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Setting a research agenda for pediatric complementary and integrative medicine: A consensus approach

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ABSTRACT

Background: Pediatric use of complementary medicine (CM) is common and offers numerous research questions about diverse therapies and conditions. Although research priorities for pediatric CM have been identified, there was a need to update in light of the rapid evolution of the field.

Methods: Building on previous work, we conducted an international, consensus-based 4-step modified Delphi process to develop and refine a pediatric CM research agenda, including on-line questionnaires and an in-person meeting. Participants included health care professionals, researchers, and educators.

Results: We received 376 responses; participants included conventional and CM providers, researchers, educators, administrators, and policy-makers from 15 countries (Australia, Bangladesh, Belgium, Canada, China, Germany, India, Israel, Italy, New Zealand, Norway, Sri Lanka, The Netherlands, United Kingdom, and United States). While it was recognized that each region must set their own priorities based on use, access, and expertise, a "minimum set" for a pediatric CM research agenda was identified.

After three rounds of surveys, participants identified the highest priorities for pediatric CM research as: (i) safety of CM therapies for infants, children, and adolescents; (ii) conditions for which CM use is highly prevalent and for which conventional medicine lacks safe, cost-effective therapies; iii) therapies/therapists to be examined for quality and reproducibility of interventions, comparative and cost effectiveness, dose, etc.; and iv) identification of relevant outcomes and outcome measurement tools.

Conclusions: The results of our study identify that "first do no harm" is the leading research priority for pediatric CM research, followed by more research on effectiveness of CM therapies for conditions not safely and effectively treated with conventional care. In order to improve pediatric health care, interdisciplinary collaborative approaches are needed between CM and conventional providers and researchers.

1. Background

Complementary medicine (CM) describes a group of diverse medical and health care systems, practices, and products that are not generally considered part of conventional medicine.[1] The US National Institute of Health National Center for Complementary and Integrative Health (NCCIH) defines a "complementary" therapy as a non-mainstream practice that is used together with conventional medicine. In contrast, "alternative medicine" is a non-mainstream practice used in place of conventional medicine; NCCIH recognizes that alternative medicine is uncommon, and use of non-mainstream approaches are often pursued concurrently with conventional treatments.[2] What constitutes CM varies by geographically and over time. "Integrative medicine" has been suggested as a more comprehensive term, involving the whole person, and inclusive of both complementary and conventional approaches.[3]

Up to 70% of Canadians and 60% of Americans use some kind of complementary therapy, and over 75% of the U.S. population use dietary supplements while 38% of Canadians use at least one natural health product.[5–8] Within Europe, surveys in the UK, Germany and Italy

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suggest that 10%–70% of the total population use CM each year.[9,10] The use of CM is also prevalent in children, with studies reporting rates of CM use as high as 70% in youth with higher rates noted in children with chronic or life threatening disease.[11–14] Given the popularity of CM use in children, several North American academic hospitals have identified Pediatric Integrative Medicine (PIM) as part of their training programs.[15] The large number of children using CM, combined with the desire to promote evidence-based practice in health care, drove the development of a research agenda on the safety and efficacy of pediatric CM therapies.[16] At that time, the need for solid scientific data on safety and effectiveness of pediatric CM therapies was identified as the most pressing issue. While comprehensive, this research agenda lacked on international collaboration and input.

Conducting a Delphi study to identify priority research areas for pediatric CM is an efficient way to obtain input from a diverse group of relevant stakeholders. A Delphi process maximizes the opportunity for both diversity of opinion as well as to build consensus, through an structured process of obtaining information from a group of experts and consisted of a series of questionnaires, each refined based on the feedback from respondents on a previous version.[17,18]

The purpose of this project was to develop an international consensus-based research agenda for pediatric CM using a Delphi study.

2. Methods

A research agenda for pediatric CM was developed and refined through employment of a 4 phase modified Delphi process. The phases 1, 2 and 4 utilized online questionnaires while phase 3 consisted of a face-to-face meeting.

2.1. Delphi phase 1

Participants from the international CM community, including health care professionals, researchers, and educators were invited to participate by completing an online questionnaire to describe their views about the important gaps in knowledge in pediatric CM that should be addressed by research.

The survey questions were revised by five experts to assure clarity:

After revision, the Delphi Phase 1 consisted of the following questions:

1 What are the important knowledge gaps in pediatric integrative medicine that you face in your work?;
2 What outcomes do you think are important to assess in pediatric integrative medicine?;
3 How should these outcomes be measured?;
4 What is your primary role (select: trainee, researcher, educator, administrator, policy maker, conventional health care provider, CM provider, combined conventional & CM provider, other (describe)?;
5 What is your country of primary residence?

