### Manual therapy and probiotic supplementation for infant colic: an evidence-based clinical evaluation

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#### ABSTRACT

**Aim:** To determine whether research evidence supports probiotic supplementation together with spinal manipulative therapy as a viable combination to significantly decrease infant colic. **Method:** Review and report findings of scientific papers that support the effectiveness of treatments with probiotics and spinal manipulative therapy for infant colic. **Result:** Considerable research suggests that probiotic supplementation could improve metabolites such as short chain fatty acids that have been shown helpful in regulation of a stress response. Both probiotics and manual therapy appear to improve functionality of the vagus nerve and parasympathetic nervous system to balance the autonomic nervous system, which could result in reduction in crying time for infants. Each treatment, individually has shown some benefits for infant colic in randomized controlled trials. Both remedies are considered safe. **Conclusion:** Research suggests there may be sufficient background to justify randomized trials utilizing a combination of probiotic supplementation and manual therapy for the treatment of infant colic. Since both treatments are considered safe and benefits have been shown, it may be appropriate for individual clinicians, faced with a colicky infant, to suggest to the parents a short clinical trial combining these two therapies.

Key Words: infant colic, probiotics, manual therapy, autonomic nervous system.

### Introduction: Infant colic: Why is finding an answer important?

While infant colic (aka excessive crying of infancy) occurs in about 20% of all infants,<sup>1</sup> inconsolable and persistent crying is often insufficiently treated. One reason for this might be that the etiology of infant colic remains unknown as scientific proof of cause has not been recognized so far. Additionally challenging is that the infant cannot be asked what and where it hurts, nor are established criteria available. Hence, the diagnosis is determined by the clinician through exclusion of other disorders.

According to the Mayo Clinic Website:<sup>2</sup>

"The baby's care provider does a complete physical exam to identify any possible other causes for the baby's distress. The exam includes: Measuring the baby's height, weight and head circumference. Listening to the heart, lungs and abdominal sounds. Examining the limbs, fingers, toes, eyes, ears and genitals. Assessing reaction to touch or movement. And looking for signs of rash, inflammation, or other signs of infection or allergies." If all this examination results in no findings and the infant is thriving, the diagnosis of infant colic can be made.

Although the etiology of infant colic is unclear, its' impact on the families is not. These consequences of infant colic, particularly on the child, have been slow to attract research. One study found by looking at the duration of infant colic, that although it has been widely characterized as limited to the first 12 weeks of life, there is significant evidence that this is not the case, for at least 50-60% of children.<sup>3,4</sup> Not only did these children cry for more than three months, they also showed emotional problems up to eight years of age.<sup>4</sup> Each developmental phase places new demands on the infant's capacity to self-regulate.

This capacity depends on the structural and functional maturity of the brain and nervous system as well as the accumulated experiences, which have already been integrated.<sup>5</sup> Social capabilities like persistent eye contact, social smiling, and melodious cooing starts at ages two and three months of age.<sup>6</sup> This preverbal communication provides a framework for practicing reciprocal regulation of attention, positive affective arousal, and self-efficacy.<sup>5</sup>

In a Norwegian study it was found that infants, who had infant colic were significantly less developed at five years of age and internalized problems more at three and five years old than the previously non-colicky children.<sup>7</sup> They concluded that infant colic should be taken into account as a risk factor for development and behavioral problems within the first five years of a child's life.<sup>7</sup>

How does excessive crying of the newborn impact parents? Infant colic affects between 17 and 25% of newborns during the first months of life, with a reported peak of excessive crying somewhere between three and six weeks of age.<sup>8,9</sup> The provisional number of births in the United States in 2020 was 3,605,201,<sup>10</sup> which would mean that between 612,884

and 901,300 baby's families were dealing with a colic infant in the US alone. These families were most likely in distress, often not only because the excessively crying child could not be consoled, but also had other issues. For example, in many cases, the colicky infant is having problems in sleep-wake organization as well.<sup>5,7</sup> And this may keep parents awake during sleep hours. Hence, they then must cope with increasing sleep deprivation, while trying to function in everyday life tasks. This can cause parents to be overwhelmed and in psychosocial distress. Furthermore, this could be followed by frequent interactional failure with the child which consequently maintains or exacerbates behavioral problems,<sup>11</sup> and therefore increases infant crying.

