

Adverse drug reactions to anthroposophic and homeopathic solutions for injection: a systematic evaluation of German pharmacovigilance databases

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ABSTRACT

Purpose Medicinal solutions for injection are frequently applied in anthroposophic medicine and homeopathy. Despite their extensive use, there is little data published on the safety of these products. Therefore, we investigated the safety of anthroposophic and homeopathic solutions for injection through a systematic evaluation of adverse drug reactions (ADRs).

Methods ADRs were extracted from the pharmacovigilance databases of eight German manufacturers. Analysed ADRs included case reports in humans only, (spontaneous) case reports from post-marketing surveillance, literature and clinical/safety trials.

Results Between 2000 and 2009, in total, 303 million ampoules for injection were sold, and 486 case reports were identified, corresponding to a total number of 1180 ADRs. Of all case reports, 71.8% (349/486) included ADRs that were listed (e.g. stated in package leaflet), and 9.5% (46/486) of the reports were classified as serious. The most frequently reported ADRs were pruritus, followed by angioedema, diarrhoea and erythema. A total of 27.3% (322/1180) were localized reactions for example; application or injection site erythema, pain, swelling and inflammation. The overall reporting rate of ADRs associated with injections was less than 4 per 1 million sold ampoules and classified as very rare.

Conclusions Our systematic evaluation demonstrated that the reporting rate of ADRs associated with anthroposophic and homeopathic solutions for injection is very low. Most reported ADRs were listed, and one quarter consisted of local reactions. These findings suggest a low risk profile for solutions for injection as therapeutically applied in anthroposophic medicine and homeopathy. Copyright © 2012 John Wiley & Sons, Ltd.

KEY WORDS—pharmacovigilance; adverse drug reactions; solutions for injection; homeopathy; anthroposophy; pharmacoepidemiology

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INTRODUCTION

Medicinal solutions for injection, manufactured in accordance with the German Homoeopathic Pharmacopoeia,¹ are therapeutically applied in homeopathy and anthroposophic medicine for a wide range of conditions. Homeopathy was developed more than 200 years ago by Samuel Hahnemann. It is based on the principles of similars, meaning that a disease can be cured by a substance that produces similar symptoms in healthy people. The therapeutic use of parenteral administration forms in homeopathy was first

described in the 19th century.² Anthroposophic medicine is a system of medicine based on the spiritual science that was developed by Rudolf Steiner and Ita Wegman. In 1923/24, Steiner^{3,4} recommended injections as one of the main routes of administration for anthroposophic medication. Nowadays, more than 90 million medicinal ampoules are sold per year worldwide. German anthroposophic and homeopathic manufacturers produce over 90% of these ampoules.⁵

Previous studies have shown that anthroposophic and homeopathic practitioners often favor the parenteral dosage form as their first choice in the treatment of acute and chronic diseases.^{6,7} Reasons for this preference are the anticipated better clinical effect of injections, the possibility to control compliance and that the exact location of administration can be chosen. Other

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advantages are that active ingredients do not have to pass the gastrointestinal tract or skin barrier and that the point of injection can be chosen in line with acupuncture points to achieve an optimal systemic or local effect.⁸

Despite the extensive use of injections in anthroposophic medicine and homeopathy, there is little data published on the safety of these products compared to other dosage forms.^{9–11} In the absence of safety data from randomized controlled trials, anthroposophic and homeopathic practitioners throughout Europe were surveyed about their experiences with safety issues of subcutaneous injection of medications. More than 98% of the practitioners never to rarely observed any adverse reaction caused by the injections. Those mentioned were local redness, haematoma, local pain and allergic reactions.⁷ Marketing authorisation holders are obliged to collect and evaluate reports on possible drug-related adverse events. A first evaluation in three German homeopathic and anthroposophic pharmacovigilance databases reported a low number of adverse reactions on solutions for injection in the period 1990 and 1999; approximately one per nine million sold doses.⁸ Pharmacovigilance procedures and systems have been significantly improved over the years. Electronic reporting systems became mandatory for serious case reports, and guidelines for pharmacovigilance were published.¹² The aim of the present study was to update the safety status of anthroposophic and homeopathic solutions for injection. Compared to other dosage forms, systematic evaluations on the safety of these parenteral dosage forms are currently lacking.

