REVIEW ARTICLE

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The Safety of Herbal Medicinal Products Derived from *Echinacea* Species

A Systematic Review

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Contents

Abstract

Echinacea spp. are native to North America and were traditionally used by the Indian tribes for a variety of ailments, including mouth sores, colds and snakebites. The three most commonly used *Echinacea* spp. are *E. angustifolia*, *E. pallida* and *E. purpurea*. Systematic literature searches were conducted in six electronic databases and the reference lists of all of the papers located were checked for further relevant publications. Information was also sought from the spontaneous reporting programmes of the WHO and national drug safety bodies. Twenty-three manufacturers of echinacea were contacted and asked for data held on file. Finally our own departmental files were searched. No language restrictions were imposed. Combination products and homeopathic preparations were excluded.

Data from clinical studies and spontaneous reporting programmes suggest that adverse events with echinacea are not commonly reported. Gastrointestinal upsets and rashes occur most frequently. However, in rare cases, echinacea can be associated with allergic reactions that may be severe. Although there is a large

amount of data that investigates the efficacy of echinacea, safety issues and the monitoring of adverse events have not been focused on.

Short-term use of echinacea is associated with a relatively good safety profile, with a slight risk of transient, reversible, adverse events. The association of echinacea with allergic reactions is supported by the present evaluation. While these reactions are likely to be rare, patients with allergy or asthma should carefully consider their use of echinacea. The use of echinacea products during pregnancy and lactation would appear to be ill-advised in light of the paucity of data in this area.

Echinacea spp. are native to North America and were traditionally used by the Indian tribes for a variety of ailments, including mouth sores, colds and snakebites.[1] The three most commonly used *Echinacea* spp. are *E. angustifolia*, *E. pallida* and *E. purpurea*. Throughout this review, unless the botanical or trade name has been specified, these preparations will be cited as echinacea.

Much of the medicinal supply of *E. angustifolia* (narrow-leaved purple cone flower), the smallest of these plants (0.5m), is still harvested from the wild. *E. pallida* (pale purple cone flower) is larger (1m) and produces a characteristic large purple flower. *E. purpurea* (common purple cone flower) can be distinguished by its oval leaves and the medicinal supply of this species is entirely cultivated. The roots are primarily used for extraction, although the aerial parts are also thought to have some medicinal properties. The chemical constituents of the three species of echinacea root differ in their alkylamide content, whereas the composition of the aerial parts do not seem to differ significantly.[2]

The predominant modern day use of echinacea is for the prevention and treatment of the common cold, influenza and upper respiratory tract infections.[3] It is also used generally as an immunostimulant/modulator.[4] There is no firm evidence for the efficacy of echinacea in any of these conditions.[3,4]

Although *E. angustifolia* is the favoured species of North America, this preference is probably due to familiarity and traditional use. In contrast, the majority of both pharmacological and clinical studies have been conducted with *E. purpurea*.[2]

Echinacea products were the second most popular herbal supplements in 2001 according to a recent analysis of sales in the US. This represents an increase of two places from the ranking in the 2000 sales analysis.[5,6] Annual sales of echinacea products have been estimated at $US300 million in the US alone, which makes up 10% of the herbal market.[7]

As the prevalence of echinacea use is high, it is imperative to evaluate its safety. This article aims to systematically review the information on the safety of echinacea from clinical studies, case reports, surveillance schemes and other investigations.

1. Literature Search

To locate papers with information relating to the safety of echinacea in humans, a systematic literature search was conducted from their inception to June 2003 in the following electronic databases: Medline, EMBASE, Cinahl, CISCOM, Amed and The Cochrane Library. The search terms were '*Echinacea purpurea*', '*Echinacea angustifolia*', '*Echinacea pallida*', 'narrow-leaved cone flower root', 'American cone flower', 'black sampson', 'hedgehog', 'Indian head', 'snake root', 'red sunflower', 'scurvy root', 'purple cone flower', 'purple Kansas cone flower', 'comb flower', 'cock up hat', 'Missouri snake root', 'Kansas snake root' and 'Sonnenhutkraut'. The following trade names were also used as search terms: 'Echinaforce®', [1] 'Myo-Echinacin®', 'Echinacin®', 'ContraInfekt®', 'Echiherb®', 'Echinacea Hevert purp. forte®', 'Echina-

1 The use of trade names is for product identification purposes only and does not imply endorsement.

truw®', 'Esberitox mono®', 'Immunopret®', 'Pascotox 100®', 'Pascotox forte-Injektopas®', 'Resplant®' and 'Skin clear®'.