Frequent emotional effects of inconsolable crying on parents causes the exhibition of signs of chronic exhaustion and overload, due to persistent alarm and sleep deficit. Repeated daily experience of infant inconsolability induces feelings of failure, diminished self-esteem, powerlessness, and depression.<sup>5</sup> Almost all affected parents confess that feelings of helplessness in the face of increasing arousal and alarm occasionally turn into a state of aggressive feelings and powerless rage toward the infant. These impulses may in turn evoke intense feelings of guilt and make the parents increasingly vulnerable. The intensity of aroused feelings may finally become fertile ground for the revival of latent conflicts with the partner or other family members, or over the mother's abandoned professional career.<sup>5</sup>

Moreover, excessive crying is significantly associated with shaking and smothering the child.<sup>12</sup> Shaken baby syndrome or abusive head trauma is the leading cause of death due to child abuse.<sup>13</sup> The mortality rate from shaken baby syndrome has been reported as 20-25%.<sup>14,15</sup> Further, even in the non-fatal cases, the shaken baby syndrome has a very poor outcome and major long-standing negative consequences are frequent.<sup>16</sup> In its minimal form, shaken baby syndrome consists of subdural hematoma. In 75 to 90% of cases, the subdural hematoma is associated with uni- or bilateral retinal hemorrhage.<sup>14,17,18</sup> Therefore, if the shaking does not lead to death, it often leads to permanent handicap.<sup>19</sup>

Remedies or methods for treating infant colic are therefore urgently needed because it puts newborn babies and their care takers at risk for a tremendous amount of distress. Additionally, infant colic may inhibit the newborn from feeling comfortable in this world and developing a feeling of deep trust. Family bonds are disrupted when the infant is most vulnerable and needs it desperately.<sup>20</sup> Furthermore, the child is at risk for parental abuse, which could lead to permanent damage or even death.<sup>14,17-19</sup> Disadvantages do not stop there; other outcomes might be developmental and behavioral problems within the first five years of a child's life.<sup>47</sup>

"Stress diathesis" models suggest that adversity in early life alters the development of neural and endocrine systems in a manner that an individual becomes predisposed to disease in adulthood.<sup>21</sup> In an animal study, mother-infant interactions in the first few days of life were categorized into high and low intensity contacts. When the pups entered adulthood the researchers looked at developmental, behavioral and endocrine responses to stress and found that the pups that had more motherly contact when newly born were significantly less fearful under conditions of novelty than the ones that had fewer interactions.<sup>22</sup> That study (though done on animals, not humans) suggests that the quality of interactions by the caregiver toward the offspring can "program" behavioral and neuroendocrine responses to stress in adulthood or vulnerability/resistance to stress-induced illness over the lifespan.<sup>22</sup>

In the case of a colicky infant, interactions between the caregiver and the child are disrupted. A child cannot focus on or enjoy a caregiver's attention when distressed to the point of excessive crying. Playfull and cuddly interactions can only happen in a state of calm. In a study where feeding problems in infants with colic were assessed, it was found that the colicky infants did not only have more feeding problems but also were less responsive towards their mothers during feeding interactions than infants in the non-colic group. Regarding parent functioning, mothers in the colic group reported higher levels of stress as compared to mothers in the comparison group.<sup>23</sup> An overwhelmed as well as psychosocially distressed caregiver most likely cannot give as much care and affection as they would like, despite their love for their child. A healthy connection is disrupted and might even be perceived by the child as rejection. Ultimately this results in more stress as well as negative psychological as well as physiological responses years later.<sup>7,22</sup>

### What treatments show promise and why?

In a systematic review<sup>24</sup> it was shown that the strongest evidence for the treatment of infant colic were probiotics, particularly Lactobacillus reuteri (L. reuteri). Unfortunately, this was the case for breastfed infants only.<sup>25</sup> However, in another scientific investigation it was found that Bifidobacterium breve (B. breve) showed efficacy in both breastfed and formula fed infants.<sup>26</sup> The second strongest evidence for an effective treatment of infant colic was manual therapy.<sup>24</sup> Probiotic supplementation and manual therapy both carry a very low risk of serious adverse events but have not shown consistent effectiveness in a sufficient number of trials to be widely adopted.<sup>24</sup>

