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Adverse events associated with pediatric complementary and alternative medicine in the Netherlands: a national surveillance study

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Abstract

Pediatric use of complementary and alternative medicine (CAM) in the Netherlands is highly prevalent. The risks of pediatric CAM use are, however, largely unknown. Therefore, a 3-year survey was carried out at the Dutch Pediatric Surveillance Unit. Pediatricians were asked to register cases of adverse events associated with pediatric CAM usage. In 3 years, 32 unique adverse events were registered. Twenty-two of these adverse events were indirect and not related to the specific CAM therapy but due to delaying, changing, or stopping of regular treatment, a deficient or very restrictive diet or an incorrect diagnosis by a CAM therapist. These events were associated with many different CAM therapies. Nine events were deemed direct adverse events like bodily harm or toxicity and one-third of them occurred in infants. Only supplements, manual therapies, and (Chinese) herbs were involved in these nine events. In one case, there was a risk of a serious adverse event but harm had not yet occurred.

Conclusion: Relatively few cases of adverse events associated with pediatric CAM usage were found, mostly due to delaying or stopping conventional treatment. Nevertheless, parents, pediatricians and CAM providers should be vigilant for both direct and indirect adverse events in children using CAM, especially in infants.

What's Known:

- The use of complementary and alternative medicine (CAM) in children is common.
- Previous surveillance studies in other countries showed severe adverse events may occur after pediatric CAM usage.

What is New:

- In the Netherlands CAM-related adverse events are rare but can occur, with variable etiology and severity (from mild to potentially life-threatening)
- Most CAM-related adverse events are not directly the result of CAM toxicities but rather are associated with withdrawal from appropriate therapies or with providers unable to recognize health-relevant states and delaying important diagnoses.

Keywords CAM · Complementary and alternative medicine · Adverse events · Surveillance study

List of abbreviations

CAM Complementary and alternative medicine
DPSS Dutch Pediatric Surveillance System

Introduction

The term complementary and alternative medicine (CAM) refers to “a broad set of healthcare practices that are not part

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of that country's own tradition or conventional medicine and are not fully integrated into the dominant healthcare system" [1]. Pediatric CAM usage is common in the Netherlands: 4.9% of children under age 12 (± 107.000) and 2.1% of children between ages 12 and 18 (± 26.000) visited an alternative therapist in 2017 [2]. Numbers about the use of "over-the-counter" CAM treatments like supplements or herbs are lacking in the general population, but 12% of children visiting a pediatrician in the Netherlands are using these kinds of CAM treatments [3]. Higher prevalences have been reported in Dutch children with chronic or life-threatening diseases, who experience side effects from conventional medicine, or do not respond to regular treatments [4–6].

Many parents believe that CAM can support regular treatments and is safe to be used together with regular medication [7, 8]. However, the safety of pediatric CAM hasn't been studied extensively and research is often limited to case reports. Nationwide surveillance systems among pediatricians revealed 8 cases of serious adverse events in Canadian children in a 2-year period and 39 cases (including 4 deaths) in Australian children in 3 years [9, 10]. Authors of both studies, however, indicated that they suspected underreporting.

Gathering more data on safety, like information on which CAM modalities are associated with higher risks, is important for obvious reasons of legislation and improving the information given to parents who are considering CAM for their child. The aims of our study were to investigate the type of adverse events associated with CAM in Dutch children visiting a pediatrician and to identify CAM therapies or practices associated with a higher risk of adverse events.

Materials and methods

Population

The Dutch Pediatric Surveillance System (DPSS) is an active online surveillance system that monitors the prevalence of a number of predetermined diseases, disorders, or incidents, by sending monthly emails to around 1300 participating Dutch pediatricians, requesting them to report on events. Between January 2015 and December 2017, a 3-year registration with the DPSS was performed to monitor adverse events related to CAM usage in pediatric patients (age 18 or younger). In 2017, Dutch pediatricians treated more than 500,000 children [11].

Survey and data analysis

As a working definition for CAM, we used a definition that was used in a similar research by Zorzela et al. [9]: CAM is a broad umbrella term for a variety of practices and products that are not considered part of the (Dutch) conventional medicine system, such as chiropractic, massage therapy, and natural health

products. Natural health products like herbs, supplements, vitamins, and minerals can be considered CAM products [12]. If they were used to treat clinically relevant deficiencies or are supplemented with proper indication however, they were not considered CAM.

