Complementary therapies in paediatric gastroenterology: prevalence, safety and efficacy studies
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Summary and General Discussion

Summary and General Discussion

The aims of this thesis were to study the use of complementary and alternative therapies in pediatrics in general and the efficacy and safety of two therapies in particular (hypnotherapy and probiotics) in pediatric gastroenterology. We, therefore, set out several studies. The first two studies investigated the prevalence of complementary and alternative medicine (CAM) use in children in the Netherlands and are discussed in part 1. Between 2003 and 2005 a large randomized controlled trial, studying the efficacy of hypnotherapy in children with functional abdominal pain and irritable bowel syndrome, was performed. It also investigated the effects of hypnotherapy on visceral sensitivity and psychological profiles of these patients. The results are discussed in part 2. Finally, part 3 describes the results of a randomized controlled trial that was set up to study the safety of two probiotics in infant feeding and its effect on the composition of faecal flora.

In this chapter we will summarize the important findings of the abovementioned studies and explore some of the major points raised by the different parts.

Part I - The Use of Complementary and Alternative medicine (CAM) in Paediatrics

According to the Dutch Centre for Statistics, in year 2004 around 5% of the children under the age of 18 had paid one or more visits to an alternative therapist. At that time nothing was known about the prevalence of CAM use in patients, visiting a paediatrician. We hypothesized that this might be much higher. To test this hypothesis, we gave questionnaires to the parents of more than 600 general paediatric patients of the St. Antonius Hospital Nieuwegein and the University Medical Centre Utrecht. The results, presented in Chapter 1, showed that a considerable amount (30%) of all children who visited a paediatrician had used one or more CAM modalities in the past year and that 18% had visited a CAM therapist. Homeopathy and phytotherapy were the most frequently used CAM modalities. Common reasons for CAM use were a desire for the child to feel better and a preference for a “more natural” therapy. Factors associated with CAM use were a high level of parental education and use of CAM by the parent. Only 40% had reported the use of CAM to the paediatrician. The majority of the parents (60%) found it important to very important that the paediatrician is able to provide information on CAM.

Research on CAM use in pediatric patients with gastrointestinal (GI) diseases has also been limited and was focused mainly on children with inflammatory bowel disease. A second study was conducted, that assessed CAM use in children with different GI diseases (Chapter 2). We hypothesized that children with functional gastrointestinal disorders had a higher use of CAM in comparison to children with organic disorders, because
it is well-known that despite long-lasting conventional therapy, a large proportion of children with functional GI disorders remains symptomatic for years.\(^1\)\(^-\)\(^3\) It was therefore reasonable to assume that parents might become dissatisfied with conventional treatment and would consult practitioners of alternative medicine. The prevalence of CAM use was assessed in 749 children, visiting paediatric gastroenterology clinics of 9 hospitals in the Netherlands. In this study population the frequency of CAM use was 37.6%. A total of 60.6% of this group had used CAM specifically for their gastrointestinal disease. This specific CAM use was indeed higher in patients with functional disorders than in organic disorders (25.3% versus 17.2%). Further analysis, however, showed that this difference was mainly caused by a relatively low use of CAM in patients with celiac disease (7.9%).

Our second objective was to determine which patient and disease characteristics, such as health status or duration of symptoms, were associated with CAM use in this patient group. Adverse effects of allopathic medication, school absenteeism, age \(\leq 11\) years and a low effect of conventional treatment were predictors of specific CAM use. Thirdly we assessed parent’s attitude towards paediatric CAM research and their willingness to participate in future safety and efficacy studies. Almost all parents (93%) considered it important that paediatricians initiate CAM research and 51% of parents were willing to participate in future CAM trials. The high prevalence of CAM use and other results of these two studies raise several points: 1] how safe is CAM use in children; 2] what is the impact on clinical care; and 3] do we need more research on paediatric CAM modalities? All three will be discussed below.

Safety of CAM usage in children.

