



Original article

# Serious adverse events associated with pediatric complementary and alternative medicine<sup>☆</sup>

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## Abstract

**Introduction:** Complementary and alternative medicine (CAM) use among children is extremely popular. Users consider CAM to be more ‘natural’, more aligned with personal health values, and associated with fewer side effects. However, few pediatric studies have investigated adverse events (AEs) associated with CAM therapies. The objective of this review was to identify serious AEs associated with use of pediatric CAM in partnership with the Canadian Pediatric Surveillance Program.

**Methods:** Active surveillance of a national representative sample of Canadian pediatricians. Participants were asked to report if they had seen any suspected serious AEs associated with CAM in the past month. Harms could be direct (associated with the CAM therapy itself) or indirect (delay in diagnosis or treatment of a serious medical condition). Details of reported AEs were adjudicated by two independent experts to assess causality.

**Results:** During the study period (January 01, 2009 to December 31, 2010), Canadian pediatricians reported 12 unique cases of suspected serious adverse events associated with CAM. Of these, detailed reports were provided in nine cases, of which eight were adjudicated as serious. Six of the eight cases were considered ‘probably’ and two ‘possibly’ caused by CAM interventions. Serious pediatric AEs identified included anaphylaxis, hallucinations, muscle weakness with elevated creatine kinase, hypervitaminosis D with possible chronic nephrocalcinosis as a consequence, and short term paralysis.

**Conclusion:** Few serious AEs were identified in this study, despite widespread use of pediatric CAM. Active surveillance is challenged by under-reporting and can be enhanced by improved communication at each patient encounter.

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## Introduction

As defined by the National Institute of Health, “complementary and alternative medicine (CAM) is a group of diverse medical and health care systems, practices and products that are not presently considered to be part of conventional western medicine”. “Complementary medicine” is used with conventional medicine; for example, use of acupuncture together with anti-inflammatory medications for pain. ‘Alternative medicine’ is used instead of conventional medicine; for example, use of homeopathy to treat allergies [1,2]. CAM use in children is

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<sup>1</sup> Additional data from this study is available upon request (short form reports not adjudicated due to lack of long detailed forms).

extremely popular [2,3,7–18]. Many CAM users consider it more ‘natural’, associated with fewer side effects, and more in alignment with personal values toward health rather than associated discontentment with conventional medicine [2–4]. It has been reported that up to 40% of healthy children and more than half (up to 75%) of children with chronic disorders use CAM [7–18]. Despite frequent use of CAM in association with conventional medicine, up to 77% of parents do not report CAM use to their children’s pediatrician [3–6].

Few pediatric studies have investigated AEs associated with CAM therapies. As a prelude to this study, our team conducted a brief national survey in which 583 Canadian pediatricians reported 42 suspected AEs associated with pediatric CAM use and an additional 488 cases of patients who had suspected delayed diagnosis/treatment associated with CAM use [18]. This survey did not distinguish between serious and non-serious events. Another survey done in pediatric specialty outpatient clinics at two Canadian tertiary centers, identified a total of 80 suspected AEs associated with the use of CAM in pediatrics, two-thirds self-reported as minor (55/80) and six as severe [19].

Despite the frequent pediatric use of CAM, few studies thus far have assessed pediatric CAM-related AEs using a population-based approach. A surveillance program done with Australian pediatricians identified 39 cases of AEs associated with CAM use in children; of those, 64% of events were rated as serious and four fatalities were due to failure to use conventional medicine [20].

The aim of this study was to identify serious AEs associated with the use of pediatric CAM identified through active surveillance of a nationally representative sample in partnership with the Canadian Pediatric Surveillance Program (CPSP).

## Methods

### Population

Pediatric patients (<18 years of age) seen by Canadian pediatricians enrolled in the CPSP program. The CPSP is a surveillance program that collects data monthly from a nationally representative sample of 2500 pediatricians and pediatric subspecialists to monitor rare diseases and conditions in Canadian children. These physicians provide coverage to a population of over seven million Canadian children and youth [21]. The Canadian Pediatric Surveillance program (CPSP) is a joint initiative by the Canadian Pediatric Society and the Public Health Agency of Canada and has been successfully used to reach Canadian pediatricians to report on childhood disorders that are high in disability, morbidity and economic costs to society, despite their low frequency. This program has successfully assessed more than 50 disorders of childhood over the past 18 years. Our study specifically aimed to identify serious adverse events associated with pediatric CAM in Canada during a 2-year period, information that would be otherwise unknown due to its low frequency and poor reporting [21].

