. In the analysis of the subgroup of seven physicians who also documented nonserious ADRs, 11 nonserious ADRs for Asteraceae-containing remedies occurred in 6961 patients, resulting in an RR of 0.13 (95% CI 0.07, 0.23). The majority of reported ADRs for Asteraceae-containing remedies were classified as uncommon. A subgroup analysis comparing phytotherapeutic and homoeopathic preparations did not reveal any relevant differences. The PRR for Asteraceae-containing remedies with respect to all other prescriptions was 1.7 (95% CI 1.0, 2.0) for the system organ class 'skin and subcutaneous tissue disorders' (six ADRs) and 1.0 (95% CI 0.3, 3.6) for 'gastrointestinal disorders' (three ADRs). Neither result was significant according to the PRR criteria developed by Evans et al.

Conclusion: This is the first study to provide a systematic overview of prescribing patterns and ADRs for Asteraceae-containing remedies in the German primary-care sector. Asteraceae-containing remedies were used frequently in this context, especially among children. Our results indicate that treatment with Asteraceae-containing remedies is not associated with a high risk of ADRs.

Background

The use of complementary therapies has increased over the past 20 years, both in terms of self-medication and physician prescriptions. In particular, herbal remedies made of undiluted plant extracts, as well as homoeopathic preparations using minerals, botanical substances and other sources in various diluted forms, are becoming increasingly important in the context of primary care. A study of general practice in Scotland by Ross et al.^[1] revealed that a substantial number of general practitioners there prescribe herbal and homoeopathic remedies as part of their daily routine, with especially high prescription rates in children. A recent questionnaire-based study in Ireland showed that 42.5% of the participating paediatric patients with atopic dermatitis had used complementary medicine, particularly herbal remedies.^[2] Another study showed that 50% of Australians use some form of complementary medicine, and that *Echinacea*-containing products are becoming increasingly popular in that country.^[3]

An important group of herbal therapies in primary care consists of remedies containing extracts of Asteraceae (Compositae). The Asteraceae family includes some of the oldest and most valued medicinal plants, such as *Arnica montana*, *Matricaria recutita*, *Chamaemelum nobile*, *Calendula officinalis*, *Echinacea spp.* and *Inula helenium*.^[4] In total, there are 420 known medicinal species in the Asteraceae family. In addition to their use in cosmetic and beauty products, this family has a long history in many traditional and complementary systems of medicine, including homoeopathy,^[5] anthroposophic medicine,^[6] traditional herbal medicine^[4] and folk medicine.^[7]

Studies have shown that Asteraceae are somewhat effective in the treatment of upper respiratory tract infections (*Echinacea spp.*^[8,9]), in the care of pain and traumatic or postoperative injuries (*Arnica montana*^[10-12]) and in the prevention and management of radiation skin reactions/dermatitis (*Calendula officinalis*^[13]). At the same time, Asteraceae are considered to be one of the most important families of allergenic plants in Europe, and there have been a number

of reports of adverse reactions, including contact eczema^[14-16] and even anaphylactic reactions,^[17] to remedies and cosmetics containing their extracts.

Nevertheless, there remains a gap between the acceptance of these remedies and knowledge about potential adverse drug reactions (ADRs).^[18-20] Additionally, there are currently no data available on the overall frequency with which Asteraceae-containing remedies are prescribed in the primary-care setting. Indeed, compared with other herbal or conventional remedies, the precise indications for which Asteraceae are prescribed are still largely unknown, and the patient surveys that have been conducted to date can provide only an approximate picture of patterns of use. Presently, systematic evaluations of risk are lacking, making it impossible to provide valid statements on the potential of these remedies to cause harm.

Therefore, the aim of the present study was to analyse prescribing patterns and the occurrence of ADRs for Asteraceae-containing remedies in primary care in Germany.

Methods

In 2003, a total of 362 physicians, all of whom were members of the German National Association of Anthroposophic Physicians (Gesellschaft Anthroposophischer Ärzte in Deutschland; GAÄD), were contacted by standard mail and informed about the EvaMed Pharmacovigilance Network, which aims to evaluate complementary remedies in primary care with regard to prescribing patterns, efficacy and safety.^[21] In case of non-response, physicians were contacted again after 4 weeks by telephone.

For a physician to be eligible, his or her medical practice had to meet a number of technical requirements, including the presence of one of seven common, computerized, patient-documentation systems, a local area network connection, and Microsoft® Windows® and Internet Explorer (i.e. as client software).

Because all physicians were members of GAÄD, they were all specialized in anthroposophic medicine, a medical system founded in the 1920s by Rudolf Steiner and Ita Wegman.^[22]

Anthroposophic medicine is regarded as an extension to conventional medicine, and anthroposophic pharmacotherapy includes preparations of botanical, mineral or zoological origin, as well as chemical substances that are either undiluted or based on the homoeopathic principle of high dilution.