In an editorial in the “Nederlands Tijdschrift voor Geneeskunde” the question was raised if the fact, that 30% of general paediatric patients use complementary therapies, is reason for concern.\(^4\) This question is not easy to answer. It is known that many CAM users consider CAM therapies “natural” and equate this with safety. They are often unaware of the fact that many of these therapies have the potential to be directly or indirectly harmful. There are several reports of severe adverse events in children, mostly due to contamination, drug interactions or direct toxic effects of herbs and dietary supplements (reviewed by Cuzzolin et al.).\(^5\) The problems of toxicity and drug interactions can be extra relevant in young children and infants whose metabolism and organ function is immature and less tolerant of even subtle changes in comparison to the adult. To date, only scant data on the frequency of adverse effects of CAM therapies in children are available, although in the last years a number of good reviews on this issue has been published. For example, a recent review on safety and efficacy of acupuncture in children found a risk of adverse events of 1.55 in 100 treatments.\(^6\) The authors concluded that acupuncture seems to be a safe CAM modality for paediatric patients, although the risk for an individual patient may be hard to determine because
certain patients, such as immunosuppressed patients or infants, can be predisposed to an increased risk, and because acupuncturists may differ with respect to their qualifications, skills and knowledge. Another recent study determined the frequency of concurrent use of conventional medications and natural health products and their potential interactions in 1800 children. Concurrent use of allopathic drugs and natural products was documented in 20% of patients, with potential interactions in one quarter of them. The authors did not investigate whether these were true interactions resulting in clinical symptoms, but the significant amount of children that used both drugs and natural products stresses the importance of studies, investigating the safety of natural health products. Finally, a meta-analysis on adverse events associated with paediatric spinal manipulation, identified 14 cases of direct adverse events involving neurologic or musculoskeletal events. Incidence rates, however, could not be inferred from these observational data.

It can be concluded that multidisciplinary collaboration of physicians with CAM practitioners is necessary to prospectively quantify risks associated with each individual CAM therapy. Since CAM therapies can also have indirect harmful effects due to missed diagnoses, delaying more effective treatments and discontinuation of prescribed drugs, also large, population-based surveillance studies need to be conducted to investigate the frequency of these harmful indirect consequences.

Impact of paediatric CAM use on clinical care

Despite high prevalences of paediatric CAM use, discussions on CAM between physicians, patients and their parents are not common practice. Although physicians will agree that it is their role to provide patients with information about all potential treatment options, most will not explicitly talk about CAM use, often because they feel uncomfortable by doing so. At the same time only 30 to 40% of the parents using CAM for their child actively disclose this to the medical provider. However, communication between families and physicians regarding CAM use is important for obvious reasons like monitoring safety and efficacy of CAM therapies and understanding better family approaches to health and illness. It is for these reasons that physicians are encouraged to discuss complementary medicine in a non-judgemental manner and to provide balanced advice about therapeutic options.

So, what should a physician discuss with parents who are either already using alternative therapies for their child or seeking information on CAM? One of the first issues to explore is whether the use of CAM diverts the child from necessary conventional treatment and thereby adversely affects the health of the child. Such a situation can raise complex legal and ethical issues with reporting child neglect and/or removing the child from parental custody as a result. Second, the physician must discuss the safety of the selected therapies and identify potential harmful effects. The efficacy of the chosen
CAM modalities must also be evaluated. The balance of evidence on efficacy and safety points to whether the therapy should be recommended, accepted or discouraged and this strategy allows an approach for providing responsible, evidence-based, patient centred care.

However, for most CAM modalities there is a lack of definitive data regarding both efficacy and safety. This may result in parental choices that are far different from those of the physician, complicating communication and shared decision making. It then may be important to realize that scientific evidence is not all that counts for a parent whose child is facing a serious illness. Parents often feel and hope that unproven complementary therapies do not offer magic bullets, but can make an important contribution to their child’s care. In other words: CAM may not cure diseases, it does often help the ill. Parental reliance on an unproven CAM therapy seems therefore reasonable if there is at least some evidence of safety, the therapy does not result in a huge financial burden and the child’s condition can be monitored during the CAM therapy with a willingness of the parents to intervene conventionally if necessary.