Further relevant publications were located by checking the reference lists of all papers, contacting colleagues with an interest in herbal medicine and searching departmental files. In addition, data were requested from the spontaneous reporting programmes of Australia (Adverse Drug Reactions Advisory Committee [ADRAC]), Germany (Bundesinstitut für Arzneimittel und Medizinprodukte [BfArM]), UK (Medicines and Healthcare Product Regulatory Agency [MHRA]), US (FDA) and the WHO Collaborating Centre for International Drug Monitoring. Twenty-three manufacturers of echinacea were contacted and asked for any information held on file. The following herbal organisations were contacted: National Institute of Medical Herbalists (NIMH), British Herbal Medicine Association, European Herbal Practitioners Association, International Register of Consultant Herbalists and Homeopaths and the College of Practitioners of Phytotherapy. No language restrictions were imposed. Combination products, isolated components of echinacea and homeopathic preparations were excluded.

All data from clinical trials, case reports, spontaneous reporting programmes and phase I studies were included in the review. Of note, there were no postmarketing surveillance studies or other systematically targeted research regarding the safety of echinacea. The data were extracted according to predefined criteria (preparation and dose of echinacea, duration of treatment, study population and number of patients exposed to the echinacea product, number and type of adverse events experienced) by the first author and validated by the second author. Any disagreements were resolved in discussion with the third author. The various forms of the obtained evidence were either described in the text or summarised in tables, but because of the diverse nature of the data sources, no statistical analysis was feasible.

2. Clinical Studies

Our search strategy identified 36 clinical studies, of which 24 were published recently (1998–2002) and 12 were published between 1950 and 1988. The most relevant of these are summarised in table I. All 12 of the early studies were case series/observational studies and involved intravenous or intramuscular injections of Echinacin® for women with various infections or children with respiratory infections.[8-19] Reporting of adverse events focused on acute reactions to the injections, namely reddening/pain at the injection site, shivering and fever. In two trials, no adverse events were observed[12,13] and a general statement as to the nature of adverse events being local and mild-to-moderate after intravenous administration was provided in one trial.[18] In the 24 more recent and rigorous trials (1998–2002), the treatments were all oral either in the form of drops, lozenges/capsules or in one case, a tea preparation.[20-43] These latter trials provide more detail than the former 12 studies. In 5 of the 24, no mention is made of adverse events at all[20,21,24,34,39] and in seven trials a general comment is made that no adverse events were observed.[23,26,30,31,33,42,43] The adverse events that are reported tend to be mild, are predominantly gastrointestinal in nature and occur at a similar frequency in both treatment and placebo groups. Two of the trials described intolerance of the actual treatment, e.g. burning sensation due to high alcohol content or an unpleasant taste.[23,42]

3. Case Reports

There were eight case reports in the literature. In the first case, a 37-year-old woman who had been taking dietary supplements as a prophylaxis on an irregular basis took a variety of vitamins and supplements (vitamin B12, vitamin B complex, vitamin E, herbal iron prep, folate, multi-vitamin, zinc, antioxidants, garlic and onion prep and evening primrose oil).[44] Fifteen minutes later, she swallowed 5mL of commercially prepared echinacea (40% alcohol in water) which was equivalent to 3825mg of whole plant extract *E. angustifolia* and 150mg of *E. purpurea.* She experienced an immediate burning of the mouth and throat. Tightness in the chest, gener-

Table I. Adverse events reported with mono-preparations of echinacea as documented in case series and clinical trials

