

Systematic Review of Treatments for Recurrent Abdominal Pain

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ABSTRACT. *Objective.* To conduct a systematic review of evaluated treatments for recurrent abdominal pain (RAP) in children.

Methods. Online bibliographic databases were searched for the terms "recurrent abdominal pain," "functional abdominal pain," "children," or "alternative therapies" in articles classified as randomized controlled trials. The abstracts or full text of 57 relevant articles were examined; 10 of these met inclusion criteria. Inclusion criteria required that the study involve children aged 5 to 18 years, subjects have a diagnosis of RAP, and that subjects were allocated randomly to treatment or control groups. The methodology and findings of these articles were evaluated critically, and data were extracted from each article regarding study methods, specific interventions, outcomes measured, and results.

Results. Studies that evaluated famotidine, pizotifen, cognitive-behavioral therapy, biofeedback, and peppermint oil enteric-coated capsules showed a decrease in measured pain outcomes for those who received the interventions when compared with others in control groups. The studies that evaluated dietary interventions had conflicting results, in the case of fiber, or showed no efficacy, in the case of lactose avoidance.

Conclusions. Evidence for efficacy of treatment of RAP in children was found for therapies that used famotidine, pizotifen, cognitive-behavioral therapy, biofeedback, and peppermint oil enteric-coated capsules. The effects of dietary fiber were less conclusive, and the use of a lactose-free diet showed no improvement. There seemed to be greater improvement when therapy (famotidine, pizotifen, peppermint oil) was targeted to the specific functional gastrointestinal disorder (dyspepsia, abdominal migraine, irritable bowel syndrome). The behavioral interventions seemed to have a general positive effect on children with nonspecific RAP. Many of these therapies have not been used widely as standard treatment for children with RAP. Although the mechanism of action for each effective therapy is not fully understood, each is believed to be safe for use in RAP. *Pediatrics* 2003;111:e1–e11. URL: <http://www.pediatrics.org/cgi/content/full/111/1/e1>; recurrent abdominal pain, treatment, children, alternative therapies, systematic review.

ABBREVIATIONS. RAP, recurrent abdominal pain; IBS, irritable bowel syndrome; RCT, randomized controlled trial; SPC, standard pediatric care; CBFI, cognitive-behavioral family intervention; BF, biofeedback; CBI, cognitive-behavioral intervention.

Recurrent abdominal pain (RAP) in children is a common disorder that has been estimated repeatedly over the last 4 decades to affect 10% to 20% of all school-aged children, with a slight increase in females after 9 years of age.¹ RAP was originally defined as a pain syndrome consisting of at least 3 episodes of abdominal pain over a period of not less than 3 months and severe enough to affect activities.² Over time, it has been consistently found that only 5% to 10% of children with RAP have an underlying organic process that contributes to their pain. Despite its seemingly benign nature, this disorder has been associated with increased school absenteeism, frequent doctor visits, family disruption, and significant anxiety and depression.³

The current practice of many pediatricians in treating children with RAP is that of support and empathy for the family with reassurance that no serious disease is present; that children likely will outgrow it; and that the child must learn to cope with it.^{4–6} With this approach, approximately 30% to 40% of children do have resolution of their pain.^{7,8} However, the remainder continue to exhibit symptoms and go on to be adults with abdominal pain, anxiety, or other somatic disorders.⁹ Pharmaceutical treatments are commonly used in an effort to manage symptoms despite the lack of data supporting their efficacy. In fact, a recent systematic review of pharmaceutical therapies for RAP done by the Cochrane Review¹⁰ found only 1 study methodologically sound enough to warrant inclusion.¹¹ The drug used in this study, pizotifen, is available worldwide but is not currently approved for use in the United States.

In an effort to improve our understanding of this syndrome, a panel of experts on functional gastrointestinal disorders recently proposed classifying children with RAP symptoms into 5 subtypes: functional dyspepsia, irritable bowel syndrome (IBS), functional abdominal pain, abdominal migraines, and aerophagia.¹² It was hoped, as demonstrated in the adult population, that it would provide a method for standardizing the clinical definition of functional gastrointestinal disorders, help various researchers study the same disorders from different points of view, and offer clinicians a positive approach for the treatment of patients.