With a prevalence of paediatric CAM use in the Netherlands of 30 to 40%, and the possibility of direct or indirect negative effects of complementary treatments, discussion on CAM use in children is important and physicians should expand every patient’s history assessment including questions regarding the use of CAM. The “don’t ask, don’t tell” approach must be abandoned and physicians need to become more knowledgeable with regard to safety and efficacy of CAM therapies in children to feel comfortable in providing effective guidance to parents. To ensure consistent, evidence-based advice on CAM by paediatricians and other physicians, standardized education on CAM therapies should be implemented in medical school, residency training, and continuing medical education programs.16,17

Research on efficacy of CAM treatments

We were surprised by the high percentage of parents (93%) who consider it important that paediatrician’s initiate CAM research and by the fact that 50% of the parents in our study were willing to participate in future CAM studies. So far CAM research in children has been limited, partly because CAM is still considered by many physicians as quackery and ineffective. Although this may hold true for some CAM modalities, this certainly doesn’t apply to all and we think that some forms of CAM (such as acupuncture, hypnotherapy or manual based therapies) are worthy of consideration for further research. The goal of this CAM research should be answering questions of efficacy and underlying mechanisms (does the therapy work and how does it work), effectiveness (does it improve outcomes), safety and risks (do benefit outweigh risks) and cost-effectiveness (is the benefit worthwhile).18
There are, however, some major hurdles to take before initiating paediatric CAM research of good quality. The first is the problem of study design. One of the most used methods in conventional research, the double blind, randomized, placebo controlled trial, is not always ideal for investigating CAM, since many of the alternative therapies are rooted in the concept of individualized care, rather than disease based treatment. Moreover, CAM treatments are often provided as a complicated “whole system” of care. Trials usually investigate only parts of this treatment approach, resulting in limited outcomes. Many CAM therapists hold that CAM treatments cannot be split up into parts that can be investigated separately. They argue that the total effect adds up to more than the sum of parts. Blinding patients to their treatment arm, to remove the placebo-effect, may also be problematic, for example in massage based therapies or body-mind modalities. Furthermore, obtaining trained practitioners with paediatric experience can be a challenge, since most CAM trainings do not offer separate education in the treatment of children. Funding is often another important obstacle. Although governments and private foundations are increasingly funding CAM research, the available budgets are still very small in comparison to budgets for conventional research. To overcome these methodological and financial hurdles, initiatives are being undertaken such as the development of an international paediatric complementary and alternative medicine network and the international society for complementary medicine research. An interesting option that needs to be explored is funding of CAM research by health insurance companies. At present, many companies reimburse CAM therapies, irrespective of effectiveness and safety. It is thus in their interest to have more adequately-sized, well-designed randomized-controlled trials on CAM with the purpose to separate unproven, or unsafe therapies, that will not be reimbursed anymore, from safe and cost-effective modalities.

Part II - Hypnotherapy for children with Functional Abdominal Pain or Irritable Bowel Syndrome

Functional abdominal pain (FAP) and irritable bowel syndrome (IBS) are functional gastrointestinal disorders, both characterized by chronic abdominal pain. In Chapter 3 an overview is given of the available literature on chronic abdominal pain and more specifically on functional abdominal pain and irritable bowel syndrome. Epidemiology, pathophysiology, diagnostic work-up, therapeutic options and prognosis are being discussed.

Since 1984, it is known that gut-directed hypnotherapy is very effective in the treatment of adult patients with irritable bowel syndrome, with the majority of patients showing long-term improvement in symptoms and quality of life. In children with functional abdominal pain or irritable bowel syndrome, however, its effectiveness had not been investigated yet. In Chapter 4 we report the findings of a randomized controlled trial
conducted in 53 paediatric patients, age 8-18 years, with long lasting complaints of FAP or IBS. We compared the effect of gut-directed hypnotherapy (HT) with that of standard medical therapy (SMT), consisting of education, dietary interventions and intervention on stress factors. Gut-directed hypnotherapy appeared to be highly effective in the treatment of children with longstanding FAP or IBS. Pain intensity and pain frequency scores decreased significantly in both groups, but HT was highly superior with a significantly greater reduction in pain scores compared to SMT. At one year follow up, successful treatment was accomplished in 85% of the HT group and 25% of the SMT group. No differences were seen in efficacy of HT between children with FAP and children with IBS.