During the 2-year study period beginning in September 2004, participating physicians continued to follow their routine documentation procedures, recording diagnoses and all prescriptions (i.e. conventional and complementary) for each consecutive patient using their existing, computerized patient-documentation system. These data were exported to a QuaDoSta PostgreSQL-database system, hosted in each practice by an on-site server.^[23] After completing each export, physicians used a browser-based interface to match individual diagnoses with the corresponding drugs or remedies that had been prescribed. Any serious ADR (see below for definition) occurring during the study period was also documented with the QuaDoSta system, using a separate input mask that prompted physicians for detailed information. All physicians were required to report any suspected serious ADRs they thought were attributable to complementary or conventional medication. Because documenting all ADRs (i.e. serious and non-serious) is very time consuming, only a subgroup consisting of seven physicians agreed to report nonserious in addition to serious ADRs. All participants received standardized theoretical and practical training with regard to ADR detection, classification and the use of appropriate terminology. Physicians were asked to send data from the QuaDoSta database to the study centre every 2 months or, in the event of serious ADRs, immediately.

All remedies containing Asteraceae extracts were identified using the German ABDA (Federal Confederation of German Pharmacist Associations database), which contains a broad range of data on all medicinal drugs and substances currently available in Germany, including information on active and non-active ingredients, pharmaceutical form, pack sizes and retail price. Subsequently, all prescriptions containing one or

more of these remedies were selected by means of complex mapping algorithms. These data were matched with information on the ADRs for Asteraceae-containing remedies that had been documented and classified by participating physicians.

The study centre evaluated all suspected ADRs reported by the physicians in terms of severity and causality. The latter was defined and assessed according to the Uppsala Monitoring Centre guidelines,^[24] in which causal relationships are classified as certain, probable/likely, possible, unlikely, conditional/unclassified or unassessable/unclassifiable. The WHO System Organ Classification (SOC) was used for further analyses.^[25] ADRs were classified according to the International Conference on Harmonization criteria as 'serious' or 'nonserious', as well as in terms of severity according to the WHO Adverse Reaction Terminology (1=mild; 2=moderate; 3=severe; 4=severe to life threatening). ADRs were classified as very common ($\geq 10\%$), common ($\geq 1\%$ and $< 10\%$), uncommon ($\geq 0.1\%$ and $< 1\%$), rare ($\geq 0.01\%$ and $< 0.1\%$) or very rare ($< 0.01\%$).^[26]

Statistical analysis was performed using SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA).^[27] Prescribing rates were determined by descriptive analysis, and the association between Asteraceae and ADRs was described in terms of relative risk (RR). The chi-squared test was used to analyse differences in prescribing frequencies for particular groups of patients. The two-tailed t-test was used for continuous data. A p-value of < 0.05 was regarded as indicating a statistically significant difference between the physicians who participated in the present study and the overall population of physicians certified in anthroposophic treatment in Germany, as well as between patients who used Asteraceae and patients who did not. In addition, proportional reporting ratios (PRRs), a method introduced by Evans et al.^[28] for generating signals of potentially unrecognized hazards from spontaneous ADR reporting data, were used. PRRs are calculated as the proportion of spontaneous reports for a given drug that are linked to a specific adverse outcome, divided by the corresponding proportion for all or several other drugs. In the

present study, PRRs were employed to investigate disproportionalities between Asteraceae-containing remedies and any other drugs that may have caused the suspected ADR and have led to similar symptoms according to the SOC hierarchy.^[25]

Age (< 18 years or > 60 years), sex, polypharmacy and multiple disease state were analysed with regard to their predisposing effect on ADRs. Based on the characterization of Veehof et al.,^[29] polypharmacy was classified as minor (2–3 drugs), moderate (4–5 drugs) or major (> 5 drugs). Multiple disease state was defined as more than two diseases diagnosed in the patient at the time of the reaction.

Additional subgroup analyses of prescribing rates were performed for patient sex, age and diagnosis (International Classification of Diseases [10th revision]);^[30] for phytotherapeutic (i.e. not homoeopathically diluted) or homoeopathic preparations; for dilutions $< D4$ ($> 1/1000$), dilutions between $D4$ and $D6$ ($\leq 1/1000 - 1/1\,000\,000$) and dilutions $> D6$ ($< 1/1\,000\,000$); and for monopreparations versus combined preparations.

Results

A total of 107 physicians agreed to join the network and to participate in this prospective observational study. Of these physicians, 38 fulfilled the technical requirements and were included in the investigation; 55% were general practitioners and 45% were specialists (23% paediatricians, 11% internists, 11% others). The physicians did not differ significantly from the overall population of physicians certified in anthroposophic treatment in Germany ($n = 362$) in terms of mean age (48.0 ± 6.1 years vs 47.5 ± 6.1 years; $p = 0.709$) or sex (60.1% vs 62.2% men; $p = 0.793$).

From September 2004 to September 2006, participating physicians documented a total of 50 115 patients, who received 199 387 prescriptions for 360 488 drugs and remedies in total. Of these patients, 18 830 (37.6%) received 25 652 prescriptions (12.9%) with a total of 42 378 remedies (11.8%) containing Asteraceae extracts (see table I). There were significant differences between the percentages of prescribed Asteraceae