Still there are questions as to the definitive pathological alterations found in these affected chil-

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dren. Current theories include autonomic nervous system instability,^{13,14} visceral hyperalgesia,^{15,16} gut dysmotility,¹⁷ stressful life events,¹⁸ or poor coping skills,¹⁹ to name a few. It is known that both the gut and the nervous system are derived from the same tissues embryologically. At the gut level is the enteric nervous system, which is made up of sensory neurons, interneurons, and motor neurons. Neuropeptides and neurotransmitters produced in the gastrointestinal tract regulate gastrointestinal motility, blood flow, secretion, and absorption.^{20,21} The enteric nervous system and central nervous system have direct effects on each other. For example, stress is known to aggravate the gastrointestinal tract by stimulating the release of neuropeptides and neurotransmitters, triggering various gastrointestinal responses. This brain-gut connection seems to be a mechanism that links the psychoemotional state with gastrointestinal dysfunction.²⁰ As we develop a better understanding of this brain-gut interaction in functional gastrointestinal disorders, our emphasis of treatment will need to move beyond the biomechanical toward a biopsychosocial model.¹⁵

Reviews of various psychological interventions for RAP have been published in narrative form,^{19,22} but to our knowledge, no systematic review of the conventional or alternative medical therapies has been conducted. Alternative therapies are those defined as "healing philosophies (schools of thought), approaches and therapies that mainstream (conventional) medicine does not commonly use, accept, study, understand, or make available."²³ We chose to undertake the review of this literature to help summarize the research that has been done in this field, to bring about guidelines to assist pediatricians in their decision making regarding appropriate health care for their patients, and, last, to list recommendations for additional research strategies in the functional gastrointestinal disorders in children.

METHODS

We conducted searches on Medline Database from 1966–2001, Cochrane Clinical Trial registry, Cochrane Database of Systematic Reviews, AMED, PsychInfo, and PubMed via NCCAM using medical subject headings and keywords "recurrent abdominal pain in children" or synonyms, "functional abdominal pain," "irritable bowel syndrome," "alternative therapies," "traditional Chinese medicine," "Ayurvedic medicine," "herbal," "homeopathy," and "osteopathy." The search was restricted to those classified as randomized controlled trials (RCTs), those conducted on children to age 18, and those published in English. The content of the full-text articles or abstracts from these searches were examined to determine whether they met criteria for inclusion in our review. In addition, the bibliographies of relevant articles and all selected articles were hand-searched, in the event that studies were incorrectly classified and not identified in the database, and reviewed for inclusion.

For inclusion, a study, regardless of sample size, needed to include children to age 18 with a diagnosis of RAP, be classified as an RCT, and show evidence that the children were allocated randomly to a treatment or control group. Crossover trials were included when all subjects crossed over and were exposed to both treatment arms. Excluded were studies on something other than functional gastrointestinal disorders, studies that included adults (>18 years), studies that lacked a control group, or those that were not randomized.

The quality of included trials was assessed by examining not only the description of randomization but also the adequacy of case definitions and blinding methods. A standardized case defi-

nition allows for the comparison of similar trials and enhances the generalizability of the results.²⁴ In studies on children with RAP, the case definition has generally been considered as 3 or more episodes of abdominal pain occurring over a minimum of 3 months and severe enough to interfere with normal activities.² These studies were assessed for their adherence to this definition. We considered a trial to be adequately blinded when it was conducted in such a manner that there was no reason to assume that those responsible for outcomes assessment would be able to distinguish between the active or control interventions.

Principle outcomes of interest were the decrease or elimination of pain episodes or pain intensity and the methods in which they were determined, use of medication, use of medical services, and functional disability. Also considered were measures of change in anxiety or depression.

Each study was assessed for its design, the participants' characteristics and heterogeneity (gender, age, socioeconomic status, source of referral), the details of the intervention, and the outcome definitions. Each study was also noted for its handling of missing data, principle measure of effect, and statistical methods.

RESULTS

Fifty-seven articles were identified. The most common reason for exclusion were 1) study of something other than RAP^{25–28}; 2) treatment was compared with another treatment rather than control^{29–31}; and 3) treatment allocation was not randomized,^{32–34} case series without controls,^{35–37} or case studies.^{38–40} The vast majority of publications identified were reviews or descriptions of RAP rather than interventional studies. Ten RCTs met inclusion criteria (Table 1). Of these, 2 were studies of pharmaceutical interventions, 4 studied dietary interventions, 2 studied behavioral interventions only, 1 involved behavioral intervention with dietary fiber as the control phase, and 1 evaluated a botanical intervention. There was a wide variation of outcome measures used within the various studies, making comparisons between trials difficult. All studies stated that they were randomized and blinded, although this was difficult to verify as details of allocation concealment and blinding were insufficient in some of the studies.