We then investigated to what extend this treatment success was due to improvement of rectal hypersensitivity (RHS), since visceral hypersensitivity, a heightened sensitivity of the gut for all kinds of stimuli, is thought to play a central role in the pathogenesis of FAP and IBS. We measured rectal sensitivity by performing a rectal barostat before and after treatment (Chapter 5). Rectal sensitivity scores showed a trend towards improvement in both SMT and HT patients, while the number of patients with rectal hypersensitivity decreased from 6/18 to 0/18 in the HT group versus 6/20 to 4/20 in the SMT group (p=0.1). No relation was found between treatment success and rectal pain thresholds. Rectal sensitivity scores at baseline were not correlated to intensity, frequency or duration of abdominal pain. We concluded that clinical success achieved with HT could not be explained by improvement of rectal sensitivity. Further studies are necessary to shed more light on both the role of rectal sensitivity in pediatric FAP and IBS and the mechanisms by which hypnotherapy results in improvement of clinical symptoms.

Two studies in adult IBS patients have shown that gut-directed hypnotherapy not only improves abdominal pain and bowel movements, but also results in reduction of anxiety and depression scores and improvement in psychological well-being. Children with recurrent abdominal pain have an increased incidence of emotional and behavioural problems and especially the association with anxiety and depression is well established. We were, therefore, interested to know if hypnotherapy in children with FAP and IBS would also be accompanied by a change in their psychological profile (Chapter 6). Behaviour and emotional symptoms were assessed by using the Child Behaviour Checklist, and patients’ self-worth by the Self-Perception Profile for Children (SPPC) and Adolescents (SPPA). At baseline, children with FAP or IBS, compared to age and gender related samples, scored above average on the CBCL in terms of internalizing and somatic problems. Adolescent girls had also higher scores for withdrawn behaviour, anxiety and depression, and attention problems. Feelings of self-worth were comparable to healthy controls. After therapy, a significant decline in the somatic complaint score was seen in both HT and SMT patients (2.3 points, p=0.01 and 1.4 points, p=0.01). No significant change of the other CBCL scale scores or self-worth scores after therapy was found in both groups. So clinical success achieved with hypnotherapy in this group
of children with either FAP or IBS was not accompanied by a change in psychological profiles as measured by CBCL, SPPC and SPPA.

Impact of this study on the care for children with FAP and IBS

Our study is the first to demonstrate that gut-directed hypnotherapy is highly effective in the treatment of children with long lasting complaints of either FAP or IBS with 85% of the children in clinical remission at one year follow-up. This high success rate is remarkable since most children were referred by other hospitals after extensive other therapies such as treatment with proton-pump inhibitors, laxatives or psychotherapy without benefit. Our results corroborate earlier data in 3 uncontrolled trials in children, in which self hypnosis or a combination of guided imagery and relaxation, a technique almost identical to hypnosis, were successfully used. The high success rate of our study is also in accordance with reports in adult IBS patients, where response rates to hypnotherapy of 61% to 100% have been reported. Should gut-directed hypnotherapy now become the treatment of choice in children with persisting complaints of either FAP or IBS in whom first line therapies like education and dietary advices have failed? Before this question can be answered, several issues need to be addressed. First, the hypnotherapy was performed by only one therapist in our study. We cannot rule out the possibility that the effect of HT will vary considerably between therapists, depending on factors like experience and rapport. Therefore, this study needs to be replicated with other hypnotherapists. Second, several other options exist for the treatment of children with FAP and IBS and these therapies should be compared with HT in randomized controlled trials. For example, cognitive-behavioural therapy (CBT) has been shown to be an effective therapy with long lasting effects for children with recurrent abdominal pain. For many paediatricians, CBT is the therapy of choice if standard medical care has failed. A disadvantage of CBT, however, is that parents can be reluctant in accepting the existence of psychosocial influences on their child’s symptoms and often refuse to engage with psychological services. This might be different with HT: in our study, gut-directed hypnotherapy was introduced to parents and children as a method of influencing and reducing the pain through the brain and was therefore probably not perceived as a psychological treatment. This may be reflected by the fact that almost all of the invited patients agreed to participate in this study. Anti-depressants are another treatment option for children with long lasting complaints of FAP and IBS, which should also be compared with hypnotherapy, not only with respect to efficacy, but also safety and cost-effectiveness.