Table I. Patient characteristics

Patient characteristics	Patients not using Asteraceae [n (%)]	Patients using Asteraceae [n (%)]	Patients, total [n (%)]
Sex^a			
male	12 686 (40.5)	7 911 (42.0)	20 597 (41.1)
female	18 599 (59.5)	10 919 (58.0)	29 518 (58.9)
Age^b (y)			
<12	14 233 (45.5)	11 354 (60.3)	25 587 (51.7)
12–29	5 008 (16.0)	1 936 (10.3)	6 944 (13.9)
30–44	4 453 (14.2)	2 211 (11.7)	6 664 (13.3)
45–59	3 835 (12.3)	1 859 (9.9)	5 694 (11.4)
>60	3 766 (12.0)	1 470 (7.8)	5 236 (10.2)
Total	31 285 (100.0)	18 830 (100.0)	50 115 (100.0)

a $p < 0.01$.b $p < 0.005$.

remedies and those of other prescribed drugs with regard to sex ($p < 0.01$) and age ($p < 0.005$). In children, the percentage of Asteraceae remedies (60.3%) was much higher than that of other drugs (45.5%), whereas for all other age groups, the percentage of Asteraceae remedies was lower compared with other drugs. The most frequently prescribed Asteraceae remedy was *Matricaria recutita* (49.9% in male adult patients, 32.3% in female adult patients and 51.7% in children). In patients aged 30–60 years, *Arnica montana* was prescribed most often (21.9%), followed by *Calendula officinalis* (19.8%). Finally, elderly patients aged >60 years were most frequently treated with *Onopordum acanthium* (34.2%) and *Arnica montana* (33.8%).

Tables II and III provide a more detailed overview of the Asteraceae-containing remedies prescribed by participating physicians. In total, 74.6% of these remedies were prescribed as monopreparations and 72.7% were prescribed as dilutions <D4 (table II). *Matricaria recutita*, the most commonly prescribed remedy, was dispensed primarily as a monopreparation (75.4%) in phytotherapeutic (i.e. rather than homoeopathic) form (59.7%). It was used most frequently for diseases of the middle ear (10.3%), the oral cavity, salivary glands and jaws (8.3%), as well as for infectious diseases, especially those of the upper respiratory system (16.2%). *Onopordum*

acanthium and *Calendula officinalis* were also dispensed primarily as undiluted preparations (82.8% and 55.0%, respectively). *Calendula officinalis* was most commonly prescribed for conjunctival disorders (16.0%), dermatitis and eczema (7.2%) and acute upper respiratory infections (22.7%).

Eupatorium cannabinum (53.9%) and *Arnica montana* (20.4%) were frequently used in homoeopathic dilutions >D6. *Arnica montana* was most commonly prescribed for diseases of the musculoskeletal system, such as arthropathies (14.8%) and lower back pain (12.0%). *Echinacea spp.* was provided in various pharmaceutical forms and dilutions to treat a variety of diagnoses such as conjunctival disorders (15.8%), dermatitis and eczema (6.0%) and upper respiratory tract diseases. *Petasites hybridus* was prescribed only as a monopreparation, was most often applied externally (83.1%) and was used primarily to treat diseases of the respiratory system.

Asteraceae-containing remedies were prescribed primarily for children, except in cases of musculoskeletal disease (3.2% for lower back pain and 14.9% for arthropathies), non-infective enteritis and colitis (52.5%), and dermatitis and eczema (59.7%), in all of which the majority of prescriptions were written for adults (table III).

In total, 344 suspected ADRs were reported for all prescriptions (i.e. conventional and complementary therapies) written during the 2-year study period (344 ADRs in 50 115 patients; frequency = 0.69%). A causal relationship with treatment was classified in 17.7% ($n = 61$) of cases as certain, in 34.0% ($n = 117$) of cases as probable/likely, in 44.3% ($n = 152$) of cases as possible, in 1.7% ($n = 6$) of cases as unlikely, and in 2.3% ($n = 8$) of cases as unassessable/unclassifiable. Of all detected ADRs (i.e. those associated with either conventional or complementary therapies) whose causality assessment was certain, probable/likely or possible, a total of 192 (55.8%) occurred in children and 14 were classified as serious. None of the serious ADRs were related to Asteraceae-containing remedies.

The subgroup of seven physicians who also documented suspected nonserious ADRs issued a total of 18 445 Asteraceae drug prescriptions