Table 1

Case definition and definition of seriousness.

Case definition for serious events associated with pediatric complementary and alternative medicine

Report any patient less than 18 years of age with serious<sup>a</sup> direct or indirect<sup>b</sup> adverse events (AEs) associated with the use of CAM.<sup>c</sup>

<sup>a</sup> Serious AE is defined as one that results in hospitalization, permanent disability, or death. Classification used by National Institutes of Health.

<sup>b</sup> Indirect AE refers to delays in diagnosis/treatment and/or inappropriate provision for a serious medical condition.

<sup>c</sup> CAM is a broad umbrella term for a variety of practices and products that are not considered part of conventional medicine, such as chiropractic, massage therapy, and natural health products. Natural health products include vitamins and minerals, herbs, homeopathic medicines, traditional medicines, probiotics, and other products like amino acids and essential fatty acids.

### Surveillance program

During the study period (January 01, 2009 to December 31, 2010), CPSP pediatricians received a monthly questionnaire asking if they have seen any cases of serious adverse events associated with pediatric CAM use in the past month.

If the physician reported a serious event on the short form, this would prompt CPSP to send a long form to the reporting physician in order to obtain a more detailed description of the case. The long form contained the definition of serious, as it can be seen in Table 1. The adjudication process would assess if the reported event was serious based on the definitions shown in Table 1. The completed forms were collated by CPSP and then forwarded to our study coordinator (LZ).

Each case report was summarized by the study coordinator based on the information provided by the pediatrician in the long form.

The study was approved by the Ethics board of the University of Alberta, through the Human Research Ethics Review Process.

### Adjudication process

After collation of the case report data, the study coordinator sent an identical information package to two independent adjudicators for assessment. Each package included: (i) a case summary; (ii) a copy of the long form; (iii) adjudication tools (specified below); and (iv) the adjudication algorithm.

Adjudicators were selected based on their relevant expertise, i.e. pediatrics, spinal manipulation, and natural health products. Each adjudicator independently provided their assessment scores (one per tool used) to the study coordinator. After independent assessment was completed, all cases were discussed by teleconference with the goal to reach consensus in the final score. If the reporting physician agreed to be contacted, and if additional information was sought by the adjudicators, the study coordinator phoned the reporting physician for clarification.

### Assessment tools

Due to unique differences between the various CAM interventions, we used three tools to assess an event: (i) Naranjo

causality scale; (ii) when appropriate, the Horn causality scale (for interactions); and (iii) WHO assessment criteria. These tools were used to assess the association between intervention(s) and serious event(s), (i) Naranjo causality scale [23] was used to assess a single natural health product/drug adverse reaction.

- (i) Naranjo is considered the ‘gold standard’ for causality assessment. The scale is a set of nine questions to be answered as ‘yes’, ‘no’ or ‘unknown’ with a point added to every ‘yes’ answered. The final assessment is: nine points is a definite adverse drug reaction (ADR); 5–8 points is a probable ADR and 1–4 is a possible ADR.
- (ii) The Horn [24] causality assessment criteria for drug interactions were used when more than one drug or natural health product was used in combination. The AE could be caused by each product in isolation or the interaction between different products.
- (iii) World Health Organization (WHO) [25] assessment criteria for AEs. The WHO Collaborating Centre for International Drug Monitoring has published descriptions of AEs, ranking causality as “certain”; ‘probably/likely’; ‘possible’; ‘unlikely’ and two separate categories for ‘conditional’ or ‘unassessible’ cases.