We used an online survey (SurveyMonkey™) distributed through dedicated CM networks: PedCAM (www.pedcam.ca), International Pediatric Integrative Medicine Network, the UK Children’s Complementary Therapy Network, and the American Academy of Pediatrics Section on Integrative Medicine. Two reminders were sent one week apart. The survey was also mailed to over 200 CM organizations in Canada and the United States for distribution to their members (e.g., American Holistic Medical Association, American Association of Integrative Medicine, National Health Practitioners of Canada). Recipients were encouraged to forward the survey to those who would be interested in this field (snowball sampling technique). One of the investigators (AV) also translated a shorter version of the survey to Dutch and sent it to pediatricians and CM providers

Data from the respondents were downloaded from Survey Monkey into Microsoft Excel™ and analyzed for themes by four independent reviewers (SV, SP, AV and KK).

We used a modified Mayring approach to identify the themes: after the reviewers identified themes, we compared and collated the themes, which were then reviewed, and any items of disagreement were discussed until consensus was reached between the four reviewers.[19]

2.2. Delphi phase 2

The results from phase 1 were summarized into selected themes and sent for feedback during the Delphi Phase 2. The phase 2 participants were identified by reviewing the publications listed in the Cochrane CM field, included studies in a systematic review of pediatric CM RCTs by Sampson et al.,[17] citations included in the PedCAM network newsflashes from the previous two years, and recommendations by the investigators (SV, SP, AV, KK) to enhance geographic and methodological diversity.

The Delphi phase 2 consisted of the following questions:

1 What are the important knowledge gaps in pediatric integrative medicine that you would add to the draft framework?
2 What are your feasibility concerns with conducting research in any of these areas (either identified in the draft framework or related to those you added above)? For example, studies of herbal medicine efficacy must take product heterogeneity into account.
3 What outcomes do you think are important to measure? e.g.,quality of life?
4 How should these outcomes be measured? e.g., when measuring quality of life, it is important to consider both the child and parent's perspective

The survey was open for two and a half weeks, with a reminder sent one week before the survey closed. When the survey closed, the data were independently analyzed for themes by the same four reviewers and any items of disagreement were discussed until consensus was reached.

2.3. Delphi phase 3- in person meeting

A total of 19 international CM researchers were invited to participate in a face to face meeting to discuss the emerging priorities and refine wording until consensus was reached. The meeting was held during an International Congress on Complementary Medicine Research meeting to take advantage of international CM research experts gathering for the conference.

The meeting was based on a focus group. The discussion guide were the results of the Phase 2 findings.The meeting allowed for detailed discussion of individual items, existing evidence, and results from the preceding questionnaires. A one page summary document identifying priority areas for pediatric CM research was developed, edited and revised by the meeting participants prior to proceeding with phase 4.

2.4. Delphi phase 4

The one page Pediatric CM research agenda summary developed in phase 3 was circulated online to all individuals, networks, and organizations invited to participate in phases 1, 2 and 3 of the Delphi process.

Ethical approval was provided by the University of Alberta Human Research Ethics Board.

3. Results

The 4 phase Delphi received 376 responses; participants included conventional and CM providers, researchers, educators, administrators, and policy-makers from 15 countries (Australia, Bangladesh, Belgium, Canada, China, Germany, India, Israel, Italy, New Zealand, Norway, Sri

Table 1
Phase 1 Results for Research priorities in Pediatric CM.

1. Therapies	a. Safety b. Effectiveness c. Research designs d. Comparative effectiveness e. Cost / Cost effectiveness
2. Conditions/Diseases (in alphabetical order, not order of priority)	a. Autism b. Attention deficit hyperactivity disorder c. Anxiety d. Asthma e. Chronic disease including functional complaints f. Colds/upper respiratory tract infection g. Otitis media h. Colic i. Depression j. Eczema k. Headache l. Infant feeding problems m. Irritable bowel syndrome n. Obesity o. Pain p. Sleep q. Health promotion/illness prevention r. Vaccination
3.Research Methodology	a. Epidemiological/Health services b. Cost effectiveness/ costs savings c. Regulatory/legal d. Measurement issues e. Standardized outcomes – use validated, published outcome measures and scales f. Whole systems research g. Placebo effect
4. Education	a. About complementary therapies b. Comprehensive approaches to common problems c. How to integrate CM into everyday practice d. Improvement of IM/CM knowledge in conventional pediatrics e. Translate research & experiential knowledge into curricula on comparative safety & effectiveness of different therapies for clinicians f. How to work with other providers in practice or community g. How to identify reputable and high quality therapists and products in local community
5.Knowledge translation/evidence based practice	Keeping up with rapidly expanding body of information: a. Access to information b. Working with media to transmit new & emerging information in the context of existing knowledge c. Standardization of treatment d. Development of clinical practice guidelines
6. Communication	a. Improvement in communication between CM/IM with parents and conventional practitioners b. Counselling parents to provide care for children c. Collaborating with referring clinicians and getting more “buy in” d. How to talk to patients e. How to promote good listening & patient centered care

Lanka, The Netherlands, United Kingdom, and United States).