METHODS

Data extraction

Retrospective evaluation of adverse drug reactions (ADRs) documented in the pharmacovigilance databases of eight German manufacturers from January 1, 2000 to December 31, 2009 was carried out. Of the eight participating manufacturers, six were homeopathic manufacturers, and two were anthroposophic manufacturers, all together covering an estimated 94% of the total sales of anthroposophic and homeopathic solutions for injection on the German market.

Inclusion criteria for data extraction were: All ADRs (terminology see ICH-E2A guidelines¹³) that were listed in the pharmacovigilance databases of the participating companies for which regulatory reporting was required. This included ADRs for which the causal relationship to drug intake was unlikely, not stated or unknown, since a possible relation to drug intake

could not be excluded. The causal relationship between the adverse event and drug administration was defined according to Uppsala Monitoring Centre guidelines¹⁴ and categorized as certain, probable/likely, possible, unlikely, conditional/unclassified, unassessable/unclassifiable; ADRs that were associated with parenteral dosage forms and with Germany as country of occurrence; ADRs reported between January 1, 2000 and December 31, 2009; ADRs reported by health care professionals and patients (both medically confirmed and medically non confirmed) and ADRs reported from post-marketing surveillance, clinical/safety studies, as well as case reports identified from literature. Excluded from data extraction were ADRs from products with active ingredients not prepared according to the according to the Homöopathisches Arznei Buch (HAB¹) and ADRs from products for which it was clear that they were applied orally.

ADRs were evaluated using a systematic data extraction protocol including details on product category: (i) single product = one active ingredient, or complex product = more than one active ingredient; (ii) calculated dilution of active substance (<1:10.000 or ≥1:10.000) to analyse whether ADRs occurred more frequently with less diluted substances compared to highly diluted substances; (iii) route of parenteral administration (subcutaneous, intramuscular, intravenous, intracutaneous, intraarticular, periarticular); (iv) amount administered (1, 2, 10 ml) to analyse possible dose-dependency in the occurrence of ADRs; (v) date of onset; (vi) source of report (spontaneous, literature, clinical studies/safety studies not published, other; such as registries, poison information centre); (vii) reporter qualifications (health professional, patient; report medically not confirmed, patient; report medically confirmed or other; lawyer); (viii) description of ADR; (ix) seriousness of ADR. Criteria for serious ADRs were: Death/life threatening, in patient hospitalization, persistent disability, anomalies/birth deficiency or medical important event; (x) listedness of ADR per case report; and (xi) gender and age of patients. All ADRs were coded in MedDRA including allocations to the system organ class (SOC).

Data analysis

Data were extracted from the pharmacovigilance databases from May to September 2010, using a data extraction Excel form and transferred to the SPSS database (IBM, SPSS (PASW) Statistics version 18.0, Somers, NY, USA). Tabulation of the different categories of ADRs was performed by descriptive analysis. Pearson's Chi-square tests were used to

analyse differences between the ADR subgroups, and a *p*-value of <0.05 was regarded as indicating a statistically significant difference. The reporting rate of ADRs of injections was calculated as the sum of ADRs reported in 10 years, per (total) amount of ampoules sold in the same period. Total sales of the number of units (ampoules) in the period of 2000–2009 were provided by each participating manufacturer. Depending on their reporting rate, ADR reports were classified into very common ($\geq 10\%$), common ($1\% < x < 10\%$), uncommon ($0.1\% < x < 1\%$), rare ($0.01\% < x < 0.1\%$), very rare ($< 0.01\%$).

RESULTS

ADR reporting

The majority of manufacturers (five out of eight) had systemically evaluated ADRs between January 1, 2000 and December 31, 2009. One manufacturer had data available for an 8-year period (2002–2009), one manufacturer for 6 years (2004–2009) and one manufacturer for 3 years (2007–2009). As shown in Figure 1, the total number of ampoules sold in Germany slightly decreased as from 2005, averaging about 28.8 million ampoules on a yearly basis during the last 5 years.

The annual total number of ADRs is depicted in Figure 2. There were significantly more case reports in the last three years, 2007–2009, compared to the previous period and when adjusted for the varying periods of reporting (*p* < 0.001).