Another hurdle to take, before hypnosis can be fully integrated in the treatment of children with FAP and IBS and to have HT become reimbursed by insurance companies, is to change the opinions that physicians have about hypnosis. After all, despite many years
of research, hypnosis still is not seen as a useful tool in medicine, because of lingering myths and misconceptions associated with this method, often caused by popular stage hypnotists. So, education of physicians and medical students on the efficacy of hypnotherapy is a prerequisite for integration of HT in conventional medicine. However, evidence of efficacy in the absence of a plausible explanatory scientific model, can be insufficient to change the opinions of the greater part of the medical community on the use of hypnotherapy. Therefore, the mechanisms by which hypnotherapy produces therapeutic effects also need to be more elucidated.

The mode of action of hypnotherapy

The mode of action by which hypnotherapy results in reduction of abdominal symptoms in patients with FAP and IBS is not completely clear. Some evidence exists that gut-directed hypnotherapy impacts IBS through a combination of effects on gastrointestinal motility, visceral sensitivity, psychological factors and/or effects within the central nervous system. Whorwell et al. demonstrated that induction of hypnosis can lead to a profound reduction in fasting colonic motility, but it is unknown whether this effect on motility persists when the patient is no longer in the hypnotic state.51 Also the effect of hypnosis on visceral sensitivity is not very clear. Two studies demonstrated a clear reduction in rectal sensitivity after hypnosis,52,53 whereas two other studies in adults failed to find such an effect.27,54 Also in our study resolution of abdominal pain after HT was not accompanied by a change in rectal sensitivity. It has been suggested that improvement of rectal hypersensitivity and hyposensitivity, found in the first two studies, was not due to hypnotherapy, but simply represented a regression to the mean; i.e. high values tend to decrease and low values to increase on repeated testing.52 This could also explain the trend towards improvement in pain thresholds we found after therapy in both HT and SMT patients, irrespective of their clinical response to therapy.

Two studies in adults have shown that an improvement in IBS symptoms after hypnotherapy parallels improvement in psychological symptoms, but whether this is a cause or a consequence of the treatment remains to be elucidated.27,28 We did not find any significant change in emotional and behavioural profile despite a strong decrease in abdominal pain. This suggests that hypnotherapy does not impact FAP and IBS in children through an effect on psychological factors, although we cannot exclude the possibility that our results would have been different using other psychological test instruments. For example, it has been suggested that hypnosis may improve IBS symptoms primarily by altering the patients focus of attention and/ or by changing his/her beliefs about the meaning of sensations from the gastrointestinal tract.27 To investigate whether this is also true in children with FAP or IBS, a similar study should be done, including instruments to evaluate patients predisposition to notice and report
physical symptoms (like the Children’s Somatisation Inventory) and questionnaires to investigate cognitions.

Another possible mode of action of hypnotherapy can be found in the brain, as it has been suggested that FAP and IBS are caused by an altered central modulation of visceral stimuli. Pain coming from the gut is thought to have two dimensions: a sensory-discriminative component and an affective-motivational component. The discriminative component of gastrointestinal pain encodes location, intensity and nature of pain and follows a route from the gut to the insula, an infolding of the temporal lobe. The affective-motivational component is thought to encode pain affect and suffering, and runs to the limbic system, particularly the part called the anterior cingulated cortex (ACC). The ACC is a critical centre involved in the “unpleasantness” of the pain and brain imaging techniques have shown that the ACC plays a key role in hypnotic pain modulation. In a study by Rainville et al. hypnotic suggestions were used to alter selectively the unpleasantness of noxious stimuli, without changing the perceived intensity. Positron emission tomography revealed significant changes in pain-evoked activity within the anterior cingulated cortex, consistent with the encoding of perceived unpleasantness, whereas primary somato-sensory cortex activation was unaltered. These are interesting findings since the ACC is one of the brain regions where IBS patients have been found to differ from healthy controls. However, so far no studies have been published evaluating the changes in ACC function after hypnotherapy in adult IBS patients or in children with FAP and IBS.