Table II. Most frequently used Asteraceae-containing remedies

Plant (<i>botanical name</i>)	Patients [n]	Different medications [n]	Prescriptions [n (%)]		phytotherapeutic preparation	homoeopathic preparation			External
			total	mono- preparations		<D4	D4–D6	>D6	
German Chamomile (<i>Matricaria recutita</i>)	5 978	63	15 774	11 897 (75.4)	9 412 (59.7)	4 660 (29.5)	1 459 (9.2)	243 (1.5)	463 (2.9)
Marigold (<i>Calendula officinalis</i>)	5 453	54	9 294	2 154 (23.2)	5 111 (55.0)	2 702 (29.1)	1 447 (15.6)	34 (0.4)	3 374 (36.3)
Arnica (<i>Arnica montana</i>)	2 756	112	6 167	3 284 (53.3)	1 165 (18.9)	2 383 (38.6)	1 359 (22.0)	1 260 (20.4)	1 442 (23.4)
Coneflower (<i>Echinacea spp.</i>)	2 672	69	4 605	1 557 (33.8)	1 383 (30.0)	2 730 (59.3)	260 (5.6)	232 (5.0)	1 939 (43.0)
Butterbur (<i>Petasites hybridus</i>)	2 201	9	3 825	3 825 (100)	6 (0.2)	1 303 (34.1)	2 516 (65.8)	0 (0.0)	3 178 (83.1)
Scotch thistle (<i>Onopordum acanthium</i>)	1 144	14	3 574	3 190 (89.3)	2 961 (82.8)	307 (8.6)	164 (4.6)	142 (4.0)	0 (0.0)
Dandelion (<i>Taraxacum officinale</i>)	1 200	38	2 527	530 (21.0)	316 (12.5)	1 726 (68.3)	219 (8.7)	266 (10.5)	4 (0.2)
Hemp Agrimony (<i>Eupatorium cannabinum</i>)	1 070	12	2 231	2 231 (100)	796 (35.7)	86 (3.9)	147 (6.6)	1 202 (53.9)	0 (0.0)
Chicory (<i>Cichorium intybus</i>)	691	35	1 716	1 096 (63.9)	36 (2.1)	964 (56.2)	567 (33.0)	149 (8.7)	4 (0.2)
Absinth/wormwood (<i>Artemisia absinthium</i>)	828	25	1 670	492 (29.5)	94 (5.6)	1 523 (91.2)	48 (2.9)	5 (0.3)	38 (2.3)
Yarrow (<i>Achillea millefolium</i>)	855	24	1 582	528 (33.4)	28 (1.8)	1 079 (68.2)	470 (29.7)	5 (0.3)	455 (28.8)
Daisy (<i>Bellis perennis</i>)	733	38	1 337	24 (1.8)	1 (0.1)	1 049 (78.5)	284 (21.2)	3 (0.2)	590 (44.1)
Edelweiss (<i>Gnaphalium leontopodium</i>)	464	7	1 138	342 (30.1)	276 (24.3)	855 (75.1)	1 (0.1)	6 (0.5)	0 (0.0)
Milk thistle (<i>Silybum marianum</i>)	324	20	826	118 (14.3)	298 (36.1)	454 (55.0)	27 (3.3)	47 (5.7)	0 (0.0)
Southernwood (<i>Artemisia abrotanum</i>)	202	8	454	97 (21.4)	2 (0.4)	426 (93.8)	26 (5.7)	0 (0.0)	1 (0.2)
Other	353	29	541	265 (49.0)	59 (10.9)	288 (53.2)	167 (30.9)	27 (5.0)	123 (22.7)
Total	18 830	557	42 378	31 630 (74.6)	16 737 (39.5)	14 080 (33.2)	8 453 (19.9)	3 108 (7.3)	7 568 (17.9)

<D4 = dilution >1/1000; D4–D6 = dilution ≤1/1000–1/1 000 000; >D6 = dilution <1/1 000 000.

Table III. Most frequent diagnoses (International Classification of Diseases [ICD; 10th revision] code^[30]) for which Asteraceae were prescribed

Diagnosis (ICD code)	Prescriptions		Most frequent Asteraceae ^a (n)
	total [n (%)]	children [n (% of total)]	
Acute upper respiratory infections (J00–J06)	5 597 (13.2)	4 483 (80.1)	<i>Calendula officinalis</i> (2109) <i>Matricaria recutita</i> (2561) <i>Petasites hybridus</i> (954)
Symptoms and signs involving the digestive system and abdomen (R10–R19)	2 272 (5.4)	1 874 (82.5)	<i>Matricaria recutita</i> (1800) <i>Taraxacum officinale</i> (243) <i>Artemisia absinthium</i> (204)
Disorders of conjunctiva (H10–H13)	1 788 (4.2)	1 570 (87.8)	<i>Calendula officinalis</i> (1486) <i>Echinacea spp.</i> (728)
Diseases of middle ear and mastoid (H65–H75)	1 697 (4.0)	1 625 (95.8)	<i>Matricaria recutita</i> (1617) <i>Calendula officinalis</i> (241)
Other infectious diseases (B99)	1 637 (3.9)	1 513 (92.4)	<i>Matricaria recutita</i> (1233) <i>Calendula officinalis</i> (464) <i>Petasites hybridus</i> (110)
General symptoms and signs (R50–R69)	1 608 (3.8)	1 048 (65.2)	<i>Matricaria recutita</i> (810) <i>Onopordum acanthium</i> (155) <i>Arnica montana</i> (153)
Diseases of oral cavity, salivary glands and jaws (K00–K14)	1 544 (3.6)	1 452 (94.0)	<i>Matricaria recutita</i> (1311) <i>Echinacea spp.</i> (141)
Other acute lower respiratory infections (J20–J22)	1 528 (3.6)	1 333 (87.2)	<i>Petasites hybridus</i> (874) <i>Eupatorium cannabinum</i> (347) <i>Matricaria recutita</i> (205)
Chronic lower respiratory diseases (J40–J47)	1 457 (3.4)	1 090 (74.8)	<i>Petasites hybridus</i> (767) <i>Eupatorium cannabinum</i> (318) <i>Matricaria recutita</i> (154)
Dermatitis and eczema (L20–L30)	1 232 (2.9)	735 (59.7)	<i>Calendula officinalis</i> (666) <i>Taraxacum officinale</i> (282) <i>Echinacea spp.</i> (277) <i>Cichorium intybus</i> (180)
Arthropathies (M00–M25)	1 030 (2.4)	153 (14.9)	<i>Arnica montana</i> (913) <i>Calendula officinalis</i> (246) <i>Gnaphalium leontopodium</i> (206) <i>Bellis perennis</i> (176)
Noninfective enteritis and colitis (K50–K52)	956 (2.3)	502 (52.5)	<i>Matricaria recutita</i> (154) <i>Artemisia abrotanum</i> (147) <i>Taraxacum officinale</i> (112)
Other diseases of the respiratory system (J95–J99)	941 (2.2)	892 (94.8)	<i>Petasites hybridus</i> (493) <i>Eupatorium cannabinum</i> (171) <i>Matricaria recutita</i> (220)
Dorsopathies (M40–M54)	925 (2.2)	30 (3.2)	<i>Arnica montana</i> (743) <i>Gnaphalium leontopodium</i> (301) <i>Calendula officinalis</i> (125)
Other diseases of upper respiratory tract (J30–J39)	858 (2.0)	610 (71.1)	<i>Matricaria recutita</i> (510) <i>Calendula officinalis</i> (440) <i>Echinacea spp.</i> (101)
Other	17 308 (40.8)	6 758 (39.0)	
Total	42 378 (100)	25 668 (60.6)	