These two most effective treatment options lead to the question: "Would efficacy increase if the two treatments were combined?" To answer this question, it is key to search for evidence for the underlying mechanisms of each

treatment. What could be the link between these different treatment approaches, and can they support or even augment each other and therefore lead to a scientifically effective treatment? It has been suggested that one cause for the infant to cry in excess might be a dysfunctional nervous system in particular the autonomic nervous system (ANS) with the vagus nerve being one of the main actors.<sup>27</sup> This would mean that in order to improve infant colic, regulation of the function of the ANS would be the primary therapeutic focus. Other researchers have suggested that an unbalanced gastrointestinal microbiome, increased intestinal permeability, and chronic inflammation are involved.1 Compiling all these findings and investigating how these factors interconnect might answer the question as to why probiotic supplementation and manual therapy could be more effective together.

## ANS interaction in the excessively crying infant: What is the connection?

The ANS, consisting of the sympathetic and parasympathetic nervous systems, controls and regulates functions of various organs like the gut, glands, and involuntary muscles throughout the body (e.g., vocalization, swallowing, heart rate, respiration, gastric secretion and intestinal motility).<sup>27,28</sup> A respected source states that one of the most important roles of the parasympathetic nervous system is to oppose the activity of the sympathetic nervous system in order to keep balance between them.<sup>27</sup> The parasympathetic connection between inner organs like the gut and the brain (gut-brain-axis) is formed by the vagus nerve as the main contributor. This leads to the vagus nerve being an important functional as well as rapid connection between the CNS and the enteric nervous system (ENS) of the gut.<sup>27,28</sup> The ENS consists of a nerve plexus embedded in the intestinal wall, which extends across the whole gastrointestinal tract from the esophagus to the anus. The estimated number of neurons is between 100-500 million and constitutes the largest single nerve cell collection in the human body. It is also called "the second brain" because of its similarities in structure, function, and chemical determinants with the brain.<sup>27</sup> The ENS afferent fibers in the abdominal vagus trunk outnumber efferent fibers by about 10 to 1.<sup>29</sup> Therefore, the vagus nerve can be considered more a sensory than a motor nerve, which conveys a vast amount of sensory information to the brainstem.<sup>29</sup>

The framework of the ENS is laid during the first gestational trimester, but the network continues to undergo modifications throughout the prenatal period and into postnatal life<sup>30</sup> and its cells arise from the same cells as the vagus nerve.<sup>27</sup> Colonization of the gastrointestinal tract by trillions of microorganisms during the early postnatal period represents a significant change from the prenatal condition that undoubtedly affects the developing ENS and consequently the vagus nerve. It has been suggested

that the early microbiome supports the development of the ENS and therefore probiotics could have further potential in clinical implications.<sup>30</sup>

It is the anatomy of the vagus nerve that ties different etiologies and symptomatology together and might explain why supporting gut health and vertebral joint function could lead to a viable treatment combination. The vagus nerve originates in the brain, in the medulla oblongata of the brainstem. Parasympathetic efferent nerve fibers primarily go to the gastrointestinal tract, heart and lungs, but also to the muscles of the soft palate, pharynx and larynx. Primary afferent fibers come from visceral organs, including taste from the tongue as well as pain, temperature and deep touch of the outer ear, the dura of the posterior cranial fossa and the mucosa of the larynx.<sup>31</sup> From the brain the vagus nerve exits the skull laterally through the jugular foramens together with the accessory nerve (CN XI). The vagus nerve then passes distally in very close proximity to the transverse processes of the Atlas (C1) and Axis (C2) between the carotid artery and the internal jugular vein, within the carotid sheath - directly behind the sternocleidomastoid muscle and just anterior to the scalenes.<sup>32</sup> At the base of the neck, the nerve enters the thorax and the right and left vagus nerve diverge after this point. The left travels into the esophagus and the right to the right bronchus.<sup>31</sup> Both left and right vagus nerves subsequently enter the abdomen through the diaphragm and branches are sent to the esophagus, the stomach and primarily to the intestinal tract — up to the splenic flexure of the large colon, forming the ENS.31