These tools have been previously used for similar purpose by our study team, the wording has been previously modified to fit CAM interventions [18]. For each intervention, the adjudicators independently rated the association between intervention and adverse event. We asked each adjudicator a concluding question: “Based on the above answers, do you consider this event: (i) improbably; (ii) possibly; (iii) probably or (iv) certainly caused by the intervention. We used words (qualitative method) to describe the likelihood of the event being associated with the intervention as it provides a clear understanding of its association. If only the tools were used with no combined assessment it would not generate a meaningful value of the total assessment.

### Definitions

**AE or Harm.** An unfavorable outcome that occurs during or after the use of a drug or other intervention but is not necessarily caused by it [22].

**Adverse effect.** An adverse event for which the causal relation between the intervention and the event is at least a reasonable possibility [22].

**Direct harm.** Harm directly associated with an intervention (product, device or practice). The causation of the effect is not necessarily present and must be assessed by the adjudication.

**Indirect harm.** The harm is indirectly related to the intervention. The use of intervention causes a delay in diagnostic or treatment and the delay itself carries the potential harm.

**Serious AEs** is defined as any event that: (i) results in death; (ii) is life-threatening; (iii) requires or prolongs hospitalization; (iv) causes persistent disability/incapacity; (v) results in congenital anomalies or birth defects; or (vi) results in any other condition which in the judgment of the adjudicators represents

Table 2

Suspected serious AEs associated with pediatric CAM cases from January 1, 2009 to December 31, 2010.

Year	Reported	Duplicate	Excluded	Pending	Confirmed
2009	8	1	0	1 <sup>a</sup>	6
2010	5	0	1	2 <sup>a</sup>	2
Total	13	1	1	3 <sup>a</sup>	8

<sup>a</sup> Pending detailed questionnaires.

significant hazards. This definition of a serious adverse event has been used by the WHO ([www.whoumc.org](http://www.whoumc.org)).

**CAM** is a broad umbrella term for a variety of practices or products that are not considered part of conventional medicine, such as chiropractic, massage therapy, and natural health products. Natural health products include vitamins and minerals, herbs, homeopathic medicines, traditional medicines, probiotics and other products like amino acids and essential fatty acids.

**Case definition.** Any patient less than 18 years of age with a serious direct or indirect AE associated with the use of CAM.

### Results

During the 2-year study period, 12 unique cases of suspected serious AEs associated with pediatric CAM use were reported by pediatricians across Canada (Table 2). Of these, long forms were not submitted by the reporting physician for three cases and as such, they could not be adjudicated.

Nine cases were adjudicated and of those, eight were considered serious. The ninth case did not fulfill the criteria for seriousness and was therefore excluded. Of the eight adjudicated cases, six cases were considered ‘probably’ caused by the CAM intervention and two as ‘possibly’ caused by the intervention.

Of the adjudicated serious cases, six were from Central Canada and the others were from Western Canada. In six of eight cases, the family initiated the CAM therapy without the advice of a health care professional.

The AEs reported and the adjudication results are summarized in Table 3. The following provides further case description:

- (i) A 4-year-old patient with juvenile idiopathic arthritis (JIA) had a past medical history of topical steroid use for uveitis and steroid joint injection. The child’s physician prescribed ibuprofen and sulfasalazine. The family decided to stop medical treatment and replaced it with ‘desensitizing drops’ and ‘faith healing/pseudo immunotherapy’. CAM use resulted in delay in recommended treatment and progression of the disease, possibly leading to permanent disability.
- (ii) A 13-year-old patient with chronic rhinitis was treated by her family with bee pollen for symptomatic relief. After the first use, she became anaphylactic with sudden airway swelling, rash and swollen eyes. On presentation to the emergency room, her heart rate was 45, she was hypotensive and wheezy. She received steroids and epinephrine, was admitted to hospital, and later discharged home.

Table 3  
Summary of cases, CAM, AEs and adjudication results.