In phase 1, 143 respondents completed questionnaires, including 29 from the Dutch survey. In phase 2, 19 of 71 invited participants responded. In in phase 3, 8 of 19 invited participants attended the meeting; in phase 4, 197 respondents provided feedback. Response rates for phases 1 and 4 are not known since the surveys were circulated through networks/organizations.

As a result of phase 1, the research priorities were categorized into six domains:

1) Therapies’ safety and effectiveness;
2) Conditions and Diseases;
3) Research methodology;
4) Education;
5) Knowledge translation and evidence based practice and
6) Communication.

As a result of Phase 2 and 3, the identification of meta-issues related to research priorities are detailed in Table 1 and include consideration of: the need for research teams that include conventional and CM researchers, practitioners, policy makers, patients/families, and payers; the unique needs of pediatrics and how this agenda differs from adult CM agendas; and the need for pediatric specific standardized interventions.

The phase 4 research agenda summary document was circulated for feedback. Most respondents strongly agreed that the content was appropriate and offered few modifications. The respondents to phase 4 did not suggest any changes in content, only minor grammatical corrections. There were many positive comments endorsing the final version of the document.

Results from phase 4 (Table 2) were collated and used to draft a final one-page document (Table 3).

Below is a summary of the challenges and opportunities identified during the 4 phases of the Delphi:

Study designs

1 For some interventions, blinding can be hard to accomplish (e.g., hypnosis, relaxation, biofeedback, massage). Single blinding should be pursued, even if double blind is not possible.
2 Crossover trials may not be not appropriate when there is carryover, i.e., continuing effects of previous intervention (e.g., training in relaxation will carry over to next arm); under these circumstances, other approaches are more suitable, e.g., multiple baseline.
3 Heterogeneity of CM practices make research challenging, including: inter-practitioner variability; and heterogeneity of CM products (e.g. Echinacea, probiotics); and lack of manufacturer consistency.

Table 2
Phase 2 and 3 Results: Meta-Issues Regarding Pediatric CM Research Priorities.

Meta-Issue
Need for research teams that include conventional and CM researchers, practitioners, policy makers, patients/families, payers
Consider unique needs of pediatrics. How is this agenda different from adult CM agenda? • Pediatric developmental/emotional stage; biological differences, psychological differences, cognitive ability to report on problems and status • Parents as proxy reporters and providers • Use of CM in children based on parental/grandparental/cultural beliefs rather than own decision/choice thus not necessarily generalizable to other children • Long-term impact, particularly for behavioral changes, biological, social and developmental changes, epigenetics
May have differences in compliance with treatment i.e. refuse based on taste, etc
Need for pediatric specific standardized interventions – well characterized, distinguish between therapist/relationship and therapy; quality, variability, standardized protocols and products between practitioners, e.g., from different countries or traditions
Emerging issues • Many CM-like therapies are becoming mainstream, e.g., probiotics, ginger, peppermint for IBS; acupuncture for pain; massage for premature babies. As this occurs, there is a concern that CM expertise will be “co-opted” by mainstream medicine (lack of respect for CM practitioner expertise) • How will health care reform in US change payment for CM and how will this affect services and outcomes? • How will global climate changes, economics (globalization), media (internet, social networking, access to cell phones, face book, survey monkey, text messages, twitter, e-consults via Skype, etc) affect health care and research? • factors may differ by country making global assumptions, statements, policies, etc impractical: i.e. health disparities, access to technology, insurance coverage, use of CM, treatment preference, etc

Study Outcomes

1 Long-term outcomes (e.g., 1–2 years or longer) are needed, but are challenging to obtain.
2 There is a lack of validated, recognized, well-known outcome measures that consider all aspects of health (e.g., vitality, resiliency), not just physical symptoms.
3 Cost-effectiveness cannot be established until efficacy is proven. Whether or not cost is the dominant factor depends on who is the decision/policymaker.