A malfunctioning ANS or hyperactive sympathetic nervous system may be especially challenging to the newborn. This is because the human infant is not born with a completely functioning and myelinated vagal system. Therefore, its development continues in the first few months postpartum through activation. For the external observer, maturation of the vagal system can be distinguished by the increased speed of how efficiently an infant calms after a disruptive challenge and the increasing time period the infant remains calm.<sup>33</sup> For example, a non-colicky infant can be soothed by being carried or touched, but this has no impact on the excessively crying infant and sometimes even worsens their symptoms, as though these children have a unique threshold or delayed response to downregulation. Interestingly, an increase in sympathetic activity has consistently been found in several studies (in adults) with crying. After resolution of crying, the parasympathetic nervous system was activated.34 Crying however is dependent on the functional integrity of the cranial nerve X (vagus).<sup>35</sup> Notably, the colicky infant does not calm down even when crying for hours or after feeding, nor does the colicky infant remain calm on a sufficiently increasing level. All these findings might show that the difference in the maturation of the

somatosensory processing pathways might be leading to the different responses or abilities to calm down between the colicky infant and non-colicky infant.<sup>36</sup> This leads to the question, what if the colicky infant is trying to activate the vagus nerve or parasympathetic nervous system through crying, but cannot?

Additionally, a lack of neuronal activation to and in the brain might affect brain development (factors detected in late effects of infant colic). Disturbances in the finetuning of interactions between myelination and functional connectivity maturation could disrupt some developmental processes. By compromising this neural network, it could be said that in the case of infant colic, an over excited sympathetic or insufficiently stimulated parasympathetic nervous system or an underdeveloped vagus nerve may be one of the underlying causes or contributing factors. Also, it can be suggested that the link between the gastrointestinal dysfunctions and brain induced stress behaviors in infant colic is the gut-brain axis formed mainly by the vagus nerve. Furthermore, an immature vagal system might impair brain development and therefore cause developmental delay. In turn, it could be hypothesized that strengthening the vagus nerve function, as the main parasympathetic actor and neural connection of the gut-brain-pathway,<sup>27,28</sup> might lessen symptoms of excessive crying and its sequelae.

# How might probiotics affect infant colic? What probiotic might be most beneficial?

Study findings of the monospecies probiotic Lactobacillus reuteri (L. reuteri) have shown in four double-blind trials,<sup>25</sup> involving 345 infants with colic, that the active treatment group had less crying and/or fussing time than the placebo group. However, significant intervention effects have only been shown in exclusively breastfed infants but were insignificant in formula fed infants. In the treatment group the mean crying and/or fussing duration was reduced by 21 minutes by day seven and 25.4 minutes by day 21.25 In these trials, infant colic was either defined by the Wessel's (crying > 3 hours per day, for > 3 days per week, for > 3weeks) or by the modified Wessel's (crying > 3 hours per day, for > 3 days per week) criteria.<sup>38</sup> This would mean that the average breast-fed colic baby was still crying and/or fussing a minimum of two hours and 35 minutes at day 21 of receiving L. reuteri. Even if it is common for infants to cry about one hour per day by 10-12 weeks old,<sup>8</sup> two and one-half hours a day in a comparable time frame, is more than double the normal crying time. Therefore, although L. reuteri showed some effect in breastfed babies, it could not be considered a scientifically validated "cure."

Further, in a later study it was discovered that the combination of Lactobacillus rhamnosus (L. rhamnosus) and L. reuteri was more effective in alleviation of colic in breastfed infants than individually. The statistically

significant difference between the probiotic and control groups was -47 minutes.<sup>39</sup> The monospecies L. rhamnosus showed no effect in the nonhomogeneous group of breastand formula fed infants.<sup>40</sup> Because Infants who received combined L. reuteri with L. rhamnosus, were all exclusively breastfed, the role of L. rhamnosus is difficult to ascertain, although there could be some type of synergistic effect since the reduced crying time was increased with a combination of both species.<sup>39</sup>