Future studies on the efficacy of hypnotherapy in children with gastrointestinal disorders

Other research on the use of hypnosis in children with GI disorders is scarce and often of poor quality. In adult gastroenterology, several studies have been performed that may have implications for future hypnosis studies in children. First, Mawdsley et al. performed a study in 17 adult patients with active ulcerative colitis. One session of gut-focused hypnotherapy resulted in a reduction of several components of the systemic and mucosal inflammatory response toward levels found previously in the inactive disease. The authors concluded that these effects provide a rationale for controlled trials of hypnotherapy in ulcerative colitis. At the same time, Miller and Whorwell published an article in which they describe the use of gut-focused hypnotherapy in 15 patients with severe inflammatory bowel disease on corticosteroids but not responding to medication. Twelve sessions of therapy resulted in a dramatic decline of corticosteroid requirements and quality of life became good or excellent in 80% of the patients. These two studies show that hypnotherapy appears to be a promising adjunctive treatment for inflammatory bowel disease and may have steroid sparing effects. Controlled trials to
define its role in the treatment of inflammatory bowel disease are justified, not only in adults but certainly also in children.

Functional dyspepsia is another interesting disorder in which the role of hypnotherapy should be investigated. It is fairly common in children and patients with persistent complaints often have co-morbidities such as depression and anxiety. Despite increased understanding on its pathophysiology, no specific therapy has emerged in recent years. Adolescents with functional dyspepsia often demonstrate delayed gastric emptying. Chiarioni et al. have shown that gut-oriented hypnosis can shorten gastric emptying in adult dyspeptic patients. Furthermore, a randomized controlled trial among 126 patients with functional dyspepsia demonstrated that HT is highly effective in the long-term management of these patients, resulting in a dramatic reduction in medication use and consultation rate. It is reasonable to assume that HT can also be effective in the treatment of children and adolescents with functional dyspepsia, but trials are needed to confirm this.

A third example of an area in the field of paediatric gastroenterology, where hypnosis studies might be of interest, is functional constipation and faecal incontinence. Follow-up studies have shown that more than 5 years after the initial presentation, 30 to 50% of the children with functional constipation continue to have severe complaints despite intensive treatment with laxatives. Treatment options for this group of patients with persistent constipation are limited: both biofeedback and cognitive behavioural therapy have shown disappointing results. Hypnosis influences colonic motility and can improve stool habits in adults with IBS. It might thus be worthwhile to perform an RCT examining the effectiveness of HT in children with persistent severe constipation. So far only one report has described self-hypnosis as an adjunct in the treatment of children with severe constipation, but no trials have been performed to date.

In conclusion, in light of the clinical trials in adult population, it seems reasonable to investigate the efficacy of hypnotherapy in several other paediatric gastrointestinal disorders. Hopefully, enough funding can be obtained for these studies.

**Part III - Probiotics in Infant Formula**

The addition of probiotics to infant formula has been shown to be an efficient way to increase the number of beneficial bacteria in the intestine in order to promote a gut flora resembling that of breastfed infants. According to the ESPGHAN Committee on Nutrition, a thorough safety evaluation must be performed, before infant formulas with added bacteria become marketed. We evaluated the safety and tolerance of the addition of two probiotic strains (L. paracasei ssp. paracasei and B. animalis ssp. Lactis) to infant feeding (Chapter 7). A total of 126 newborns were randomized to receive a starters formula supplemented with probiotics or a probiotic-free formula for the first three months of life. Eighty infants continued the study until they were 6 months old.
Growth measurements were taken monthly at healthy baby clinics. Diaries were used to monitor behaviour, infections, use of antibiotics, as well as stool characteristics. Normal growth occurred in all infants and no statistically significant differences were detected between the probiotics group and the control group for gain in weight, length and head circumference. Infants in the probiotics group produced softer and more frequent stools during the first three months of life. No differences were found in crying and sleeping hours, number of parent-diagnosed infections, antibiotic use, visits to the general practitioner and number of adverse events. We concluded that the use of a starter formula supplemented with *L. paracasei* ssp. *paracasei* and *B. animalis* ssp. *lactis* in early infancy is safe, well tolerated and has no adverse effects on growth and infant behaviour.