a Documenting more than one Asteraceae was permitted.

(6081 phytotherapeutic; 12 437 homoeopathic) for 6961 patients. Altogether, 11 nonserious ADRs for Asteraceae-containing remedies were reported (pharmaceutical form: 8 × oral administration; 1 × ocular; 1 × subcutaneous; 1 × embrocation). Seven of these ADRs occurred in adults (two men, five women) and four in children (three boys, one girl). Six of these patients had multiple diseases (≥ 3) and seven of them were being treated with more than two drugs simultaneously. A causal relationship with Asteraceae treatment was classified as possible for five ADRs and as probable/likely for six ADRs. All 11 nonserious ADRs occurred in patients who were prescribed Asteraceae-containing remedies that had been prepared homoeopathically. With the exception of ADR no. 1 (table IV), which occurred in a patient who was prescribed a D4 dilution, all other patients who experienced an ADR had received a D1 (i.e. 1/10) or D2 (i.e. 1/100) dilution. A detailed description of each case is given in table IV.

The overall frequency of ADRs among patients treated by this subgroup of physicians was 0.16% (11 ADRs in 6961 patients). ADRs related to *Echinacea spp.* (five ADRs in 1520 patients; frequency = 0.33%) were classified as uncommon (see table V). ADRs related to *Calendula officinalis* (three ADRs in 2135 patients; frequency = 0.14%), *Silybum marianum* (one ADR in 223 patients; frequency = 0.45%), *Artemisia abrotanum* (two ADRs in 236 patients; frequency = 0.85%) and *Taraxacum officinale* (one ADR in 687 patients; frequency = 0.15%) were also classified as uncommon. ADRs associated with *Solidago virgaurea* were classified as common, with one ADR occurring among 65 patients (frequency = 1.5%), whereas ADRs for *Arnica montana* and *Matricaria recutita* were rare. Overall, the RR of experiencing an ADR during the study period while using Asteraceae was 0.13 (95% CI 0.07, 0.23).

Because 10 of the 11 ADRs occurred in patients who received remedies that had been diluted <D4 (>1/1000), all prescriptions for remedies diluted <D4 and \geq D4 were re-evaluated. For dilutions <D4, the overall frequency of ADRs was 0.19%, whereas the overall frequency of ADRs for dilutions \geq D4 was 0.04%. The only

ADR associated with higher dilutions occurred in a patient who had received a remedy containing highly diluted *Arnica montana*. This led to a change in classification from 'rare' (total) to 'uncommon' for dilutions \geq D4. For Asteraceae-containing remedies diluted <D4, the frequency of ADRs was only marginally higher than that for all of the preparations combined; as a result, no change in classification was necessary for dilutions <D4. The resulting PRR for Asteraceae with respect to all other prescriptions was 1.69 (95% CI 0.97, 1.96) for the SOC 'skin and subcutaneous tissue disorders' (seven ADRs) and 0.98 (95% CI 0.34, 3.61) for the SOC 'gastro-intestinal disorders' (three ADRs). However, none of the results were significant according to the PRR criteria developed by Evans et al.^[28]

Discussion

This prospective, multicentre, observational study of a large sample of children and adults treated in the German primary-care sector by physicians specialized in anthroposophic medicine shows that Asteraceae-containing remedies were used frequently in this context, especially among children. The most commonly prescribed Asteraceae was *Matricaria recutita*, followed by *Calendula officinalis*, *Arnica montana* and *Echinacea spp.* *Matricaria recutita* was used to treat diseases of the middle ear, oral cavity, salivary glands and jaws, as well as infectious diseases of the upper respiratory system. In the entire sample of 18 830 patients who received Asteraceae-containing remedies, no serious ADRs were reported. In the focus group of 6961 patients in whom nonserious ADRs were also reported, 11 nonserious ADRs occurred (frequency = 0.16%). In this subgroup of patients, ADRs were detected only for *Echinacea spp.*, *Calendula officinalis*, *Matricaria recutita*, *Artemisia abrotanum*, *Arnica montana*, *Silybum marianum*, *Taraxacum officinale* and *Solidago virgaurea*. Most of the reported ADRs were classified as uncommon and were associated with skin and subcutaneous tissue symptoms. However, our analysis of PRRs did not indicate an accumulation of ADRs or generate a signal suggesting an increased risk.