Study	Echinacea preparation	Study population taking echinacea	Adverse events
Röseler,[8,9] 1950 and 1952	Echinacin® 0.2mL IV for 8–9d	226 women with mixed periuteral infections	Shivering within 30–90 min of injection, followed by fever and lymphopenia; slight leukocytosis 24–48hr later
Moell,[10] 1951	Echinacin® 0.1mL–1.2mL IV for 8–10d	120 women with periuteral infections	Adverse events similar to those reported in case series by Röseler,[8,9] plus subjective complaints: headache, dizziness, tiredness, occasional nausea and abdominal pain in 10% of cases
Priese,[11] 1954	Echinacin® 0.1–1.0mL IV for an average of 6d	60 women with postpartal mastitis	Symptomatic response similar to those reported in case series by Röseler[8,9]
Volz,[12] 1957	Echinacin® (0.1g/2mL) IM 1–2mL twice daily for 3–21d	45 children with whooping cough	No adverse events were observed A slight reddening at injection site One child had elevated temperature for 12hr
Heesen,[14] 1964	Echinacin® IV 0.5–5mL within 2d and repeated up to 15 times over several weeks	>500 children with tuberculosis	Acute response: shivering, headache, vomiting and fever
Heesen and Orzechowski,[16] 1973	Echinacin® 1–2mL IM for 3d, followed by 3 times weekly for 2wk, 2–3wk total	Nearly 300 small children with whooping cough	Transient pain at injection site and a small increase in temperature
Baetgen,[17] 1984 controlled study	Injections of Echinacin®: 2 mL/d in children and 1 mL/d in infants for 3–10d	170 children with whooping cough	'Erythema and localised pain at the injection point were occasionally reported'
Baetgen,[19] 1988 retrospective comparative study	Echinacin® 3–4 IM injections on consecutive days for 3–4d	1280 young children with respiratory infections	'Remarkably well tolerated' One case of redness at injection site Three cases of allergic skin reaction
Anonymous, Madaus AG files,[41] 1991 open controlled study	Echinacin® lozenges (88.5mg aqueous EP) four times daily for 6wk	38 marathon runners (n = 79 total in trial)	General complaints of various muscle aches, joint pains, GI upsets and headaches were reported equally by 1–3 participants in both groups
Melchart et al.,[23] 1995; 3 studies PC RCT	(a) Two studies (1 and 2) involved oral ethanolic extract of EP roots 30 drops (330mg) daily (b) One study (2) involved extract of *E. pallida* roots 380g dried ethanolic extract in a capsule daily (c) One study (3) involved an ethanolic extract of EP herb 30 drops of (0.8–0.9g) three times daily for 5d	12 male healthy volunteers in each study (n = 94 total in 3 trials)	Most subjects in study 3 reported a burning sensation due to the high alcohol content in both treatment and control solutions No other adverse events reported
Anonymous, Madaus AG files,[42] mid-1990s multicentre study	Echinacin® lozenges: one lozenge three times daily for 4–6wk	1231 patients with relapsing respiratory and urinary infections.	Most common adverse events were unpleasant taste (n = 21), nausea/vomiting (n = 6), recurrent infection (n = 5), sore throat, abdominal pain and diarrhoea (n = 3 for each), difficulty in swallowing (n = 2), others (n = 19)

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Table I. Contd

Study	Echinacea preparation	Study population taking echinacea	Adverse events
Melchart et al.,[27] 1998 DB PC RCT	Ethanolic extract of EP or EA: 50 drops twice daily for 12 wk (Monday to Friday)	99 (EP) and 100 (EA) volunteers without acute URTI infections (n = 289 total in trial)	18 EA recipients had 21 adverse events and 7 dropped out 10 EP recipients had 13 adverse events and 2 dropped out 11 placebo recipients had 12 adverse events and 1 dropped out; none were serious or required intervention
Grimm and Muller,[28] 1999 DB PC RCT	EC31J0 (EP pressed juice) 4mL twice daily for 8wk	54 patients with a history of more than 3 colds/respiratory infections in a year (n = 109 total in trial)	11 and 7 patients with adverse events, of which 4 and 3 dropped out in treatment and placebo group, respectively Most adverse events were mainly GI upsets, dizziness and tiredness in both groups
Brinkeborn et al.,[29] 1999 DB PC RCT	Echinaforce®, EPC or EPR: two tablets three times daily for not longer than 7d	182 healthy adult volunteers (n = 246 total in trials)	Echinaforce®: 7 adverse events EPC: 8 adverse events EPR: 12 adverse events Placebo: 6 adverse events The majority were GI in nature
Gallo et al.,[32] 2000 prospective case control study in pregnant women	Various capsules/tablets 250–1000mg daily; tinctures 5–30 drops daily (alcohol content 25–45%) Mostly EA or EP One case of *E. pallida* duration 5–7d 112 women used in first trimester 17 in all 3 trimesters.	206 pregnant women (112 women used echinacea preparations in the first trimester; 17 were exposed in all 3 trimesters; 206 in disease-matched control group)	Comparison with control group suggested no increased risk of major malformations due to echinacea ingestion during organogenesis
Schulten et al.,[35] 2001 DB PC RCT	EC31J0 5mL twice daily for 10d	41 patients with the first signs of a cold (n = 80 total in trial)	6 EC31J0 recipients experienced 8 adverse events 6 placebo recipients experienced 9 adverse events GI adverse events were reported most frequently
Vonau et al.,[36] 2001 DB PC RCT crossover	Echinaforce® 800mg of EP extract (95% plant, 5% root) twice daily for 6 months	50 patients with recurrent genital herpes	Nausea without vomiting = 4 Echinaforce® recipients versus 2 placebo recipients; 1 of these patients suffered severe diarrhoea on drug and discontinued treatment after 2 months
Rostock,[37] 2001 controlled, open pilot study	EP 8mL or EP pressed juice 24mL daily for 21d	128 breast/ colourectal cancer patients (n = 187 total in trial)	No. of adverse events were similar in 8mL group to control and less in 24mL group 1 case each of elevated liver enzyme levels and leukopenia 3 cases each of allergic skin reaction and vertigo No other serious/potentially serious adverse events