We also investigated the effect of adding these two probiotic strains on the composition of the faecal flora. This was done by analysing the faeces of all infants of the above-mentioned study at the age of 1, 3 and 6 months. (Chapter 8). The presence of *Bifidobacterium animalis* and *Lactobacillus paracasei* could clearly been shown in faecal samples of treated infants without causing any further changes in microbiota composition in comparison to the control group.

Do we need to add probiotics to infant feeding?

The newborn is first colonized by microbes at birth. The development of his or her microbiota depends on different factors like genetics, mode of delivery, and type of feeding. Breastfeeding results in a microbiota, containing mainly Bifidobacteria and Lactobacilli, while the microbiota of formula-fed babies is more diverse, also containing substantial quantities of Bacteroides, Enterobacteria and Clostridia species. It has been suggested that the observed differences in microbiota contribute to the lower incidence of infections, allergies and GI disturbances in breastfed infants compared to formula-fed infants. Therefore, in the last decade many attempts have been made to modulate the microbiota of the formula-fed infant by providing the infant with probiotics. These studies, including ours, have shown that the addition of probiotics is generally safe, well-tolerated and has no effects on growth and behaviour. One could easily jump to the conclusion that in the near future, probiotics should be added to infant formula. However, a few questions need to be answered before this recommendation can be made. First, most of the above mentioned studies have only evaluated the short-term safety of probiotic administration, often up to 6 or 12 months. The long-term safety needs to be examined as well and currently, little is known about the long-term effects of probiotics on the developing immune system and metabolic functions. Second, different probiotic strains may have different metabolic activities, so trials are needed to investigate which of the currently used probiotics are best for this purpose and in
what dose. Related to this question, the need of combining probiotics with prebiotics (non-digestible food ingredients) must also be examined in more detail.

Finally, and perhaps most importantly, what is the evidence that addition of probiotics indeed results in a decrease of infections, allergic manifestations and GI disturbances in formula-fed infants? Limited evidence exists that several probiotic strains can result in a lower number of infections and a reduced prescription of antibiotics in the first year of life, but more studies are necessary to confirm these observations. A few studies have shown some benefit in the prevention of atopic eczema, but other studies have failed to support this (reviewed by Prescott and Bjorksten). One of these studies showed that supplementation with Lactobacillus GG during pregnancy and early infancy did not alter the incidence nor severity of atopic dermatitis, but was associated with an increased rate of recurrent episodes of wheezing bronchitis, suggesting that probiotics may have negative health effects. In conclusion, awaiting further trials on long-term safety, dose-response effects and clinical efficacy, there is at present not enough evidence to recommend the addition of probiotics to formula feedings for healthy infants.

The use of probiotics in children with constipation.
Supplementation with L. paracasei ssp. paracasei and B. animalis ssp. lactis was in our study associated with an increase in defecation frequency and softer stools. Several other studies in infants have documented similar effects of probiotics or synbiotics (i.e. the combination of prebiotics and probiotics) on stool frequency and/or consistency. Furthermore, advantageous effects of probiotics on stool consistency and frequency have been reported in constipated children. Constipation is a frequent symptom in bottle-fed infants with prevalences of up to 17%. It would be interesting to explore the significance of our findings in a larger study in infants, adequately powered to examine possible differences in the incidence of constipation. Such a study may also help to answer the question whether the presence of prebiotics are a prerequisite to induce the effect of probiotics on stool consistency and frequency, as seen in our study. Another possibility is to address the effects of the combination of these two probiotic strains in infants who already have developed constipation. The difference in stool characteristics between the two study groups disappeared in the second trimester. We hypothesize that this was due to the fact that the infants started with solid foods in the 4th month, thereby influencing the gut flora significantly. Additional studies, comparing the microbiota of healthy versus constipated infants, may help to unravel the still unknown mechanisms by which probiotica can influence defecation patterns. It has been shown that probiotics can accelerate colonic transit time in healthy adults and increase faecal moisture, but more research is needed to shed light on these mechanisms.
Future of probiotics in paediatric gastroenterology