Characteristics of ADRs

Out of 486 case reports, 1180 ADRs were reported since some patients experienced more than one ADR per case report (Table 1). The overall reporting rate

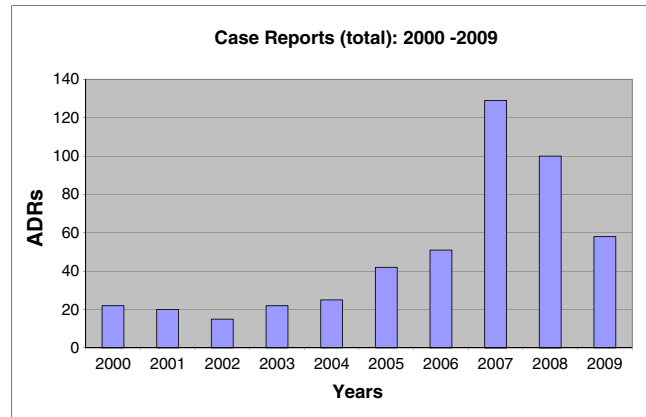


Figure 2. Total number of case reports with anthroposophic and homeopathic solutions for injection in Germany

of ADRs with injections in the period 2000–2009 was calculated as 3.89 per million ampoules and classified as very rare. Although the reporting rate for the last 3 years (2007–2009) was doubled in comparison to the 10-year period, e.g. 8.07 per million ampoules, it was still categorized as very rare. All 486 case reports represented 161 individual products for injection (some products appeared more than once in the pharmacovigilance database). 9.5% (46/486) of all product-related case reports were serious. However, case reports of serious ADRs had a low reporting rate

Table 1. Overview of category and number of ADRs (2000–2009)

Category	Frequency	Reporting rate ^a
Number of reported ADRs (2000–2009)	1180	3.89
Number of reported ADRs (2007–2009)	697	8.07
Number of case reports ^b	486	1.60
number of individual products	161	-
non-serious ^c	90.5% (440)	1.45
serious	9.5% (46)	0.15
listed	71.8% (349)	1.15
unlisted	27.8% (135)	0.45
not known	0.4% (2)	-
Source		
spontaneous	94.0% (457)	1.51
literature	0.2% (1)	< 0.01
clinical studies	5.8% (28)	0.09
Reporter		
healthcare professional	73.5% (357)	1.18
consumers	10.9% (53)	0.17
not known	16.6% (76)	-
Age		
0–18 years	2.5% (12)	0.04
19–64 years	57.6% (280)	0.92
≥65 years	27.1% (132)	0.44
not known	12.8% (62)	-

^aCalculated as number of ADRs/total amount of ampoules (million) sold.

^bPer case, more than one ADR can be reported.

^cPercentile may add to less or more than 100% due to rounding.

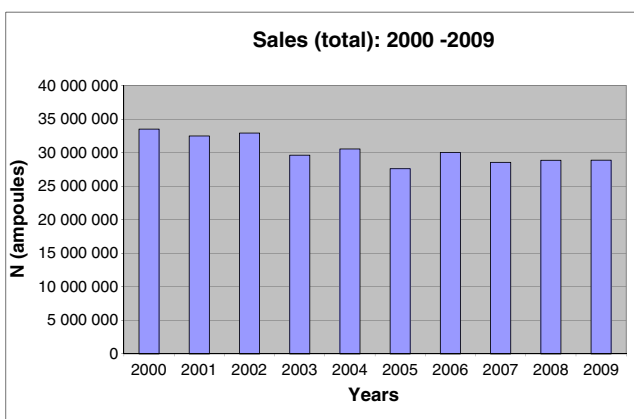


Figure 1. Total sales of anthroposophic and homeopathic solutions for injection (ampoules) in Germany

of 0.15 per million ampoules. The majority (71.8%) (349/486) of case reports included ADRs that were listed, e.g. the ADR was listed in the Summary of Product Characteristics or package leaflet (Table 1). Most cases (94%) were reported spontaneously and by health-care professionals (73.5%). The majority of ADRs (57.6%; 280/486) occurred in adults (19–64 years). 27.1% (132/486) was reported in patients over 65 years. Few ADRs were reported in children till 18 years of age (2.5%; 12/486). In 12.8% (62/486) of the cases, the age was unknown.

The five most frequently reported ADRs were pruritus, angioedema (swelling of dermis or subcutaneous tissue), diarrhoea, erythema and nausea (Table 2). Most ADRs reported were classified as skin and subcutaneous tissue disorders, general disorders and administration site conditions. 27.3% (322/1180) of all reported ADRs was a local reaction, coded as application or injection site erythema, pain, swelling, inflammation, itching (results not shown).