This paper is the first to provide a systematic overview of prescribing patterns and ADRs for Asteraceae-containing remedies. Our approach was based on the innovative QuaDoSta PostgreSQL database system, which has already been shown to be suitable and effective for reporting and evaluating prescribing patterns in respiratory tract infections.^[31] In contrast to other methods for conducting epidemiological surveys of ADRs and prescribing patterns in complementary primary care,^[32,33] QuaDoSta is linked to physicians' existing computerized patient documentation systems and can be incorporated fully into their daily routines. This helps avoid the typical questionnaire biases of double entries or missing data and guarantees high external validity. Although the acceptance of information technology in general practice has increased considerably in recent years,^[34] there are still barriers to its acceptance among physicians and each data source has its specific limitations.^[35]

A major limitation of the present study was the assessment of causality, which was difficult in some cases because of the high rate of polymorbidity, co-medication and unclear clinical symptomatology. In particular, it was difficult to provide a valid risk assessment for combined preparations such as *Aquilinum comp.*[®] (containing *Solidago virgaurea* and *Taraxacum officinale*), which appeared to cause abdominal pain in one patient. For these reasons, we decided to choose a method of risk assessment that would be conservative and could overestimate the real risk by a factor of two. Although our sample size was large, it would have been helpful to have a larger sample to detect signals for uncommon ADRs and infrequently prescribed remedies.

While spontaneous reporting systems tend to suffer from under-reporting bias,^[36] we attempted to maximize compliance by providing all participating physicians with specialized training for QuaDoSta. However, our results may nevertheless underestimate the true number of ADRs. This being said, only physicians with additional training in anthroposophic medicine participated in our study, and it can be assumed that they were more likely to prescribe (and thus report) herbal remedies than the average physician. By the

same token, anthroposophic physicians may have been less likely to report ADRs for anthroposophic or herbal medicines because of a potential bias towards favouring these approaches and the belief that these are safer than conventional drugs.

This, in turn, leads to another possible bias: although the physicians in our study were instructed to report suspected ADRs, it is conceivable that they focused only on ADRs that they expected to see, such as allergic reactions. As a result, 'unexpected' ADRs may have been missed. Moreover, the 11 ADRs reported for Asteraceae-containing remedies were all categorized as possible or probable/likely in the causality assessment, which may suggest that physicians were only reporting ADRs in cases where they felt certain of the causative role played by the remedy. In total, only 14 of all 344 reports classified the causal relationship as 'unlikely' or 'unassessable/unclassifiable'. Therefore, it may be somewhat unrealistic to expect reports of unexpected ADRs in general practice.^[37]

Another limitation of our study is the fact that Asteraceae-containing remedies in Germany are prescribed not only by anthroposophic physicians, but also by other physicians and pharmacists. Thus, our findings must be interpreted in light of our specific setting and cannot be used to draw more general conclusions on the safety of Asteraceae. Finally, from a pharmacological point of view, each plant has its own chemical profile, and different parts of a plant may contain different chemically active ingredients. Thus, although there may be similarities within certain groups of remedies, making generalizations about different preparations is problematic.

As expected from a review of the literature, *Matricaria recutita* and *Calendula officinalis* were most frequently prescribed to treat various types of infection, as well as diseases of the respiratory tract and oral symptoms. Surprisingly, *Echinacea*, which is commonly regarded as a substance that enhances adaptive immune function,^[38] was prescribed for a broad variety of indications, including cases of eczema and dermatitis. As expected, *Arnica montana*, which in several studies has been shown to be effective in

Table IV. Description of all 11 reported adverse drug reactions (ADRs) for Asteraceae-containing remedies

No.	Sex	Age (y)	Medication (Asteraceae)	Pharmacological form	Polypharmacy minor, moderate, major (n)	Diagnosis (ICD code ^a)	Multiple disease state, yes/no (n)	ADR	WHO severity grade ^b	Causal relationship ^c	Duration (days)	Action	Dechallenge ^d
1	F	50	Arnica planta tota D4 [®] ; dilution; 20 mL (<i>Arnica montana</i>)	Oral	Major (9)	Cellulitis of finger and toe (L03.0)	Yes (5)	Pustule	2	Possible	1	Stop	Yes
2	F	1	<i>Echinacea</i> /argenteum [®] ; globules; 20 mL (<i>Echinacea pallida</i> ^e)	Oral	No (1)	Viral infection (B34.9)	No (1)	Urticaria	1	Probable	2	Stop	Yes
3	M	12	Aquilinum comp. [®] ; globules; 20 mL (<i>Solidago virgaurea</i> , <i>Taraxacum officinale</i> ^f)	Oral	No (1)	Mycosis (B49)	No (1)	Abdominal pain	2	Probable	5	Stop	Yes
4	M	9	Contramutan N; syrup; 100 mL (<i>Echinacea angustifolia</i> ^g)	Oral	No (1)	Fever (R50.9), acute upper respiratory infection (J06.9)	No (1)	Vomiting	2	Possible	3	Stop	Yes
5	M	30	Euphrasia comp. ointment; 5 g (<i>Echinacea angustifolia</i> , <i>Calendula officinalis</i> ^h)	Ocular	Moderate (4)	Blepharoconjunctivitis (H10.5)	Yes (3)	Conjunctiva irritation, marginal blepharitis	2	Possible	2	Stop	Yes
6	M	47	Bolus alba comp.; powder; 50 g (<i>Artemisia abrotanum</i> , <i>Matricaria recutita</i> ⁱ)	Oral	Minor (3)	Acute gastroenteritis (A09)	Yes (6)	Gastralgia	1	Possible	2	Stop	Yes
7	F	45	<i>Echinacea</i> Mund und Rachenspray; spray; 50 mL (<i>Echinacea pallida</i> , <i>Calendula officinalis</i> ^j)	Oral	Minor (3)	Acute pharyngitis (J02)	No (1)	Allergic reaction	1	Possible	1	Stop	Yes
8	F	71	Bolus alba comp.; powder 50 g; (<i>Artemisia abrotanum</i> , <i>Matricaria recutita</i> ^j)	Oral	No (1)	Acute gastroenteritis (A09)	No (1)	Allergy	1	Probable	6	Stop	Yes