In a study where B. breve was used, effectiveness was also shown in formula fed infants.<sup>26</sup> So, would a multispecies probiotic with the addition of B. breve be a more effective choice to treat infant colic in breastfed and formula fed infants? Breast milk contains multiple and beneficial health enhancing microbes such as Bifidobacterium subspecies (B. spp). Multiple studies have reported that breastfed infants have a higher abundance of beneficial B. spp. compared with formula fed infants.<sup>41,42</sup> Furthermore, in a recent review, where infants who received either breast or formula milk were compared, they found that feeding type modulates microbiome composition.43 Moreover, they found that breastfed infants' fecal samples not only consisted of higher amounts of B. spp. but also of Lactobacillus spp. (L. spp.) and contained fewer pathogens.43 In another study, in which the microbiomes of infants who received extensively hydrolyzed or amino acid formula were compared with infants receiving human milk, it was found again, that the amount of B. spp. was higher in breastfed infants.<sup>44</sup> The predominant presence of B. spp. in breast milk could have accounted for the fact that supplementation of L. reuteri has shown improvement with breastfed infants only.<sup>25</sup> When the two (L. spp. and B. spp.) are working in synchronicity, infant colic could improve in the formula fed colic infants too.

Just mixing B. and L. spp. together will not lead to an effective probiotic treatment. A probiotic formula needs to be carefully chosen, containing powerful human microbial strains from the area of treatment with scientific relevance. Therefore, a considered probiotic supplement needs to focus on individual properties of the bacterial strains, identity, safety as well as technological issues, such as stability and targeted release. Against this background, an example study report was written for a gynecological application, where 127 presumptive lactobacilli isolates of vaginal origin were collected. A step-by-step selection was done meeting specific criteria like compatibility and growth enhancement, which finally lead to a preparation consisting of four individual L. strains that possess particular significance in women's urogenital health.<sup>45</sup>

Evidence for why B. spp. most likely play an important role in early life is that they are the dominant bacteria in a healthy newborn gut microbiome.<sup>46</sup> One major function of the Bifidobacterium genus is to contribute to gut homeostasis and host health with the involvement in the production of short-chain fatty acids (SCFA).47,48 In fact, it was found that SCFA production is increased with increased amounts of B. spp.47,49 Study findings showed that SCFAs, such as butyric acid, have a positive direct effect on vagal afferent terminals situated in the gut mucosa, which ultimately helps - through the gut-brain-axis — with the regulation of brain function.<sup>27,50,51</sup> Additionally, it was shown in a study that breastfed infants displayed lower inflammatory cytokine profiles than formula fed infants.<sup>52</sup> This might be partially due to breast milk containing significant amounts of B. spp. and therefore SCFAs such as butyrate. Butyrate can regulate gut permeability by reducing pro-inflammatory cytokines and increase anti-inflammatory cytokine circulation.53 This in turn decreases inflammatory stress to the infant's body. On the other hand, it may be considered that formula fed infants do have a higher tendency for inflammatory processes to occur, and therefore could experience more dysfunctions in the gut and the brain as a consequence of diminished amounts of B. spp.

How are B. spp. introduced to the baby's gut? In a study where meconium of newborns was analyzed, it was found that the number of bacterial strains increased with time after birth and accumulated at an estimated rate of 1.2 strains per day.54 The earliest species detected were facultative anaerobes (can live with and without oxygen) from the Enterobacteriaceae and Bacilli, notably Streptococcus and Enterobacter. First obligate anaerobes (die in an oxygen environment) were detected after 25 hours, including Clostridia, whereas B. spp. were found more than 100 hours after birth,<sup>50</sup> which indicates that breastfeeding, or external components, like oral (retrograde) translocation,<sup>55</sup> introduces the newborn to B. spp. Another external source to introduce the newborn to B. spp. could be supplementation. A study has shown that administration of certain probiotic strains of bacteria (mainly B. spp. and L. spp.) can positively alter the metabolic profile of the host through production of neurogenic metabolites that positively influence the nervous system including the brain, as well as support an anti-inflammatory environment.27,47