Characteristics of serious ADRs

ADRs were classified as serious when patients in question were either hospitalised (80% of cases; 37/46), significantly disabled (11% of cases; 5/46) or experienced a life-threatening situation (9% of cases; 4/46). In almost half of the case reports of serious ADRs, a causal relation to injection of the medication was assessed as unlikely (48%) (22/46). In 37% (17/46), the causal relationship was assessed as possible, in 13% (6/46) as probable. For one case, an assessment was impossible to make. The 46 serious ADRs were reported with 31 individual products. For most products (65%) (20/31), one serious ADR was reported. Per individual product, reporting rates of serious ADRs ranged from 29.1 (highest) to 0.08 (lowest)

per million ampoules. The outcome of the serious ADRs was in most cases unknown (43.5%) (20/46). 23.9% (11/46) of patients with serious ADRs had recovered, 8.7% (4/46) were recovering and 23.9% (11/46) had not recovered. Pain in extremity (32.6%) (15/46), brain stem infarction (8.7%) (4/46), aphthous stomatitis (8.7%) (4/46), cerebral ischemia (8.7%) (4/46) and tongue disorder (8.7%) (4/46) were labelled as the five most frequently reported serious ADRs. Most frequent SOCs for serious ADRs were musculo-skeletal and connective tissue disorders (32.6%) (15/46), gastrointestinal disorders (26.1%) (12/46), nervous system disorders (17.4%) (8/46) and respiratory thoracic and mediastinal disorders (6.5%) (3/46). The brain stem infarction was reported in one patient only. This was presented within the database as four separate case reports since the patient was injected simultaneously with four different products. This serious ADR was assessed as possibly related to injection of the medication. With aphthous stomatitis (causality assessment; unlikely) and cerebral ischemia (causality assessment; possible), the serious ADR also occurred in one patient only, which was injected simultaneously with four individual products. Further analyses were carried out to determine the reporting rates of serious ADRs as compared to non-serious ADRs in the different subgroups and product categories. Case reports of serious ADRs occurred significantly more frequently as compared to those of non-serious ADRs in (i) male subjects, (ii) subjects of 65 years and older, (iii) upon injection with complex products, (iv) with products of a dilution <1:10.000 and (v) upon intramuscular injection (Table 3). In these specific subgroups, reporting rates for serious ADRs were low, ranging from 0.03 to 0.15 per million ampoules.

DISCUSSION

To our knowledge, this is the first study that provided a thorough evaluation of collected and spontaneous reported ADRs for parenteral dosage forms of anthroposophic and homeopathic medications. Between 2000 and 2009, 486 cases were identified in Germany with a total of 1180 reported ADRs. In relation to the overall sales data of ampoules within that period (303 million), the reporting rate of ADRs as associated with solutions for injection was found to be very rare, i.e. less than four ADRs per million ampoules. Compared to other countries worldwide, anthroposophic and homeopathic solutions for injection are most frequently prescribed in Germany.⁵ The sales of ampoules in Germany was shown to decrease in the time-frame as analysed. Due to the 'nachzulassung'

Table 2. ADRs^a and system organ class most frequently reported

ADR	Frequency	Reporting rate ^b
Pruritus	5.3% (62)	0.20
Angioedema	3.5% (41)	0.14
Diarrhoea	3.2% (38)	0.13
Erythema	3.0% (35)	0.16
Nausea	3.0% (35)	0.16
System organ class	Frequency	Reporting rate ^b
Skin and subcutaneous tissue disorders	25.2% (298)	0.98
General disorders and administration site conditions	17.9% (211)	0.70
Gastrointestinal disorders	12.6% (149)	0.49
Nervous system disorders	7.0% (83)	0.27
Vascular disorders	6.4% (75)	0.25

^aPreferred term according to MedDRA.

^bCalculated as number of ADRs/total amount of ampoules (million) sold.