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Table I. Contd

Study	Echinacea preparation	Study population taking echinacea	Adverse events
Kim et al.,[38] 2002 DB PC RCT	Standardised extract of EP, urEPA or EPA for 4wk	8 healthy female volunteers in each of the 3 groups (n = 48 total in trial)	2 of 48 participants experienced adverse events urEPA group: self-reported anxiety, nervousness and heart palpitation EP group: bilateral arthritic symptoms in wrist, metacarpophalangeal and proximal interphalangeal joints Both resolved on discontinuation
Barret et al.,[40] 2002 DB PC RCT	An encapsulated mixture of unrefined EP herb (25%), root (25%) and EA root (50%) 1g six times daily on the first day of illness and three times on each subsequent day of illness for up to 10d	73 registered students with common colds of recent onset (n = 148 total in trial)	22 adverse events were reported by 15 participants: 9 adverse events by 7 participants in the placebo group and 13 adverse events by 8 participants in the treatment group Placebo group: stomach ache (n = 3), nausea (1), belching (1), thirst (1) and abdominal pain with diarrhoea (1) Treatment group: sleeplessness (1), heartburn (1), nausea (1), stomach ache (1), upset stomach (1) and bad taste in mouth (3) The remaining adverse events were not specified

DB = double blind; **EA =** *Echinacea angustifolia*; **EP** = *E. purpurea*; **EPA** = *E. purpurea/E. angustifolia*; **EPC** = *E. purpurea* concentrate; **EPR** = *E. purpurea* radix special prep; **GI** = gastrointestinal; **IM**= intramuscular; **IV**= intravenous; **PC** = placebo-controlled; **RCT** = randomised controlled trial; **urEPA** = ultra-purified *E. purpurea/E. angustifolia*; **URTI** = upper respiratory tract infection.

alised urticaria and diarrhoea developed within 30 minutes. The patient was transferred to hospital by ambulance after self-administering 75mg of promethazine orally. The patient was observed for 3 hours and her symptoms resolved completely without the need for further treatment. The women had a history of atopy and subsequently exhibited a positive skin prick reaction to an aqueous echinacea solution.

Following the publication of the above case report and discussion,[44] the author pursued his investigation by examining the reports on echinacea from the Australian surveillance programme (ADRAC) and those suggestive of allergy were evaluated in greater detail by anonymously surveying the healthcare professionals who had reported the cases and from one unreported case. Serum was collected for further analysis where possible. Four cases of adverse reactions to echinacea were evaluated in addition to the woman from the case report above.[45] Three of the patients had positive skin prick tests (SPTs). Three of the patients reported repeated spontaneous 'challenges' and symptoms after further ingestion of echinacea.

The additional four cases included a 19-year-old female who suffered an acute asthma attack and severely itchy and watery eyes and a runny nose within 10 minutes of her first ever exposure to an echinacea-containing tea.[45] Symptoms resolved gradually over several hours. She had intercurrent problems of seasonal allergic rhinitis, nasal polyposis and sinusitis without asthma. No other food or medication had been ingested for over 12 hours. One week after the event, she had a positive SPT of a 3mm wheal with an aqueous echinacea solution.

The second of the four cases involved a 31-year-old health professional who within 20 minutes of ingestion of an echinacea-containing tablet experienced generalised urticaria, facial and upper airway angioedema, difficulty swallowing, bronchospasm, dizziness and disorientation.[45] Symptoms resolved gradually over several hours. During 3 of the 4 preceding days she had taken the same echinacea tablets and had experienced headache and mild facial angioedema within 20 minutes of each administration, but had no reaction on the echinacea-free

day. The patient was known to be allergic to latex and had a long history of perennial allergic rhinitis with seasonal exacerbation. She complained that sulphite-containing dried fruit would trigger urticaria, flushing, mild wheezing and nasal obstruction. On one occasion she had experienced exercise-related anaphylaxis. Further investigation implicated previous ingestion of rye or mushrooms (4–5mm positive SPTs to both) or NSAIDs. No further episodes have occurred with avoidance of these substances. The patient, a trained observer, could not recall exposure to these agents or latex on the days in question and considered the reactivity to echinacea ingestion to be consistent. However, a SPT with the aqueous echinacea solution 1 year on from the event proved to be negative.