A dysbiosis or insufficient amount of SCFA or lactic acid producing bacteria, like B. spp. could lead to an increased number of inflammatory metabolites, which then could cause a malfunctioning neural system including the brain. Furthermore, evidence has shown that an increased risk for immune disorders like allergies and infections may result.<sup>43,47,52</sup> Hence, it could be argued that inflammation as well as dysbiosis might be decreased with a probiotic containing B. spp. In fact, B. spp. might be the deciding factor in a probiotic formula to reduce discomfort and crying in the formula fed colicky infant. Not only the formula fed infant could benefit, but also the breastfed colicky infant, because supplementation with a multispecies probiotic containing B. spp. could increase the speed of gut microbiome and ANS balance. However, formula fed or breastfed, based on study results, the colicky infant could benefit from a multispecies probiotic containing B. spp. by a reduction of aggravating factors. Moreover, studies have shown that commensal gut bacteria strengthen vagal function and therefore gut-brain-axis interaction.<sup>27</sup>

Probiotic supplementation may correct a dysbiotic microbiome, which in turn changes the metabolite composition and causes an increase in production of SCFAs, neurotransmitters, like serotonin as well as antiinflammatory cytokines such as Interleukin<sup>10,47,56</sup> Further, this change in metabolite composition results in a decrease of inflammation and improvement in gut health, as well as a stress response like crying.48,49 Additionally, vagus nerve endings in the intestinal wall (ENS) are activated by bacterial metabolites. With proper bacterial metabolite production, the vagus nerve is stimulated and its function as well as its development improves. Consequently, parasympathetic input from the gut to the brain and in the brain is increased,<sup>27</sup> which may improve brain maturation and therefore decrease the potential for developmental delay.36,37 All these findings could support a randomized trial using a multi-species probiotic with B. as the leading probiotic bacteria.

### How might manual therapy affect infant colic?

Within the general population, manual therapy is an often sought alternative therapy by parents of an unsettled, fussy and irritable infant.<sup>57</sup> Practitioners working with colicky infants have experienced repeatedly, that inconsolable crying can disappear after only a few treatments. Unfortunately, scientific evidence has not been able to prove significant effectiveness through a sufficient number of randomized controlled trials. One reason is that randomized controlled trials are difficult to develop for newborns and they are quite costly as trials are in general, which makes funding a challenge. Further, studying this subject has been difficult because of varying definitions and measurements in an already low number of studies. Additionally, it is commonly believed (though not proven and increasingly unlikely) that infant colic is a self-limiting disorder. In a recent systematic scoping review, it was therefore concluded that findings for the effectiveness of spinal manipulation to manage infant colic for crying time and sleep disturbances were inconclusive.58

That said, there are randomized trials that show statistically significant improvement in cry times with SMT.<sup>59</sup> Further, anecdotal manual therapy successes are encouraging and may have some value. Why else would so many parents seek this treatment option?<sup>57</sup> Is it simply a parental placebo response? Based on a randomized controlled study done

by Miller et al.<sup>59</sup> where the crying time reduction was statistically significant at day eight and was not susceptible to parental bias, the answer would be no. In their study it was also observed that the drop out rate in the non-treatment group was significantly higher, suggesting that parents didn't find the trial helpful and began looking for other types of care.<sup>59</sup> Considering that it is the parents that spend the most time with the infant, this observation might be valuable.

Accordingly, in an article by Hughes and Bolton<sup>60</sup> it was determined: "The evidence suggests that chiropractic has no benefit over placebo in the treatment of infantile colic. However, there is good evidence that taking a colicky infant to a chiropractor will result in fewer reported hours of colic by the parents. And therefore, in a clinical scenario where the family is under significant strain, where the infant may be at risk of harm and possible long term repercussions, where there are limited alternative effective interventions, and where the mother has confidence in a chiropractor from other experiences, the advice is to seek chiropractic treatment."

It has not been adequately explained why manual therapy seems to decrease or alleviate symptoms of infant colic. It has been proposed that the ANS might play a role.<sup>57</sup> The complexity of the ANS becomes apparent when it fails to function. Because a complex system is constructed of multiple connections, it becomes a challenge when trying to track it back to its origin, which is a prerequisite for correction. On the other hand, a complex system is a multipathway system and compensatory routes may be necessary. Therefore, in the event of malfunction, critical systems like the musculoskeletal and nervous system will still be maintained, except in a state of compromised and maladaptive autonomic neuroplasticity.<sup>61</sup> Further complicating the impact of malfunctioning of the ANS is that it is conceptualized as the intermediary between the human internal and external environments (i.e., vagus nerve afferent), whereas the brain is optimizing adaptation to internal and external stressors (i.e., vagus nerve efferent).<sup>62</sup> A faulty or dysregulated ANS might therefore not be able to access the external environment correctly and consequently the brain cannot sufficiently adapt to stressors.