ADRS TO ANTHROPOSOPHIC AND HOMEOPATHIC SOLUTIONS FOR INJECTION

Table 3. Serious versus non-serious case reports

Category	Serious	Reporting rate ^a	Non-serious	Reporting rate ^a	p-value
Male ^b	6.8% (33)	0.11	17.9% (87)	0.29	0.001 ^c
Female	2.5% (12)	0.04	72.5% (353)	1.17	
Not known	0.2% (1)	-	-	-	
0–18 years	0.0% (0)	-	2.5% (12)	0.04	
19–64 years	0.8% (4)	0.01	56.8% (276)	0.91	0.001 ^c
≥ 65 years	5.3% (26)	0.09	21.8% (106)	0.35	
Not known	3.1% (16)	-	9.7% (46)	-	
Single product	0.0% (0)	-	11.7% (57)	0.18	0.05 ^c
Complex product	9.3% (45)	0.15	78.8% (383)	1.26	
Not known	0.2% (1)	-	-	-	
Listed	7.4% (36)	0.12	64.4% (313)	1.03	0.25
Unlisted	1.9% (9)	0.03	25.9% (126)	0.42	
Not known	0.2% (1)	-	0.4% (1)	-	
<1:10.000	8.6% (42)	0.14	65.8% (320)	1.06	0.01 ^c
≥1:10.000	0.6% (3)	0.01	24.1% (117)	0.39	
Not known	0.2% (1)	-	6.2% (3)	-	
1 ml	5.3% (26)	0.09	63.0% (306)	1.00	0.31
2 ml	3.9% (19)	0.06	26.5% (129)	0.43	
Other/not known	0.2% (1)	-	1.0% (5)	-	
sc injection ^d	0.4% (2)	<0.01	29.2% (142)	0.47	0.001 ^c
im injection	2.1% (10)	0.03	8.0% (39)	0.13	
sc injection ^d	0.4% (2)	<0.01	29.2% (142)	0.47	0.01 ^c
iv injection	4.2% (20)	0.06	41.2% (200)	0.66	
im injection ^d	2.1% (10)	0.03	8.0% (39)	0.13	0.05 ^c
iv injection	4.2% (20)	0.06	41.2% (200)	0.66	

^aCalculated as number of ADRs/total amount of ampoules (million) sold.

^bPercentile may add to less or more than 100% due to rounding.

^cIndicating a significant difference between % of serious and non-serious case reports, using the Pearson's Chi-square test.

^dData on the most frequently used parenteral dosage forms are depicted.

of these products (re-registration of marketing authorisation in Germany), companies withdrew a number of these products from the market. They were not able to make the huge investment required (time and money-wise) to maintain marketing authorisation. With the participating anthroposophic and homeopathic manufactures, almost full coverage of the German market was reached. Thus, the present findings are expected to be highly representative for the safety status of anthroposophic and homeopathic medications in general.

Most ADRs were reported in adults aged 19 to 64 years, whereas few ADRs were reported in children. The low number of ADR reports in children could be explained by the current German regulation for authorisation of parenteral dosage forms. Those parenteral dosage forms with a therapeutic indication are often not indicated for children under the age of 12 years because the specific indication does not apply to children. Furthermore, physicians usually do not prefer solutions for injection in children.

In 9.5% of all case reports, ADRs were classified as serious. Compared to non-serious ADRs, they seemed to occur significantly more frequent in males, in adults of 65 years and older, with complex products and products with dilutions <1:10.000. The higher frequency

of serious ADRs in men and in patients of 65 years and older does not seem to be specifically related to homeopathic and anthroposophic medicinal products since a correlation between increasing age and higher ADR reporting rates is generally known.¹⁵ It has also been described that men may have a poorer health status than women in a number of physical symptoms and conditions.¹⁶ The finding that 9.5% of all case reports were serious seems relatively high, but has to be interpreted with caution. First, a broad definition of ADRs was applied in this analysis. All ADRs for which regulatory reporting was required were extracted. This included ADRs where causality assessment to injection of the medication was unlikely or unknown. Almost half of the case reports on serious ADRs (48%) were assessed as unlikely related to the medicinal product and could have been caused by the severity of the on-going disease and/or co-morbidity of patients. Other studies on anthroposophic and homeopathic medications did not report of any serious ADRs.^{9–11,17} One explanation might be the under-reporting of non-serious and listed ADRs in the present study. Most package leaflets of anthroposophic and homeopathic medications state that adverse reactions that are not listed in the leaflet should be reported to a physician or a pharmacist. This may lead

to under-reporting of listed non-serious adverse reactions. Nevertheless, the reporting rate of serious ADRs as observed with injections in the present analysis was rare (0.15 per million ampoules). In comparison, a recent review on the benefits and safety of corticosteroid injections in the management of knee osteoarthritis reported on severe infectious complications upon injection as high as 1 in 3000 injections.¹⁸ The reporting rates of ADRs associated with anthroposophic and homeopathic solutions for injection appeared to be more comparable to those of intra-articular saline and hyaluronic acid injection in the treatment of osteoarthritis.^{19,20}