The third case was a 56-year-old man who reported new onset of a documented asthma coincident with the ingestion of echinacea tablets for treatment of an intercurrent upper respiratory tract infection.[45] On three separate occasions, he developed severe difficulty breathing and coughing within 2 hours of ingestion of these tablets. He had intercurrent problems of allergic rhinitis. There was no known food or drug allergy and he was taking no other medication during this period. Symptoms re-

Table II. Adverse events reported with mono-preparations of echinacea from the ADRAC (Australia), BfArM, (Germany), MHRA (UK), FDA (US) and WHO (international) monitoring bodies[a]

Adverse event classified by body system	Frequency of adverse events				
	ADRAC	BfArM[b]	MHRA	FDA[b]	WHO
Application site	0	4	0	0	3
Body as a whole – general	19	45	3	6	71
Cardiovascular	3	5	2	2	8
Central and peripheral nervous	13	17	1	1	37
Endocrine	0	0	1	0	1
Gastro-intestinal	15	32	1	13	48
Haemopoietic	0	0	1	0	0
Hearing and vestibular	0	1	0	0	1
Heart rate and rhythm	4	3	2	0	14
Liver and biliary	8	1	1	4	21
Metabolism and nutrition	0	4	2	0	3
Muscular and skeletal	8	7	4	1	19
Neurological	0	0	7	0	0
Platelet, bleeding and clotting	2	2	0	1	7
Psychiatric	4	2	3	3	8
Red blood cell	0	0	1	0	3
Respiratory	26	13	2	0	39
Reproductive – female	0	0	0	0	1
Reproductive – male	0	1	0	0	1
Skin and appendages	30	69	4	5	127
Special senses	0	4	0	0	5
Urinary	7	8	1	0	13
Vascular (extracardiac)	2	6	0	0	10
Vision	1	3	1	1	6
White cell and reticuloendothelial system	2	3	0	0	6
Term not accepted in WHO-ART	0	0	0	3	4

a Extract period: ADRAC, BfArM and WHO searched October 2001; no exact date is available for initial inclusion of echinacea in these programmes. MHRA searched July 1963–Oct 2001. FDA searched early 1993–October 1998.

b A total of five deaths were reported (FDA [1], BfArM [4]).

ADRAC = Adverse Drug Reactions Advisory Committee; **BfArM** = Bundesinstitut für Arzneimittel und Medizinprodukte; **MHRA** = Medicines and Healthcare Product Regulatory Agency; **WHO-ART** = WHO Adverse Reaction Terminology.

solved within a few days of stopping echinacea. A SPT with the test aqueous echinacea 6 months after the event was negative.

In the fourth case report, a 48-year-old female experienced a maculopapular rash over her thighs and abdomen within 2 days of ingestion of echinacea tablets that had been taken to prevent infection.[45] The rash resolved within 1 week with use of topical corticosteroids. A week later, she recommenced treatment from the same bottle and redeveloped a similar, but more severe and generalised, pruritic rash within 48 hours. It settled gradually over a period of 6 weeks and required a course of oral corticosteroids to assist resolution. She had intercurrent problems of non-allergic (vasomotor) rhinitis and took no regular medication. A SPT with the test solution of aqueous echinacea was negative.

A 41-year-old man experienced four episodes of erythema nodosum, each proceeded by a prodrome of myalgias and arthralgias, fever, headache, malaise and sometimes a sore throat that lasted from a few days to 2 weeks.[46] Various treatments for infections were used, but the condition only responded to prednisone. Recent medications included loratadine and St John's wort. The patient routinely took echinacea at the onset of influenza-like illnesses and specifically recalled using it for each of the prodromes preceding his erythema nodosum. He could not identify an episode not associated with this treatment. He discontinued his echinacea therapy, but continued to take St John's wort and loratadine and at a 1 year follow-up reported no recurrence of erythema nodosum.