Malfunctioning of the vagus nerve, which innervates structures in the head, neck, thorax and abdomen, could therefore change physiological responses of cells, tissues, organs and systems in these areas. Fortunately, adaptive systems are activated or inhibited efficiently, but not excessively, so that the human body can cope with these challenges. However, there are several processes in which body systems either are overstimulated or inadequate in their response to stimulation. It is the cost of adaptation that may trigger pathophysiology.<sup>63</sup> A recent study highlighted that modulation of the ANS has been a mechanism underlying the interventions in complementary and integrative techniques such as manual therapy,<sup>61</sup> which supports the notion that chiropractic manipulation could counteract a malfunctioning central nervous system (CNS) or ANS.<sup>64</sup>

In the case of the colicky infant, their systems are still in the developmental stage. At this early stage synchronization of operating systems is limited and drawing from sufficient resources to compensate may be lacking. Body systems in a newborn have just begun to incorporate gained experiences, which are very sparse at this point. This is especially critical when examing the capacity of the immature nervous system. Furthermore, integration of external experiences is limited because in the excessively crying child, body systems are occupied in coping with internal aggravations. Internal hyperactivity in the nervous system most likely causes a state of constant fright and flight, which creates an unpleasant tumult. This turmoil may not be counter acted, even when crying for hours, because the parasympathetic nervous system is not able to rise to the challenge. What occurs in the infant will sooner or later be transported to the empathic care giver, which may in turn create more aggravation and ends in the entire family being overwhelmed.

How might spinal manipulative therapy (SMT) work with infant colic? It has been proposed that when the position of the head migrates forward - as, for example, with prolonged prenatal constraint - increased strain is placed on the muscles and ligaments of the head, neck, and shoulders. This abnormal head posture could result in altered joint positions and ultimately dysfunction, which then leads to abnormal neuronal afferent information to the brain and body.<sup>65</sup> Considering the anatomical close proximity of the cranial nerves V to XII to the cervical spine and the brainstem, it would make sense, that an increase in adverse mechanical tension in the cervical spine may unfavorably act on the brainstem and cranial nerves V through XII. Hence, dysfunctions of the upper cervical spine could be one of the mechanisms that decreases parasympathetic input to or from the brain. Restoration of cervical function should then result in a balanced ANS. In a study by Moustafa et al. it was found, that improved cervical function improved sympathetic skin response as well as reduced longitudinal stress and strain on the cervical elements.65 Another review showed that SMT, by stimulating the vagal nerve, improved autonomic imbalance.64 It has been found that one of the main key factors leading to these improvements is a network of neurophysiological connections between the cervical spine mechanoreceptors and the ANS.65 This suggests that not only in theory spinal corrections balance the ANS and reduce nerve interference, but also in practice, manual therapy may manifest a shift away from sympathetic dominance.65

Intuitively it is often assumed that the excessive crying of the infant stems from discomfort. At birth, newborns are equipped with basic connections involved in pain processing, but major maturation and organization of their pain control networks occurs postnatally. Maturational differences in pain network could be related to specific patterns of sensitivity and regulation observed in crying of colicky infants compared to non-colicky infants. Therefore, excessive crying in infants could be due to differential pain thresholds, pain perception, and duration of response after painful stimuli.66 Since SMT has been shown to result in both local and regional pain reduction, as well as positively influence the CNS with a general reduction of pain sensitivity,<sup>67</sup> it becomes a viable choice of treatment for the newborn. This statement is supported by an experimental research project which showed that SMT influenced the incoming/ascending pain signals (local nociceptive input affecting dorsal horn excitability or temporal summation) and/or the excitability of the central pain regulating mechanisms.<sup>67,68</sup> Their research suggested that discomfort or an overexcited nervous system could be balanced with SMT.