A previously used Australian questionnaire on adverse events related to pediatric CAM usage was translated into Dutch and adapted to the Dutch situation [10]. The questionnaire included questions on the age of the child, details on the type of CAM that had been used, the health complaint for which treatment was sought, and the adverse event that occurred. The classification of a treatment as CAM was verified by the authors via the case description that was provided by reporting pediatrician. The submitting pediatricians were asked to indicate the likelihood that the adverse event was related to CAM usage (causality), using the following values based on the WHO UMC scale: certain, probable, possible, and unassessable. Thereafter, the three authors reviewed the cases to see if other potential causes of adverse event had been excluded. If there were any doubts regarding the causality, the case description, or the adverse event, the reporting pediatrician was contacted by one of the authors.

The adverse events were categorized as indirect, direct, or potential based on consensus by the three authors of this article considering the information provided in the case descriptions. For these categories, we used a similar definition as the Canadian study by Zorzela et al. [9] but we added a category named "Potential." The definitions of these categories can be found in Table 1.

To describe the severity of an adverse event, a scale based on the Common Terminology Criteria for Adverse Events (CTCAE) was used since it considers the effect of the adverse event on activities of daily living (ADL) which is an important measure in children. The following scale was used: mild, when the patient had hardly any discomfort and was able to continue daily activities; moderate, when the patient had so much discomfort that he or she was not able to continue daily activities; severe, when the adverse event impacted daily activities and required treatment; life-threatening, when the patient could have died; and fatal, when the patient died due to the adverse event.

Results

Reports

During the 36-month study period, a total of 32 unique complete cases were collected. The children involved in the registered cases were between 10 weeks and 16 years old.

Adverse events

In 22 cases, the adverse event was indirect due to delay or cessation of a regular diagnosis or treatment ($n = 16$), a

Table 1 Definition of adverse event categories

Indirect	Delay or cessation of a regular diagnosis/treatment and/or an inappropriate treatment of a medical condition
Direct	Related to the use of the specific health intervention
Potential	Risk of an adverse event but harm had not (yet) manifested

deficient or extremely restrictive diet ($n = 4$), or an incorrect diagnosis by a CAM therapist ($n = 2$). In the 9 cases, the adverse event was directly associated with the specific CAM therapy. One-third of these were infants. In one case, the pediatrician had identified a risk of harm, but an actual adverse event had not (yet) occurred.

Eight cases were deemed to be mild, 12 moderate, 8 severe, 3 life-threatening, and 1 potentially life-threatening. Five children were hospitalized, including one child with a 4-week stay

at the Pediatric Intensive Care Unit. In 18 cases, the pediatricians indicated that the causal relationship between the adverse event and the CAM usage was “certain,” in 3 cases the relation was “probable,” in 9 cases it was “possible,” and in 2 cases the relation was “unassessable.” The details of the cases are shown in Tables 2, 3, and 4.

Therapies involved in adverse events

A wide variety of CAM treatments had been used in the registered cases. The most used therapies were dietary supplements/vitamins ($n = 5$), orthomolecular therapy ($n = 4$), and homeopathy ($n = 4$), followed by naturopathy ($n = 3$). Indirect adverse events were associated with many different CAM modalities (Table 2), whereas direct harm was only seen after use of supplements/vitamins, manual therapies, and (Chinese) herbs (Table 3). In 25% of the cases ($n = 8$), it was a physician that was administering the CAM therapy.

Table 2 Indirect adverse events

CAM specifics	Adverse event description	Diagnosis or indication	Age (years)	Severity	Relation between CAM and adverse event
Bioresonance	Social isolation by withholding child from school and social gatherings	Alleged sensitivity to electromagnetic radiation	15	Severe	Certain
Bioresonance	Asthma exacerbation due to cessation of conventional medication	Food allergies	9	Severe	Certain
Chiropractor: manipulation of the neck	Malnutrition due to delay in conventional diagnosis and treatment. The problem turned out to be the breastfeeding technique	Excessive crying	0	Severe	Certain
Herb therapy: herbs and cessation of medication	Failure to thrive due to cessation of conventional medication	Autoimmune hypothyroidism	8	Severe	Probable
Homeopathy	Insufficient iron reserves with risk of deep anemia by refusing supplementation	Anemia	14	Mild	Unassessable
Homeopathy	Septic shock due to delay in adequate treatment leading to long-term ICU stay due to ruptured appendicitis and multiple organ failure	Appendicitis	14	Life-threatening	Certain
Homeopathy	Unnecessary diet	Abdominal complaints, diagnosed by CAM therapist as t-TGA negative celiac disease	13	Mild	Certain
Homeopathy	Missing of window for proper conventional treatment and persisting of facial palsy due to delay caused by using homeopathic treatment first	Peripheral facial palsy	4	Moderate	Possible
Kinesiology	Urticaria and risk of anaphylaxis during uncontrolled peanut provocation	Severe peanut allergy	6	Mild (potentially life-threatening)	Certain
Naturopathy	Family stress due to incorrect diagnosis and treatment	Psychological problems (ADHD/autism)	13	Moderate	Possible
Naturopathy: Diet restrictions and cessation of medication	Serious exacerbation of ulcerative colitis due to cessation of conventional medication, resulting in colectomy	Ulcerative colitis	14	Life-threatening	Certain