Laboratory evidence and clinical studies have demonstrated the importance of probiotics in mediating intestinal functions by maintaining intestinal integrity, reducing the ability of pathogenic bacteria to adhere to the intestinal mucosa, and modulating the intestinal immune function. Therefore, probiotics are seen as attractive tools in managing several paediatric gastrointestinal disorders. For example, there are clear benefits described in acute infectious diarrhoea, antibiotic-associated diarrhoea, functional abdominal pain disorders, infantile colic, and necrotizing enterocolitis in preterm infants. More studies are, however, needed to gather information on dose-response effects, the use of “mixes” versus single-strain probiotic agents, and appropriate administrative regimes. For other conditions, there is currently insufficient evidence to already recommend the use of probiotics, such as prevention and treatment of food hypersensitivity or the treatment of Crohn’s disease. The lack of strong scientific evidence and the many questions that still need to be answered are in contrast to daily life. Probiotics are intensively marketed by the industry and consequently widely used by both adults and children. The available probiotic products are highly heterogeneous with differences in composition, biological activity, and dose. Is this all reason for concern? The safety of probiotics has been described in a number of reviews which, despite the relative short durations and limited set-up of many studies, in general conclude that consumption of probiotics results in a neglectable risk to the consumer. However, there are still some concerns regarding the risk of infections and adverse metabolic effects. The recent large study with probiotics in patients with acute pancreatitis, where the study group had a significant higher mortality than the placebo group, demonstrates that the use of probiotics is not completely without risks and stresses the importance of regulating the use of probiotics, especially by vulnerable patient groups.

Probiotics, a CAM therapy?

Probiotic agents were already prescribed in the eighties by homeopaths, naturopaths and orthomolecular medicine therapists, who recognized the importance of a healthy intestinal microbiota and its influence on general well being. For decades, probiotics were regarded as a CAM therapy and publications on probiotics were indexed in Medline under the subset of complementary medicine. As such, our safety study on probiotics was included in this thesis on complementary therapies. In recent years however, probiotics have become increasingly prominent in mainstream gastrointestinal research, with almost 900 articles indexed in PubMed last year. Knowledge on the interaction mechanisms of probiotics with the human host is rapidly increasing. It is thus an example of a therapy that should no longer considered to be part of CAM anymore, but is becoming integrated in conventional medicine.
Concluding remarks on CAM in paediatrics

The high use of complementary and alternative therapies by Dutch paediatric patients is undeniable and it is very unlikely that this positive attitude of parents towards CAM will be reversed in the immediate future, nor that more conservative physicians, such as members of the Dutch society against quackery, will be able to prevent this trend continuing. Health insurance companies in the Netherlands increasingly acknowledge the significance of CAM and reimburse CAM therapies, often due to a strong demand by the public. Furthermore, a growing number of paediatricians is interested in integrating elements of CAM into their conventional practice. Although this tolerance towards CAM is welcomed, some healthy scepticism remains necessary. Several CAM therapies that have been subjected to the same scrutiny that conventional therapies are, have been shown to be ineffective. Additionally, although the number is small, serious adverse effects have occurred in children. Therefore, all CAM therapies should be subjected to rigorous evaluation of its effectiveness and safety, especially in a vulnerable group like young children. Only this way, we can head towards integration of evidence-based CAM modalities into paediatric practice. Until then, one should try to recognize both possibilities and limitations of CAM therapies and separate chaff from wheat.
Reference List


Lewith GT. Funding for CAM. BMJ 2007 November 10;335(7627):951.


Summary and General Discussion


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(77) Chouraqui JP, Grathwohl D, Labaune JM, Hascoet JM, de M, I, Leclaire M et al. Assessment of the safety, tolerance, and protective effect against diarrhea of infant formulas containing mixtures of probiotics or probiotics and prebiotics in a randomized controlled trial. Am J Clin Nutr 2008 May;87(5):1365-73.