Two German cases of adverse events with mono-preparations of echinacea have been described.[47] The first involved a 40-year-old male who took Echinacin® for 3 days (120 drops/day). He developed fever, lymphadenopathy and exanthema in the shin area and blood tests revealed 13% monocytosis. He was treated with antihistamines and made a full recovery within 2 days. The second case involved a 19-year-old male who took an echinacea extract. He later developed a worsening of his influenza symptoms. He then took an antibacterial, amoxicillin and ibuprofen and developed protracted shock with generalised increased vascular permeability and rhabdomyolysis. He was admitted into intensive care, but subsequently died.

4. Spontaneous Reporting Programmes

4.1 Adverse Drug Reactions Advisory Committee (ADRAC), Australia

There were 63 case reports of adverse events involving mono-preparations of echinacea from the ADRAC (table II). Causality was classified as possible in 36 cases, probable in 17 and certain in 10.

4.2 Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM), Germany

The BfArM reported 107 case reports of adverse events involving mono-preparations of echinacea (table II). In all cases, mono-preparations of echinacea were the suspected drugs causing the adverse events. These included three anaphylactoid reactions and five occurrences of anaphylactic shock. In all but one of these cases, echinacea was taken intravenously or intramuscularly. In one of these anaphylactoid cases, the patient died and causality was described as possible. There were three other deaths that were unrelated to echinacea ingestion.

4.3 Medicines and Healthcare Product Regulatory Agency (MHRA), UK

The MHRA reported 21 cases of adverse events possibly involving echinacea; 20 of these were mono-preparations (table II). No causality was confirmed.

4.4 FDA, US

There were 47 reports of adverse events with echinacea from the FDA; 22 of these involved mono-preparations (table II). In at least two of the cases, the echinacea product was not the only herbal product being taken. Three cases were believed to be due to contamination of the product, with selenium, arsenic and lead. There were four cases of hepatitis, with one of these resulting in a death. However, no

Table III. Causality assessment of suspected adverse reactions – WHO definitions

Causality term	Definition
Certain	A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration and that cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically and use a satisfactory rechallenge procedure as necessary.
Probable/likely	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, which is unlikely to be attributed to concurrent disease or other drugs or chemicals and that follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but that could also be explained by concurrent disease or other drugs or chemicals.
Unlikely	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration that makes a causal relationship improbable and in which other drugs, chemicals or underlying diseases provide plausible explanations.
Conditional/unclassified	A clinical event, including laboratory test abnormality, reported as an adverse reaction and about which more data is essential for a proper assessment or the additional data are under examination.
Unassessable/ unclassifiable	A report suggesting an adverse reaction that cannot be judged because information is insufficient or contradictory and which cannot be supplemented or verified.

patient details or causality information is available for these reports.

4.5 WHO, Sweden

The WHO held reports of adverse events with mono-preparations of echinacea from Australia, Austria, Belgium, Canada, Denmark, Germany, Ireland, New Zealand, Netherlands, Norway, South Africa, Sweden, Switzerland, the UK and the US. Detailed reports (216) were available from all of these countries, excluding Austria and the UK (table II).

The causality estimates of these reports were: unlikely (8), unclassified (33), unclassifiable (13), possible (105), probable (26), certain (10) and no drug-reaction relationship reported (21) [see table III for WHO definitions of suspected adverse event classifications]. Of the ten cases in which the causality was defined as certain, seven were identical to cases in the ADRAC database (table IV).

This information was obtained from the WHO, with the caveats that the information is not homogenous, at least with respect to origin or likelihood that the pharmaceutical product caused the adverse reaction, and that the information does not represent the opinion of the WHO.

5. Manufacturers

Nine of twenty-three manufacturers responded to our request for information regarding echinacea products (one request came back unopened). Madaus AG, Germany were the only company able to provide information on in-house clinical trials on mono-preparations of echinacea via published material (table I).

6. Herbal Organisations

Five herbal organisations were contacted, three of which replied. The International Register of Consultant Herbalists and Homeopaths had no reports of adverse events with echinacea. The NIMH has used a yellow card system since 1994 and in that time has had one report on echinacea that involved a possible individual allergic reaction. The College of Practitioners of Phytotherapy replied that they did not yet operate a yellow card system.