Table 2 (continued)

Orthomolecular therapy	Obesity and related complaints due to stopping of conventional treatment	Fatigue and weight gain, diagnosed by CAM therapist as euthyroid thyroid problem	16	Moderate	Certain
Orthomolecular therapy: diet restrictions	Prolonged lethargy due to inadequate treatment and delay of proper treatment	General malaise and hypothyroidism	14	Moderate	Possible
Orthomolecular therapy: diet restrictions and supplements	Failure to thrive, problems with continence and defecation	Abdominal pains and eating problems	5	Moderate	Certain
Osteopathic medicine	Family stress due to incorrect diagnosis of craniosynostosis	Agitation	0	Mild	Certain
Other, namely Chronic Lyme therapist	False hope, very high costs, painful injections with high doses antibiotics and delay of appropriate therapy	Chronic pain and chronic fatigue, diagnosed by CAM therapist as seronegative Lyme disease	15	Moderate	Certain
Other, namely, chronic lyme therapist	Unnecessary diet and antibiotics, delay of an appropriate therapy	Chronic fatigue diagnosed by CAM therapist as seronegative Lyme disease	15	Moderate	Possible
Other, namely, energy medicine and reintroduction of gluten	Bowel complaints after introduction of gluten	Celiac disease	15	Mild	Certain
Other, namely, Mesology	Family stress due to unachievable diet	Abdominal pains	3	Mild	Unassessable
Therapeutic massage and reintroduction of gluten	Return of celiac disease complaints when therapist advised to reintroduce gluten after healing therapy	Celiac disease	3	Moderate	Certain
Unknown therapy	Delayed introduction of solid foods with risk of eating disorders and food allergies	Alleged reflux	1	Mild	Certain
Unknown therapy: diet restrictions and IV iron	Family stress due to unachievable diet and risk of adverse events from IV iron injections	Painful upper legs and back	14	Mild	Possible

Discussion

To the best of our knowledge, this is the first European study that has investigated adverse events associated with pediatric CAM usage using a nationwide surveillance system. In line with previous surveillance studies in Canada [9] and Australia [10], we found a wide variety of adverse events, ranging from intoxication and transient hypothyroidism to multiple organ failure. In most reported cases, the adverse event was caused indirectly by delaying, stopping, or changing a conventional diagnosis or treatment, a deficient or very restrictive diet or an incorrect diagnosis by a CAM therapist. The reports of these indirect adverse events were associated with a myriad of different therapies. This seems to suggest that indirect adverse events are a potential risk of any given CAM, unrelated to the type of treatment. One possible explanation for the occurrence of these adverse events is insufficient medical knowledge of the involved CAM practitioner to recognize health-relevant states, resulting in unsafe practices and

advices. Several of the CAM practitioners, however, were also a medical doctor, suggesting that lack of medical knowledge is not the only potential factor. Since it is known that important parental reasons for turning to CAM are a preference for a “more natural” therapy and fear of side-effects related to conventional medicine [3, 4], it may also be possible that parents deliberately chose to ignore conventional treatment advice or even decided to visit a CAM practitioner before seeking conventional medical help.

Only a limited number of CAM therapies were involved in direct adverse events. The involved therapies were supplements/vitamins, manipulation of the head and neck, and (Chinese) herbs. We found that one-third of the children involved in these adverse events were infants. It is known that supplements, vitamins, and (Chinese) herbs can cause serious harm, especially in (young) children, whose metabolism and organ function are immature and less tolerant in comparison to adults [13–17]. Our finding that manipulations of the head and the neck were associated with

Table 3 Direct adverse events

CAM specifics	Adverse event description	Diagnosis or indication	Age (years)	Severity	Relation between CAM and adverse event
Herb therapy: Chinese herb ointment	Secondary adrenal insufficiency due to exogenous corticosteroids	Eczema	5	Life-threatening	Certain
Manual therapy: manipulation of the neck	Torticollis with subluxation C1-C2 due to cervical manipulation	Crying and agitation	0	Severe	Possible
Orthomolecular therapy: folic acid supplements	Mild central nervous system depression by intoxication with folic acid	Recovery after chemical and radiation therapy for brain cancer	10	Moderate	Possible
Osteopathic medicine: manipulation of the neck	Transient facial palsy	Intestinal cramps	0	Severe	Certain
Supplements and vitamins: apricot kernel supplements	Abdominal complaints, vomiting, sickness due to intoxication with amygdalin	Prevention of disease	6	Moderate	Possible
Supplements and vitamins: iodine supplements	Congenital hypothyroidism of the newborn due to iodine intoxication of the pregnant mother	Prevention of miscarriage	0	Severe	Certain
Supplements and vitamins: vitamin B1 (90 RDA) and B6 supplements (70 times RDA) from the Internet	Neuropathy and fatigue due to intoxication with vitamin B6	Postoperative recovery in child with spina bifida	16	Moderate	Certain
Supplements and vitamins: vitamin B1 and B6 supplements	Toxic levels of vitamin B6 with the risk of a polyneuropathy	Down syndrome	4	Severe	Probable
Supplements and vitamins: vitamin B6 supplements	Chronic fatigue due to intoxication with vitamin B6	Down syndrome	12	Moderate	Possible