Research Topics and Funding

1 It is recommended to start with diseases where conventional

Table 3
Final Pediatric CM Research Agenda Summary.

An international consensus-based Delphi process to develop a pediatric CM research agenda

Pediatric use of complementary medicine (CM) is common, and offers numerous research questions about diverse therapies and conditions. Although research priorities for CM have been identified [Deng], they have not specifically focused on pediatric populations. CM research for pediatric populations requires special consideration for at least five reasons: (i) the broad age range represented, which encompasses different stages of growth, development, behavior, physiology, and metabolism; (ii) the vulnerability of children; (iii) proxy reporting and decision-making by parents/caregivers; (iv) the potential for pediatric exposure to have long term effects and (v) unique ethical challenges related to each of the above.

Building on previous work [Kemper], we employed an international consensus-based Delphi process to develop a pediatric CM research agenda. We received 376 responses; participants included conventional and CM providers and researchers as well as educators, administrators, and policy-makers from 15 *countries (Australia, Bangladesh, Belgium, Canada, China, Germany, India, Israel, Italy, New Zealand, Norway, Sri Lanka, The Netherlands, United Kingdom, and United States). After a four phase Delphi, participants identified the highest priorities for pediatric CM research as: (i) safety of CM therapies for infants, children, and adolescents; and (ii) conditions for which CM use is highly prevalent and those for which conventional medicine lacks safe, cost-effective therapies. While it was recognized that each region must set their own priorities based on use, access, and expertise, the following were proposed as a "minimum set" for a* ***pediatric*** *CM research agenda:*

1. Safety. *Assess potential adverse events including "direct" harms such as side-effects and interactions, and "indirect" harms, such as delays in diagnosis or treatment, decreased treatment adherence, or excessive cost.*

2. Conditions. *High priority conditions included (in alphabetical order): atopy (e.g. asthma, allergies, eczema); cancer; digestive health (e.g. colic, constipation, diarrhea, irritible bowel syndrome, inflammatory bowel disease, reflux); infection and (auto) immunity (e.g. upper respiratory tract infection, urinary tract infection, otitis media, diabetes, juvenile idiopathic arthritis); neurodevelopmental and behavioural health (e.g. autism, attention deficit hyperactivity disorder, depression, anxiety, sleep); obesity; pain (e.g. headache, abdominal pain, joint pain); and health promotion and disease prevention.*

3. Therapies/therapists. *There is a clear need for research regarding (i) the quality and reproducibility of interventions (recognizing the heterogeneity of products and practices); (ii) comparative effectiveness and cost effectiveness; and (iii) pediatric dosage (dose, duration, intensity, frequency, acceptability/palatability) and interactions, and (iv) pediatric expertise of providers. Therapies of greatest interest include (in alphabetical order): acupuncture, ayurveda, dietary supplements/natural health products, energy medicine, homeopathy, manual therapies mind-body, nutrition, whole system approaches (e.g. anthroposophic medicine, naturopathy, TCM) and multiple simultaneous interventions.*

4. Outcome measurement *requires valid and reliable tools that consider and measure: (i) multiple perspectives (e.g., child, family, provider, cultural, economic); (ii) multiple dimensions of health (e.g., physical, emotional, psychological, behavioural, social, spiritual); (iii) duration of effect (both short and long term outcomes); (iv) health promotion; (v) safety (adverse events, direct and indirect costs); and (vi) non-invasive age appropriate biomarkers (e.g. heart rate variability, salivary cortisol).*

To improve pediatric health care, multi/transdisciplinary collaborative approaches are needed between CM and conventional providers and researchers. We urgently need resources to translate new and existing pediatric research evidence into policy and practice.

medicine does not offer a cure or has treatment options with significant side effects; evaluating common symptoms rather than conditions.

2 Securing research funding can be challenging, especially for pediatric CM research.
3 It is essential to include clinicians and CM practitioners in research. An interdisciplinary research team increases the chances of success in funding competitions.

4. Discussion

First introduced in 1999,[16] a pediatric research agenda highlighted the need for further research on the effectiveness and safety of pediatric CM. In order to develop an updated research agenda that reflected international-consensus, we conducted a 4 phase Delphi with participants from 15 countries. Participants identified common research goals (safety, conditions, therapies and outcomes measurements), while remaining flexible enough for a more refined agenda to be adapted by different regions and countries to suit their specific needs.

