Novel and Alternative Therapies for Childhood Constipation

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Constipation is a worldwide problem that affects many children. Treatment of constipation is largely based on clinical experience rather than on evidence-based controlled clinical trials. Stool softeners and cathartic agents in combination with behavioral interventions constitute the programs most commonly used to facilitate painless and frequent defecation. Long-term treatment is needed for most patients, and approximately 30% of children beyond puberty continue to struggle with symptoms of constipation, such as infrequent, painful evacuation of stool and fecal incontinence. Not surprisingly, chronicity of these bowel complaints may cause significant interference with the child’s emotional growth and development. Development of new therapeutic strategies is necessary in order to treat these challenging patients more effectively. This review provides an overview of novel and alternative therapies, such as new drugs, surgery, and probiotics, that are being proposed for the treatment of childhood chronic constipation.

Introduction
Mineral oil, polyethylene glycol, lactulose, bisacodyl, senna, and milk of magnesia are just a few examples of the frequently prescribed compounds for the management of childhood constipation. What they all have in common is that they are generally recommended based on clinical practice or experience, with little evidence of long-term efficacy. Very few large double-blind, randomized, controlled studies have been performed in children with chronic constipation, which should be surprising considering that constipation is the chief complaint in 3% to 5% of visits to pediatricians and represents 10% to 25% of referrals to pediatric gastroenterologists [1]. Moreover, constipation is a worldwide problem with a prevalence ranging from 7% to 30% in both Western and non-Western countries [2].

The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition recently issued a clinical practice guideline on evaluation and management of constipation in infants and children. Their recommendations include education, disimpaction, and maintenance therapy, consisting of dietary changes, medication use, and behavioral modification [3]. Although these measures are effective in the majority of children, a sizable proportion needs long-term therapy, and some patients do not achieve successful outcomes. After 1 year of treatment, up to 50% of children are not free of symptoms, and approximately 30% continue to struggle with constipation beyond puberty [4–6].

Thus, new, more effective interventions are needed for constipated children. The aim of this report is to provide an update on novel and alternative therapies that are already available or have the potential to be helpful options when conventional treatment fails.

Novel Drugs
Advancements in the understanding of the gastrointestinal enteric nervous system and epithelial function have led to the development of new classes of drugs for treatment of chronic constipation. These include substances that bind to serotonin receptors or are chloride channel activators.

Tegaserod
Serotonin plays an important role in regulating gastrointestinal function, and 95% of all serotonin in the body is present within the gastrointestinal tract. Tegaserod is a novel selective serotonin receptor agonist that acts at 5-HT4 receptors in the gut wall. It stimulates the peristaltic reflex, enhances intestinal secretions, and inhibits visceral sensitivity [7,8]. It is also a potent prokinetic agent in the upper and lower gastrointestinal tract [9]. Tegaserod has proved effective in adults with constipation-predominant irritable bowel syndrome (IBS) and chronic constipation without IBS symptoms and seems beneficial in patients with functional heartburn. Large double-blind, placebo-controlled trials have demonstrated a significant increase
in the frequency of stools, improvement of stool consistency, and reduction in abdominal symptoms in adults taking tegaserod [10–13]. Most side effects occurred with similar frequency in placebo and treatment groups, except for diarrhea, which was more common in the tegaserod group. Diarrhea was generally transient and self-limiting and did not need any treatment. Investigators found similar results for efficacy and adverse events in a study performed in adolescents with constipation-predominant IBS [14]. To date there has only been one abstract reporting experience with the use of tegaserod in four children with severe chronic constipation [15]. Preliminary results from a retrospective study conducted at our center coincide with those from the adult studies, showing increased bowel movements, decreased abdominal symptoms, and minimal side effects in children with a variety of gastrointestinal complaints.

**Lubiprostone**

Lubiprostone is an oral bicyclic fatty acid that selectively activates type 2 chloride channels of the gastrointestinal epithelium, resulting in increased fluid secretion. This increase of chloride-rich intestinal fluid softens the stool and accelerates small intestinal and colonic transit [16]. Lubiprostone was approved by the US Food and Drug Administration (FDA) in January 2006 for use in adults with chronic idiopathic constipation after positive results were reported from two double-blind multicenter phase III studies. These studies demonstrated significant improvements in defecation frequency, straining, and stool consistency [17,18]. Overall, lubiprostone appeared to be well tolerated, with nausea, diarrhea, and headache the most common complaints. No studies of lubiprostone in children have been performed yet.

**Alvimopan**

Another drug that might have potential for treatment of constipation is alvimopan. This agent is a peripherally acting opioid receptor antagonist with a high affinity for μ-opioid receptors. These receptors are the sites where opioid binding causes interruption of the coordinated rhythmic contractions of the colon and produces fluid secretion [19]. It is unclear whether alvimopan is effective only in opioid-induced constipation or also in subgroups of constipation. Alvimopan has not been approved yet by the FDA and remains a research drug. Enteral naloxone can also improve stool output for children who have opioid-induced constipation, but it carries the risk of introducing withdrawal symptoms that can be harmful to the patient [20].

**Probiotics**

It is becoming increasingly clear that gut bacteria have an important effect on health. The general public is confronted with this notion through promotion of different yogurts containing a variety of probiotics that are now commercially available and marketed to promote “a healthy gut.” Probiotics are defined as “live microorganisms, which when administered in adequate amounts confer a health benefit on the host” (WHO definition). They have traditionally been thought to be useful in the prevention and treatment of various gastrointestinal diseases, including infectious diarrhea, antibiotic diarrhea, and traveler’s diarrhea [21]. Recently two large human double-blind crossover randomized studies using two different species of probiotics showed improvement in constipation symptoms. One study used one to three portions of *Bifidobacterium animalis* strain DN-173 010 and reported a significant reduction of colonic transit time (varying from 10% to 40%), especially in subjects with slow transit (transit time >40 hours), although no change was observed in the number of stools per week [22]. The other study, using *Lactobacillus casei* Shirota, showed significant improvement in self-reported severity of constipation and stool consistency with a slight but significant increase in stool frequency [23]. In contrast to these studies, the only double-blind, placebo controlled, randomized study of the effectiveness of *Lactobacillus GG* as an adjunct to lactulose for children with constipation failed to show any additional benefit of the probiotic [24••].

No probiotic-related adverse effects were reported in the studies. The mechanism of action by which probiotics lead to shortening of gut transit time or increased defecation frequency has not been elucidated yet. Some researchers hypothesize that a product of bacterial origin may decrease sigmoid tone or stimulate colonic motility [25]. Another proposed mechanism is that increasing the concentration of bifidobacteria in the gut modifies the profile of gut microflora and consequently affects transit time [26]. Further studies are needed to assess the clinical efficacy of different species of probiotics in children and to understand the mechanism underlying their effect.

**Electrical Stimulation**

Another approach to treatment of constipation is electrical stimulation of the bowel, either through sacral nerve stimulation or, less invasively, using transcutaneous electrical stimulation. Urologists have used both techniques for treatment of detrusor instability and urinary retention in adults and children [27,28]. Simultaneous improvement of bowel symptoms was often noted by researchers, leading to the idea of using electrical stimulation for the treatment of functional bowel disorders [29,30].

Reports from only a few pilot studies have been published related to sacral nerve stimulation; these studies showed encouraging results in adults with slow transit constipation and those with feelings of incomplete evacuation [31,32]. Defecation frequency improved, together with abdominal and bloating symptoms. Infection of the implant, pain, and recurrent cystitis are some of the most common side effects.