RDA recommended dietary allowance

(severe) adverse effects in young children is in line with previous publications [18, 19]. A meta-analysis of adverse events in 2007 described 14 direct adverse events after spinal manipulation, including subarachnoid hemorrhage or paraplegia [18]. Stricter regulation on the use of supplements, (Chinese) herbs and manipulation therapies, especially in young children, and better training of therapists may be warranted.

Our study, as well as other surveillance studies, demonstrates the necessity of developing reliable information for parents and CAM providers on the safe use of CAM therapies in children. When buying over-the-counter products like supplements, vitamins, or (Chinese) herbs, parents should be encouraged to discuss this use with their pediatrician or pharmacist. Moreover, both parents and CAM therapists should be made aware that, irrespective

Table 4 Potential adverse events

CAM specifics	Adverse event description	Diagnosis or indication	Age (years)	Severity	Relation between CAM and adverse event
Naturopathy: food supplements	Potentially life-threatening situation due to risk of anaphylaxis in an child with a serious food allergy based on a prescribed supplement that the pediatrician was just in time to stop	Alleged deficiencies and “sick” colon	1	Potentially life--threatening	Probable

of the used CAM therapy, they should never delay, stop, or change a regular treatment without consulting a physician. Pediatricians should become aware that using a CAM therapy can lead to stopping or changing of a regular treatment. The identification of this potentially dangerous effect of CAM therapies is often obscured by the scarce communication about CAM between doctors and parents [3, 5, 8]. Therefore, physicians should actively discuss CAM usage on a regular basis.

Since the adverse events were extremely diverse, both in CAM modalities and in type of events, it is not possible to advice against certain CAM therapies. Only in the case of supplements, vitamins, head/neck manipulation, and (Chinese) herbs, we found therapy-specific adverse events. The low frequency of the reported events is, obviously, not enough to ban these practices in children, but increased awareness among CAM users, health professionals (including CAM providers), and health inspectorates regarding the risks of these CAM modalities seems required. Continuing surveillance for adverse events related to CAM use (similar to the surveillance of regular medicine usage), preferably worldwide, is necessary to increase knowledge on the safety of these and other CAM therapies.

We found 32 unique valid cases in 36 months. When adjusted for population size differences, this result is comparable to an earlier Australian study by Lim et al. [10] in which 39 confirmed cases were reported over a similar period of 3 years. As in the Australian study, we suspect underreporting of adverse effects in our study, since 50% of the cases were registered in the last 3 months when we actively created more attention for this study. Moreover, it is reasonable to assume that milder cases of CAM-related adverse events are only seen by the children themselves, their parents, or general practitioners, who are not included in the Dutch pediatric surveillance system. It is therefore impossible to make reliable estimations on the true prevalence of CAM-related adverse events. Another limitation of these types of studies is the fact that associations between CAM use and adverse events cannot

always be made with certainty. We mostly relied on reports from the reporting pediatricians to assess causality, and no formal or structured assessment tool was used.

In conclusion, this nationwide surveillance study shows that, given the high percentage of Dutch children using CAM, relatively few cases of adverse events due to pediatric CAM were found, but there were indications of underreporting. Parents, physicians, and CAM providers should be encouraged to be vigilant for direct and indirect adverse events whenever CAM therapies are used, especially in young infants.

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Data Availability The collected data can be made available in Dutch and after removal of personal information in the submitted cases.

Compliance with ethical standards

Conflict of interest The authors have indicated they have no potential conflicts of interest to disclose. JPR was and BV is employed at the Martini hospital in Groningen but both did not work for the research department that funded this study.

Ethical approval This is a surveillance study. The Research Ethics Committee of the St. Antonius Hospital in Nieuwegein, Netherlands has confirmed that no ethical approval is required.

Consent to participate N/A

Consent for publication N/A

Code availability N/A

Authors' Contributions BV coordinated the data collection, performed the analysis of the results and wrote the draft and final version of the manuscript. JPR and AV conceptualized and initiated the survey, contributed to the analysis of the results, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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