4.1. Safety

Given the widespread use of CM, high quality safety data are needed to support informed and safe use.[20,21] Several pediatric studies have assessed safety of CM interventions through different methodologies. For example, some national pediatric surveillance studies have used a monthly questionnaire to assess the incidence of adverse events related to CM therapies. The first, done by Lim et al.[22] in Australia, identified 39 adverse event reports associated with CM therapies over 36 months; four of them resulted in death. A similar study done by Zorzela et al.[23] in Canada over a 24 month period identified 8 serious adverse events associated with CM; none were fatal, but all led to hospitalization.

Since adverse events are uncommon, large scale observational studies may be needed, such as those carried out in adult populations.[24,25] To our knowledge, population-based observational pediatric research to assess AE is underway for spinal manipulation[26] and to identify AE associated with concurrent use of natural health products and prescription medications.[27]

Adverse events associated with CM may fall into two categories: (i) direct harms associated with the use of the therapy; (ii) indirect harms, associated with potential delay in diagnosis or treatment of a serious medical condition.[28] The work of Lim and Zorzela have identified that serious AEs associated with CM may be caused by a delay in the appropriate use of a conventional therapy. There is a need for greater pediatric training of CM providers to recognize "red flags", i.e. signs and symptoms of serious pediatric illness, so that they may refer children for conventional care when appropriated to do so.

4.2. Conditions/Therapies

Epidemiologic studies of pediatric CM use have confirmed widespread use.[11–14] Conditions treated and therapies used are diverse and heterogeneous, with regional differences that may be due to culture, local availability, and other factors. We invite each region or country to modify or expand on our research agenda so that it suits their particular needs. For example, we are aware of recent efforts where researchers partnered with pediatric CM stakeholders to identify priority research areas and questions to advance the effective use, impact, and requirements of integrative medicine for children, youth, and families in the United States.[29]

CM practices and products can be of special interest in conditions for which conventional therapy is not effective or requires long-term pharmacological therapy. For example, chronic pain can benefit from acupuncture, massage, and music therapy.[30,31] Ulcerative colitis can benefit from probiotics, especially VSL#3, which is supported by the European Society of Gastroenterology as an adjuvant therapy for managing inflammatory bowel disease.[32]

Heterogeneity exists among all CM practices and is exacerbated due to lack of national training standards and accreditation for many CM professions, including the lack of pediatric training for many CM disciplines. This is an area that has to explored and optimized, and represents an opportunity for collaboration among different CM disciplines, as well as with conventional care.

Outcome Measurement

Recent studies suggest that there are problems both in outcome selection and outcome reporting in studies of complementary therapies.[33,34] Work must be done to identify and minimize outcome bias, as is being done for conventional therapies.[35–37] Due the heterogeneity of CM interventions, there is a diverse range of needs for outcome measurement and corresponding need for valid and reliable measurement instruments. A guideline to identify core outcome sets has been drafted and can be used as a starting point for CM researchers.[37]

The previous pediatric research agenda [12] identified priority areas suitable for CM research, including: diseases that impose a heavy burden of suffering to patients for which current mainstream therapies are unacceptable or insufficient, and conditions for which complementary therapies offer a reasonable option or are already in use by patients. The current international consensus-based Pediatric CM research agenda identified safety of CM interventions as the foremost priority for research. Other priorities included identification of most relevant conditions for CM research (as identified in the previous research agenda), as well as methods to improve the quality and reproducibility of interventions in the pediatric population and to assure adequate measurement tools for the outcomes investigated. A major change between the two research agendas is the emergence of methodological considerations as important and relevant to pediatric CM research.

5. Limitations

Surveys have several limitations, including selection bias. Our study reached nearly 200 experts in the field residing in 15 different countries, but we do not know the number of individuals who did not choose to respond. In addition, it is possible, although unlikely, that the same person could have responded the survey more than once, if different emails were used to respond to the Delphi. Reassuringly, responses reached saturation on each phase, such that nothing new was being suggested by additional respondents. By phase 4, we not only achieved a much shorter list of priorities than had been generated at the start, but also received very positive feedback that priorities had been accurately reflected. There was consensus on the final wording from the international community, with agreement on what was said, and how it was said.

6. Next steps

To improve pediatric health care, interdisciplinary collaboration is needed between CM and conventional providers, researchers, and educators. This research agenda represents a beginning, not an ending, and we encourage regions and countries to work with local stakeholders to modify it as appropriate for own needs.

7. Conclusions

The results of our study identify that “first do no harm” is the leading research priority for pediatric CM research, followed by more research on effectiveness of CM therapies for conditions that are not safely and/ or effectively treated with conventional care. In order to improve pediatric health care, interdisciplinary collaboration is needed between CM and conventional providers, researchers and educators.

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