Confirmed suspected case	CAM treatment	Adverse events (AE)	Classification of AE		Adjudication
			Direct	Indirect	
Juvenile idiopathic arthritis	'Healing touch' pseudo-immunotherapy	Progression of juvenile idiopathic arthritis		Treatment delay	Probable
Allergic rhinitis	Bee pollen	Anaphylaxis	Product		Probable
Upper respiratory tract infection	Herbs	Rhabdomyolysis	Product		Possible
Anorexia nervosa	Blood type diet	Weight loss, failure to thrive, requiring tube feeds	Practice	Diagnosis delay Treatment delay	Direct: probable Indirect: probable
Chronic psoriasis	Datura tea	Hallucinations	Product		Probable
Bloody diarrhea	Osteopathy/traditional Chinese medicine	Anemia and progression of Crohn's disease		Diagnosis delay Treatment delay	Probable
Healthy child	Vitamin D supplementation	Vomiting, hypercalcemia, hypertension	Product		Probable
Back pain	Spinal manipulation	Spinal cord ischemia	Practice		Possible

- (iii) An 11-month old patient had recurrent upper respiratory tract infections; the family initiated herbs (HRP-C, pigs ears, *Cotyledon orbicullata*). Three weeks after initiation of these herbs, the patient developed muscle pain, muscle weaknesses and dark urine. Medical assessment was sought; laboratory results showed CPK of 55 000. The patient required hospitalization for 10 days and was later discharged home.
- (iv) A 13-year-old patient used a 'blood type diet' and senosides initiated by a CAM provider due to constipation. She used this diet for approximately 6 months prior to being seen by a physician. She developed severe weight loss and failure to thrive, requiring hospital admission for 6 days and tube feeds for 5 weeks. She was diagnosed with anorexia nervosa.
- (v) A 10-year-old patient with previous diagnosis of psoriasis had one cup of tea made of Datura plant. Shortly after drinking it, the patient had visual and auditory hallucinations and delirium. She received lorazepam in the emergency room to treat hallucinations and was admitted to the hospital for observation. The patient was later discharged home with no other complications.
- (vi) A 12-year-old boy was given traditional Chinese medicine herbs and a combination of wheat soy, protein powder, slippery elm, aloe vera and fish oil, by a family member to treat bloody diarrhea. After 1 year of CAM therapy, the patient was diagnosed with Crohn's disease and admitted to the hospital for 10 days. He received prednisone and a blood transfusion.
- (vii) An 8-month old baby was given up to 4000 IU vitamin D per day by his parents. The patient developed vomiting, irritability, and dehydration. High blood pressure was noted at presentation, along with abnormal laboratory results: parathyroid hormone was below the normal

for age and Vitamin D 2-hydroxy was very high. The patient required hospitalization for 4 days, received hyperhydration, calcitonin and magnesium supplementation. The child was discharged home with possible chronic nephrocalcinosis.

- (viii) A 13-year-old patient was seen by a chiropractor for back pain after a motor vehicle collision. The treatments, which included spinal manipulation, lasted for 1 h three times a week. After one of these treatments, the patient developed muscle weakness and paralysis later that same day. The patient had a spine MRI done which was reported as spinal cord ischemia. He was hospitalized for 6 days and discharged home. His symptoms fully resolved.

One case was excluded as the event was not considered serious after adjudicated by our team. It was a report of a 2-year old with an infected scalp lesion. The parents refused antibiotics, preferring expressed breast milk at the lesion site and then use of Chinese herbs. When these alternative treatments were ineffective, the patient was treated with antibiotics. Although this case represented a case of delay in treatment, it did not fulfill the criteria for seriousness and was therefore excluded.

## Discussion

This study is one of the few population-based studies to identify serious AEs associated with the use of CAM in a pediatric population. Our approach was strengthened by combined use of independent, interdisciplinary expert opinion who adjudicated cases using standardized definitions and validated tools [18].

Clinically relevant harms were sought, whether directly associated with the CAM therapy itself or associated with a delay in diagnosis or treatment of a serious medical condition. Our decision to include indirect harms came from the results of our

preceding national survey, in which respondents identified this as a potential area of major concern [17].

Few serious AEs were reported in our study. During the 24 months of our survey, 12 suspected cases of an adverse event related to CAM use were reported. Sixty-seven percent ( $n = 8$ ) were confirmed as severe, of which 75% ( $n = 6$ ) were adjudicated as probably and 25% ( $n = 2$ ) possibly related to the CAM intervention. Lim [20] had used a similar surveillance method in 2011 and identified 46 reports of harms associated with pediatric CAM over a 36-month period, of which 64% ( $n = 29$ ) were considered severe, life threatening or fatal by the reporters, including four cases of death. They also reported 44% ( $n = 20$ ) of patients had been harmed due to failure to use conventional medicine.