Furthermore, in healthy individuals, acute stress triggers an increase in sympathetic activity, which often includes an increase in threshold, that is induced by descending inhibition. This indicates a bi-directional relationship, where the ANS not only reacts, but stress modulates ANS activity.<sup>69</sup> In this regulatory circuit, the brainstem plays a central role by connecting the cerebrum, the cerebellum and the spinal cord with each other. Through these connections the brainstem modulates the function of major systems like the cardiac, respiratory and gastrointestinal systems by sending vagal efferent information to these organs.<sup>70</sup> This is why vagus nerve stimulation has become a therapeutic avenue in several inflammatory or painful disorders such as musculoskeletal diseases.<sup>71</sup>

This could mean that in the case of infant colic a dysregulated CNS or ANS could be balanced by upregulating the vagus nerve function with SMT. In a 2020 study<sup>64</sup> a mechanism for how the activated vagus nerve (parasympathetic system) counterbalanced the activity of the sympathetic system was explained. Vagal stimulation releases neurotrophins including brain-derived neurotrophic factor and nerve growth factor. Brain-derived neurotrophic factor is an important neuronal growth factor that regulates neuronal maturation, neurogenesis, synaptic plasticity and survival.<sup>64</sup> Nerve growth factor acts as a modulator of the hypothalamic-pituitary-adrenal axis and therefore contributes to maintaining the neuroendocrine systems.<sup>64</sup> The neuroendocrine system controls the body's response to stress, meaning that if it functions correctly, a stress response can be terminated<sup>36</sup> in the infant when needs like hunger are well managed. Further research has found that infants who had chiropractic care for infant colic showed significantly

fewer emotional and sleep problems as toddlers.<sup>72</sup>

### How would these two treatments work together?

If in fact, excessive crying (aka infant colic) is at least partly due to an overactive sympathetic or underactive parasympathetic nervous system, where the vagus nerve is the main parasympathetic contributor,<sup>27</sup> then strengthening<sup>28</sup> or decreasing irritation to the vagus nerve could balance the ANS and therefore decrease a stress response like crying. Strengthening of the vagus nerve function can be achieved by metabolites which are produced by probiotic bacteria. Further, manual therapy in the cervical region, with mechanical strain on vagal structures is reduced, can result in proper function of the ANS. Combining these two therapy forms, which have already shown to be both safe and useful by themselves<sup>24</sup> by approaching the problem of an excessively crying infant from two different angles at least in theory — could produce a reasonable working solution for testing. Both therapies have demonstrated some reductions in crying times. Is there any potential to trial them together to see if they could synergistically work together for more significant crying time reductions?

Summarizing and connecting research findings could answer how these two treatment methods might prove scientific efficacy when combined. Infants with colic are more responsive and can manifest increased reactivity, but they also have a diminished regulatory capacity. Infant colic seems to involve a regulatory capacity problem in addition to a reactivity disorder.<sup>36</sup> Probiotics increase neural function by activating afferent vagal fibers in the ENS, which send information to the brain. SMT on the other hand restores proper function of vagal activity at the cervical spine. By addressing the problem at different areas of the nervous system, the effects might be augmented for faster balance capabilities of the ANS and therefore faster calming down of the colicky infant from an excited state.

As for recommendation, what probiotic species combination should be used in a supplement for colic infants, it is difficult to say because only thorough scientific laboratory evaluation and testing as explained in the study done by Domig et al.<sup>45</sup> might give an evidence based combination. As no scientifically effective probiotic has statistically significant evidence as of today,<sup>27</sup> these authors suggest that L. spp.<sup>25,39,40,43</sup> and B. spp.<sup>26,41-44</sup> in combination might be most likely to improve the condition of infant colic in both breastfed and formula fed infants. Since no RCT has shown what species combination is the right one for all colic infants, families with a colic infant might be supported best by the clinician when using a multispecies probiotic with L. spp. as well as B. spp. in combination with SMT.

#### Conclusion

Both probiotics and manual therapy have shown some

benefits for the excessively crying infant. It should be considered that chiropractic care along with a multispecies probiotic combined may be more effective than each method by itself. If so, improvement should be seen in all infants, regardless of their feeding type. Not only should crying time decrease or become less intense, but also gut health and immune function should improve and most of all, the infant-parent relationship becomes a nourishing experience for both. The risk/benefit ratio suggests that further studies that combine these two types of therapies could be a reasonable way forward to help infants and their parents.

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