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Table IV. Contd

No.	Sex	Age (y)	Medication (Asteraceae)	Pharmacological form	Polypharmacy minor, moderate, major (n)	Diagnosis (ICD code ^a)	Multiple disease state, yes/no (n)	ADR	WHO severity grade ^b	Causal relationship ^c	Duration (days)	Action	Dechallenge ^d
9	F	49	Argentum nitricum comp.; ampule; 10 × 1 mL (<i>Echinacea pallida</i> ^e)	Subcutaneous	Minor (2)	Urinary tract infection (N39.0)	Yes (4)	Redness, pruritus	2	Probable	6	Stop	Yes
10	M	1	<i>Calendula wundsälbe</i> (<i>Calendula officinalis</i>)	External	Moderate (4)	Allergic contact dermatitis (L23.9)	Yes (4)	Allergic reaction, eczema	1	Probable	6	Stop	Yes
11	F	39	<i>Carduus marianus</i> ; capsule; 100 (<i>Silybum marianum</i>)	Oral	Minor (3)	Varicose veins of lower extremities (I83.9)	Yes (6)	Hyperhidrosis, comedones	2	Possible	8	Stop	Yes

a Diagnosis according to the International Classification of Diseases (10th revision)^[30]

b Severity according to the WHO Adverse Reaction Terminology (1 = mild; 2 = moderate; 3 = severe; 4 = severe to life threatening).

c Defined and assessed according to the Uppsala Monitoring Centre guidelines.^[24]

d Rechallenge was not carried out in any of the cases.

e *Argentum metallicum*.

f *Chelidonium majus*, *Dropteris filix-mas*, *Phyllitis scolopendrium*, *Pteridium aquilinum*.

g *Eupatorium perfoliatum*, *Aconitum*, *Belladonna*.

h *Euphrasia*.

i *Acorus calamus*, *Anisi stellati*, *Arsenicum album*, *Carbo Betulae*, *Carvi*, *Gentiana lutea*, *Geum urbanum*.

j *Argentum nitricum*, *Eucalyptus globulus*, *Gingiva bovis*, *Savia officinalis*, *Tonillae palatinae*.

k *Argentum nitricum*, *Chlorophyceae ferm*, *Eucalyptus globulus*, *Thuja occidentalis*.

F = female; M = male.

Table V. Frequency of reported adverse drug reactions (ADRs) within Asteraceae species used in herbal remedies from the subgroup of physicians who documented all suspected ADRs

Plant	ADR no. ^a	All preparations ^b			Homoeopathic preparations (<D4 ^c)			Homoeopathic preparations (>D4 ^c)		
		ADR (n)	patients ^d (n)	frequency (%)	ADR (n)	patients ^d (n)	frequency (%)	ADR (n)	patients ^d (n)	frequency (%)
<i>Arnica montana</i>	1	1	1562	0.06	0	638	0	1	844	0.12
Eye		0	5	0	0	3	0	0	2	0
Skin		0	527	0	0	187	0	0	23	0
Open wound		0	36	0	0	0	0	0	36	0
Oral administration		1	1045	0.10	0	357	0	1	621	0.16
Injection		0	273	0	0	91	0	0	160	0
Suppository		0	2	0	0	0	0	0	2	0
<i>Echinacea (purpurea, pallida, angustifolia)</i>	2, 4, 5, 6, 7	5	1520	0.33	5	1051	0.48	0	199	0
Eye		1	188	0.53	1	100	0.01	0	6	0
Skin		0	759	0	0	586	0	0	127	0
Open wound		0	1	0	0	0	0	0	1	0
Oral administration		3	625	0.48	3	323	0.93	0	45	0
Injection		1	56	1.79	1	36	2.78	0	20	0
Suppository			6	0	0	6	0	0		0
<i>Calendula officinalis</i>	5, 7, 10	3	2135	0.14	3	1347	0.22	0	359	0
Eye		1	646	0.15	1	369	0.27	0	200	0
Skin		1	1112	0.09	1	763	0.13	0	10	0
Oral administration		1	460	0.22	1	110	0.91	0	113	0
Injection		0	44	0	0	8	0	0	36	0
Suppository		0	3	0	0	3	0	0		0
Nose		0	94	0	0	94	0	0		0
<i>Silybum marianum</i>	11	1	223	0.45	1	111	0.90	0	25	0
Eye		0	31	0	0	0	0	0	1	0
Oral administration		1	171	0.58	1	109	0.92	0	1	0
Injection		0	24	0	0	1	0	0	23	0
Suppository		0	1	0	0	1	0	0		0