The ADRs that were identified were mostly related to skin and subcutaneous tissue disorders and/or general disorders and administration site conditions. About one quarter of ADRs was related to the injection procedure itself. With respect to the relative safety of the frequently applied parenteral dosage forms, most serious ADRs were reported with intramuscular injections. No conclusions could be drawn about the overall safety of the different parenteral dosage forms since it was not possible to calculate sales data per administration dosage form.

Our present study suffered from some unavoidable limitations. The first one was that of under-reporting of ADRs to the manufacturers. Practitioners and other healthcare providers may not always report on expected or unexpected ADRs. However, our findings were in line with data from a study by Hamre *et al.*¹⁷ in which adverse effects were monitored intensively. In this study, an incidence rate of one ADR per 382 patient-months of anthroposophic medications use (all dosage forms) was observed. With a daily dose of 0.7, a calculated ADR incidence rate in the Hamre study would be classified as very rare (<0.01%) as well. Furthermore, comparable results were reported in a European survey among anthroposophic and homeopathic practitioners.⁷ The majority of practitioners (87%) had never or very rarely (1 or <1:10,000 treated patients) observed an ADR with anthroposophic or homeopathic solutions for injection, whereas 2.6% had rarely observed any ADR and 1.7% occasionally (8.9% gave no response). A second major limitation of the present study was that data analysis was performed on reporting rates, rather than incidence rates of ADRs. Incidence rates of ADRs could not be calculated since no information was available on how many ampoules for injection were used by patients in total, or in subgroups of patients. Reporting rates were calculated on the basis of the number of ampoules sold. However, ampoules sold are not necessarily prescribed and used by patients. Case reports for which it was

clear that the solutions for injection were administered orally, were excluded from data analysis. However, due to off-label use, sales data may have represented patients that took ampoules orally rather than parenteral. Based on practitioner's prescription behaviour,^{7,17} the oral use of ampoules is not expected to be high; nevertheless, it cannot be excluded. A major general limitation of pharmacovigilance data is that they highly depend on the quality of the reporting and monitoring system. During the last three years in Germany, as well as in other European countries, pharmacovigilance procedures have been considerably improved. The introduction of Volume 9a guidelines for pharmacovigilance which came into force in 2008 has attributed to this improvement. In the present study, it became apparent that the collection and spontaneous reporting of ADRs had significantly increased during the last 3 years when compared to the previous years. Improved pharmacovigilance procedures may have contributed to this increase. Repetition of this evaluation of pharmacovigilance data within a time frame of 5 years is therefore warranted. High-quality prospective observational studies are also necessary to further substantiate the safety profile of homeopathic and anthroposophic solutions for injection. Such studies on safety have been described for ayurvedic and homeopathic medicine in India.^{21,22} The recently described EvaMed Pharmacovigilance network, may provide such information for anthroposophic and homeopathic products.²³

CONCLUSIONS

This is the first study that provided a systematic evaluation of the safety of anthroposophic and homeopathic solution for injection from pharmacovigilance databases. Our results suggested that these solutions for injection have a low-risk profile. This included complex products and those that were not highly diluted. These results may provide reliable data for risk-benefit ratio calculations of anthroposophic and homeopathic parenteral dosage forms.

CONFLICTS OF INTEREST

This study was initiated and financially supported by the European Coalition on Homeopathic and Anthroposophic Medicinal Products (ECHAMP). Companies whose products were investigated in the present study are active members of ECHAMP. The companies and ECHAMP had no right of final editing and/or approval of the manuscript. During the past three years, MJ and EB have received research grants to investigate the

efficacy of products of two of the eight participating companies. There is no conflict of interest for MS in the study.

KEY POINTS

- ADR reports associated with injections of anthroposophic and homeopathic medicinal solutions were very rare.
- Most ADR reports were related to skin/subcutaneous tissue disorders and general/administration site disorders.
- Almost three quarters of reported ADRs were listed.
- One quarter of ADR reports was related to the injection procedure itself.

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