Patient safety is a complex issue that benefits from multiple approaches to ascertain the “truth”. Active surveillance has been found to surpass passive surveillance in terms of both quantity and quality of reports [26,27]. Although, case reports have limitations, including the potential for recall bias, lessons learned from pharmacovigilance confirm the majority of drug recalls originate as case reports [28]. Our study has significant strengths: (i) it is the first nationwide survey done with 2500 Canadian pediatricians who serve more than 7 million children to measure the incidence of serious adverse events associated with CAM; (ii) it reports the number of reported new cases of serious complications associated with CAM over a 2 years period; and (iii) each reported case was adjudicated by experts to assess if the event was serious and the likelihood of the association with the intervention. We benefitted from the best approaches used in patient safety the use of standardized tools in combination with experts’ judgment [29].

Like any survey, ours had limitations, such as potential response bias, non-response bias, recall bias, and attrition bias. In order to provide monthly CPSP reports, our study required pediatricians to be aware of their patient’s CAM use as well as the potential associated AEs. Unfortunately, the medical literature documents the ongoing lack of inquiry by physicians regarding their patients’ CAM use [3–6]. This lack of inquiry is compounded by patient unwillingness to attribute AEs to “natural” therapies [2–5] or to disclose potential CAM-related harms to healthcare professionals [30]. However, while physicians are notorious for lack of participation in surveys; the CPSP does have high response rates, as high as 83%, with an average of around 48% [31]. This does provide some confidence in the level of disclosure reported herein.

The identification of adverse events is also done inconsistently by conventional medicine [32–38]. The majority of FDA warnings are issued based on spontaneous case reports [28]. As an example of adverse event rates associated with a common over-the-counter medication, one may consider adverse events associated with non-steroidal anti-inflammatory drugs (NSAIDs) use in children. During a 4-year period, 19 reports of adverse events were associated with NSAIDs in Australia. The most common of these were rash and gastro-intestinal symptoms, however, one patient died of asthma exacerbation [39]. Pediatric patients are also burdened by the lack of large clinical trials investigating the use of drugs, as well as off-label use of drugs in this population is around 30% [40].

To facilitate disclosure, we distributed a poster for physicians to place in their waiting rooms, encouraging patients to discuss their CAM use with their doctors. Despite our efforts, we feel the AEs associated with pediatric CAM use may be the result of under-reporting in this study. This could be due to the lack of communication between pediatricians and patients about the use of CAM therapies. This is summarized by four of the eight serious events reported being associated with delay in diagnosis or treatment of a serious illness. Open communication develops a trusting relationship that fosters the sharing of relevant clinical information, be it positive or negative. It is also important in patient centered care, contributing to an understanding of patient health-related beliefs, values and preferences [41,42]. In the absence of knowing what therapies parents are choosing and children are taking, the continuity and safety of care are compromised. Encouraging ongoing communication is imperative to effective patient care and active surveillance. An alternative explanation for the relatively few reported cases in our study is that serious AEs are infrequent in children seeking care from CAM providers.

## Conclusion

Few serious AEs associated with the use of CAM therapies were identified in this study. We identified six probable and two possible serious AEs associated with pediatric CAM use based on a survey of a representative sample of 2500 pediatricians. Taken together, the study raises questions of possible under-reporting of cases to pediatricians, a lack of inquiry regarding CAM use on the part of pediatricians, or of the relative infrequency of serious AEs associated with CAM therapies. Active surveillance is a valuable method of reporting AEs but can be challenged by under-reporting. Reporting can be enhanced by encouraging improved communication at each patient encounter.

## Contributions

L.Z. administered the data and drafted the manuscript. H.B., J.Y., A.G. and S.M. adjudicated the cases and drafted the manuscript. S.V. supervised the adjudication and drafted the manuscript. All authors approved the final manuscript.

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## Conflict of interest

None declared.

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