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Table V. Contd

Plant	ADR no. ^a	All preparations ^b			Homoeopathic preparations (<D4 ^c)			Homoeopathic preparations (>D4 ^c)		
		ADR (n)	patients ^d (n)	frequency (%)	ADR (n)	patients ^d (n)	frequency (%)	ADR (n)	patients ^d (n)	frequency (%)
<i>Matricaria recutita</i>	6, 8	2	3064	0.07	2	1483	0.13	0	526	0
Eye		0	1	0	0	0	0	0	1	0
Skin		0	147	0	0	125	0	0	20	0
Open wound		0	12	0	0	0	0	0	12	0
Oral administration		2	1602	0.12	2	479	0.42	0	491	0
Injection		0	42	0	0	21	0	0	2	0
Suppository		0	1690	0	0	856	0	0		0
Nose		0	94	0	0	0	0	0		0
<i>Artemisia abrotanum</i>	6, 8	2	236	0.85	2	224	0.89	0	12	0
Oral administration		2	235	0.85	2	224	0.89	0	11	0
Injection		0	1	0	0	0	0	0	1	0
<i>Solidago virgaurea</i>	3	1	65	1.54	1	52	1.92	0	9	0
Oral administration		1	62	1.61	1	51	1.96	0	7	0
Injection		0	3	0	0	1	0	0	2	0
<i>Taraxacum officinale</i>	3	1	687	0.15	1	495	0.20	0	70	0
Eye		0	31	0	0	0	0	0	1	0
Oral administration		1	590	0.17	1	483	0.21	0	42	0
Injection		0	38	0	0	11	0	0	27	0

a See table IV.

b No ADRs were experienced for patients taking any of these compounds as phytotherapeutic preparations (3564 patients in total).

c <D4 (>1/1000); ≥D4 (≤1/1000).

d Double entries possible.

the treatment of osteoarthritis, was prescribed for arthropathies and low back pain.^[12,39]

Petasites hybridus has been found to be effective for prophylaxis against migraine,^[40] asthma^[41] and bronchitis.^[42] In anthroposophic medicine, *Petasites hybridus* is thought to harmonize the rhythmical interaction between the mental and physical components of the human body, especially in inflammatory diseases of the respiratory tract (e.g. acute and chronic bronchitis, bronchopneumonia and asthma). Our data show that remedies containing *Petasites hybridus* are indeed prescribed for these conditions: in the present study, *Petasites hybridus* was prescribed most frequently as a cough syrup or as an embrocation.

Prescribing patterns for Asteraceae in our study were similar to those described by Noonan et al.^[43] for *Echinacea* spp. and *Matricaria recutita* and by Alves and da Silva^[44] for *Matricaria recutita*. Both groups of investigators found prescribing rates for children similar to those seen in our analysis. However, to our knowledge, the present study is the first to include data on ADRs and prescriptions of Asteraceae-containing remedies in elderly patients. Future studies, especially of herbal remedies in elderly patients, will help determine whether prescribing patterns in this group differ from those in other populations.

Finally, in agreement with previously published investigations, most of the ADRs observed in the present study involved skin disorders and subcutaneous tissue complaints. However, our analysis of PRRs did not generate any signals that would suggest a link between the reported ADRs and the Asteraceae-containing remedies prescribed during the study. Despite the frequent use of these remedies in primary care, pharmacoepidemiological data on this plant family are still rare and single cases of contact sensitization have been reported, especially for *Arnica montana* und *Matricaria recutita*.^[45] As Paulsen^[15] notes in a study of contact sensitization from Asteraceae-containing herbal remedies and cosmetics, all other evidence can be regarded as anecdotal. Additionally, allergic reactions may also be triggered by cross-reactivity between Asteraceae and other environmental allergens.^[3,46]

It could be hypothesized that diluted remedies should cause fewer ADRs compared with undiluted herbal drugs, because the former contain only very small quantities of the active substance. However, no ADRs were observed in patients who received Asteraceae-containing remedies that were dispensed as phytotherapeutic preparations. In contrast, 11 ADRs were observed in patients who received homoeopathic preparations. Moreover, the analysis comparing homoeopathic preparations diluted <D4 and ≥D4 did not reveal any relevant differences.

Conclusions

This is the first study to provide a systematic overview of prescribing patterns and ADRs for Asteraceae-containing remedies in the German primary-care sector. Asteraceae-containing remedies were used frequently in this context, especially among children. Most of the ADRs observed in the present study involved skin disorders and subcutaneous tissue complaints. Our results indicate that treatment with Asteraceae-containing remedies is not associated with a high risk of ADRs. The data in this regard are especially clear for *Arnica montana*, *Calendula officinalis*, *Matricaria recutita* and *Taraxacum officinale*. For the other Asteraceae (e.g. *Silybum marianum*, *Artemisia abrotanum* and especially *Solidago virgaurea*), a larger sample with more prescriptions is needed to assess ADR risk properly.

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