7. Discussion

All of the safety data on echinacea collected in this review have to be interpreted with caution because of their anecdotal nature. Reports of transient adverse reactions following the ingestion of echinacea do not provide sufficient evidence that it is responsible for these symptoms since many other

Table IV. Adverse events reported with mono-preparations of echinacea as documented in case reports from the surveillance programmes of the Adverse Drug Reactions Advisory Committee (ADRAC) and WHO in which causality was classified as 'certain'

Patient characteristics	Echinacea preparation	Concomitant medication	Adverse reaction	Treatment given	Laboratory data/other information	Outcome/additional notes
Female 37 years, Australia[a]	Echinacea 5mL single dose	None stated	Anaphylactoid reaction, diarrhoea, paraesthesia, chest pain and urticaria	Self-administered promethazine 75mg and transferred to hospital by ambulance	Positive skin prick test and serum assay for Echinacea-binding IgE	Recovered without sequelae
Female 56 years, Australia[a]	Echinacea 2mL daily for 3mo	Captopril 25mg daily for essential benign hypertension	Myalgia, rash vesicular and nausea	None stated	None stated	Recovered without sequelae
Female 27 years, Australia[a]	Echinacea three tablets daily	None stated	Arthralgia and myalgia	None stated	Rechallenge led to recurrence of symptoms	Recovered without sequelae
Female 60 years, Australia[a]	Echinacea no details on dose	None stated	Hypertension	None stated	Rechallenge led to recurrence of symptoms	Recovered without sequelae
Female 57 years, Australia[a]	Echinacea one unit daily, unknown time period	None stated	Dysuria	None stated	Same reaction occurred on numerous occasions over the past 3y when patient took echinacea	Unknown
Female 32 years, Australia	Echinacea four tablets in a single dose	None stated	Headache, angioedema, urticaria, bronchospasm, fatigue, dizziness, dysphagia, face oedema and confusion	Echinacea ceased	None stated	Recovered without sequelae
Female 21 years, Australia	Echinacea liquid 900mg daily topical for 1y	Atenolol 50mg for essential benign hypertension	Psoriasis aggravated	None stated	None stated	Recovered without sequelae
Male 16 years, Australia[a]	Echinacea three tablets for 3d	None stated	Paraesthesia, face oedema, skin exfoliation, fever, jaundice, hepatomegaly and peripheral oedema	None stated	Positive skin prick test and serum assay for echinacea-binding IgE. Patient allergic to grass pollens and dust mites, suffers from allergic rhinitis	Recovered without sequelae
Female 53 years, Australia[a]	Echinacea 5000 two capsules daily for approximately 5d	None stated	Dizziness, palpitation, increase in micturition frequency and nausea	Echinacea ceased; no medical attention available while travelling	Recommenced capsules a few days later and relapse of symptoms occurred	Recovered without sequelae

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Table IV. Contd

Patient characteristics	Echinacea preparation	Concomitant medication	Adverse reaction	Treatment given	Laboratory data/other information	Outcome/additional notes
Male 32 years, Australia	Cenovis® echinacea 4500 at a dosage of 135mg daily for approximately 5mo	Vitamin B complex and vitamin C	Depression and insomnia	None stated	No previous history of depression	Recovered without sequelae
Female 34 years, Germany[b]	Echinacin IV	None stated	Angioedema	None stated	Rechallenge led to recurrence of symptoms	Recovered without sequelae
Male 35 years, Germany[b]	Echinacin IV single dose	Pheneticillin potassium and meditonsin	Dyspnoea, urticaria, face oedema, flushing and abdominal pain	None stated	None stated	Recovered without sequelae
Female 27 years, New Zealand[b]	Echinacea extract	None stated	None stated	None stated	Rechallenge led to recurrence of symptoms	Recovered without sequelae

a Case report appeared in both the ADRAC and WHO databases.

b Case report appeared in WHO database alone.

Ig = immunoglobulin; **IV**= intravenous.

factors, such as the health status of the patient, other concomitant medications, the time course of events and the nature and dose of the echinacea preparation, are often unknown.

Despite the comprehensive search procedures, the material that is uncovered is likely to be an under-representation of the frequency of suspected adverse events due to under-reporting. This problem is more pronounced with herbal medicines than conventional pharmaceutical agents. This may be partly due to the misconception that herbal medicines are natural, safe and, therefore, an association between an adverse event and a herbal medicine may not necessarily be made. There is also evidence that patients are less likely to report adverse events from herbal medicines to their doctor than those from conventional medicine.[48]

Information on adverse events during clinical studies is very limited. Clinical trials involve relatively small numbers of participants for short periods of time. Clinical trials are usually set up to ascertain the efficacy of a treatment and the reporting of any adverse events does not seem to be a priority. This seems to be particularly true of the older, non-randomised case series/observational studies of echinacea, which all involved intravenous or intramuscular administration of echinacea. Minor adverse events were reported in some of the studies, with a focus on the acute reactions to the injections. However, in many of the studies, adverse events were not mentioned or treatment was described as 'well tolerated'.

Reporting of adverse events in the more recent trials is variable, with some reporting nothing or using statements such as 'remarkably well tolerated' and 'no specific adverse events were reported'. The adverse events that were reported were generally mild, such as gastrointestinal upsets. Overall, as in most clinical trials, safety is not focused on and reporting of adverse events is inadequate. If adverse events are noted, it is possible that the methodology of collection is different between trials.

There were eight case reports in the literature.[44-47] Mullins and Heddle[45] re-examined five of these cases and found that three of the five

patients responded to a SPT with an aqueous echinacea preparation at a later date. The death of the 19-year-old with 'flu-like symptoms' that worsened is unlikely to be due to his echinacea ingestion and, in fact, this case did not appear in either the BfArM or the WHO surveillance reporting programmes.

The duration of echinacea administration in the clinical studies tends to be short-term (days as opposed to weeks), although a few of them extend to 12 weeks. There are no safety data regarding long term use of *Echinacea sp.*

The data sources reviewed in this paper indicate that the echinacea used varies greatly in both botanical composition and dose. From this information, it is impossible to say whether any specific product or preparation may cause more adverse events than any other.

The information available from the spontaneous reporting schemes was significant, but cannot provide evidence of prevalence or causality. As mentioned previously, there is potential for under-reporting of adverse events, particularly with herbal medications. However, there are also problems with the data that is reported; the dose is often unknown, individuals frequently take multiple medications that may or may not be reported and the ultimate outcome is not always reported. It is possible that there is some overlap in the data from the various reporting schemes, although in the case of echinacea it does appear that each reporting scheme provides additional information on adverse events. Overall, the data obtained from these schemes suggest that adverse events are rare, mild and reversible, although there appears to be some areas of potential concern.

Concerns over allergic reactions with echinacea have previously been reported.[45] The spontaneous reporting schemes seem to support the possibility of allergic problems with echinacea in a minority of cases. Symptoms such as anaphylactic shock, anaphylactoid reaction, allergic reaction, bronchospasm and dyspnoea are cited and although determination of causality is variable, a high proportion of these cases are rated as 'possible', 'probable/likely' or 'certain'. However, it is also important to point out that in about a quarter of these cases, echinacea had been administered intravenously or intramuscularly.

Arthralgia and myalgias may also be associated with echinacea. There was some reporting of muscular/joint aches that were associated with echinacea ingestion in two of the clinical trials[38,41] and in one of the case reports.[45] These are also present in the spontaneous reporting schemes, with myalgia in particular, being associated with causality assessments of 'possible', 'probable/likely' or 'certain' and occurred in two of the ten 'certain' cases obtained from the WHO data. However, muscular and joint aches could be associated with the cold or influenza symptoms for which the echinacea product is administered.

Gastrointestinal complaints were prevalent in both spontaneous reports and in clinical trials; nausea, abdominal pain, diarrhoea and vomiting were reported most frequently. The most prevalent adverse events were in the 'skin and appendages' section, with such conditions as pruritus, non-specific rash, erythematous rash and urticaria.

A further problem with these data is the lack of reliable drug utilisation data, making a percentage calculation of adverse events with number of courses difficult. However, it has been estimated that 1–4% of the general population uses echinacea in a given year.[4]

Of the 13 adverse events cases from the surveillance programmes with causality rated as 'certain', 9 of these did not specify a brand name. Therefore, the quality of the echinacea in question is unknown. Of the 12 case reports identified in the literature, only 2 involved concomitant medication. In both cases, this was medication for essential hypertension and the adverse events were not related to this condition. Interactions are not thought to be a problem with echinacea, although theoretically they could decrease the effects of immunosuppressants.[49] It is important to note that although some of the adverse events were not pleasant and were potentially life-threatening, 11 of the 12 cases reported the outcome as ' recovered without sequelae'. In the remaining case, this information was not available.

Information from the herbal organisations did not yield any significant data. However, it is important to note that of the five organisations that were contacted, only one (NIMH) operate a yellow card system.

8. Conclusion

In conclusion, the evidence from clinical studies and surveillance programmes suggests that echinacea products have a good safety profile if they are taken in the short-term. Data on long-term oral use is not available. If adverse events occur they tend to be transient and reversible, with the most common symptoms being gastrointestinal and skin-related. However, the previous association of echinacea with allergic reactions does seem to be supported by the surveillance programme data in the present study. These reactions, albeit rare, suggest that atopic patients and those with asthma should carefully consider their use of echinacea. The use of echinacea products during pregnancy and lactation would appear to be ill-advised given the paucity of available data in this area.

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