Pharmaceuticals

Of the 2 studies that evaluated the use of pharmaceuticals, 1 examined the use of famotidine for the treatment of functional abdominal pain with dyspepsia and the other tested pizotifen for the treatment of abdominal migraines. Although the use of other pharmaceuticals, such as anticholinergics, antiemetics, antidepressants, and simethicone, have been commonly used by clinicians to manage symptoms associated with childhood RAP, no studies identified tested their efficacy for the treatment of functional abdominal disorders in children.¹⁰

Famotidine

Famotidine, an H₂-receptor antagonist, was tested on 25 children in a double-blind, placebo-controlled, crossover trial.¹ Each child was given 0.5 mg/kg/dose twice daily (maximum: 40 mg/d) or placebo for a 3-week treatment period (treatment period 1) then switched to the other treatment for 3 weeks (treatment period 2).

Inclusion Criteria

Children who were eligible for the study were 5 to 18 years of age, had a minimum of 3 episodes of

TABLE 1. Systematic Review of Treatments for Recurrent Abdominal Pain in Children

Study	Author	No. of Subjects		Age Range (Years)	Study Criteria		Intervention	Outcome Measured	Psychiatric Measures	Subgroup of GI Disorder	Referral Source
		Treatment	Control		Inclusion	Exclusion					
1	See et al ¹	N = 25 Crossover design		5-18	Apley, dyspepsia	Diarrhea, constipation IBS/blood, psych/GU, abnl labs, medication	Famotidine × 3 wk	Abdominal Pain Score = PFS+PSS+PIS Global assessment	None	Dyspepsia/ FAP	½ Primary care ½ Tertiary care
2	Symon and Russell ¹¹	N = 14 Crossover design		5-13	Abdominal pain ×6 mo, occurring 2×/mo, lasting 2 h, facial pallor, relative with HA/migraines	Abnl labs, abnl physical exam	Pizotifen × 2 mo	Index of severity, index of total misery, weight	None	Abdominal migraine	Primary care
3	Feldman et al ¹⁶	N = 52 n = 26	n = 26	8	>2 mo 1×/wk, affect activities	Abnl labs, weight loss, devel/behav/ emotional problems	10 g F × 6 wk	50% decrease in pain frequency, intensity of pain	None	RAP	Primary care
4	Christiansen ⁴⁸	N = 31 n = 15	n = 16	3-15	2 pain episodes in 6 wk	organic dz	330 g vs 10 g F × 7 wk	Parent pain diary	None	RAP	Primary care
5	Lebenthal ⁴⁹	N = 38 n = 21 n = 17 n = 21 n = 17 n = 39	n = 38 n = 21 n = 17 n = 21 n = 17 n = 39	6-14	Diagnosed RAP	Abnl labs	Lactose-free vs lactose-containing formula	Parent pain diary	None	RAP	Tertiary care
6	Dearlove et al ⁵⁰	N = 39 n = 21 n = 18	n = 39 n = 21 n = 18	>3 y	RAP	none listed	Lactose-free vs lactose- containing formula	Global assessment	None	RAP	Primary care
7	Sanders et al ⁵¹	N = 16 n = 8	n = 16 n = 8	6-12	Apley	Major surgery, organic disease, Lac Intol, constipation/ diarrhea, psychiatric disorder/DD	Cognitive/behavioral vs wait-list	Patient pain diary (VAS) Parent pain observation Teacher pain observation Parent/patient interaction observation	RBPC, CTRS	RAP	Primary General public
8	Sanders et al ⁴	N = 44 n = 22	n = 44 n = 22	7-14	Apley	Major surgery, organic disease, medication, lactose intol, const/diarrh, psychiatric disorder/DD	Cognitive/behavioral vs SPC	Parent pain diary (VAS) Parent pain observation Maternal care giving Child self-coping/adjustment Missed activities Treatment expectancy Measure of relapse	CBCL	RAP	Tertiary care and psychology
9	Humphreys and Gevirtz ⁵²	N = 61 F = 15 F+BF = 15 F+BF+CBI = 16 F+BF+CBI + Parent = 15	n = 61 n = 15 n = 15 n = 16 n = 15	4-18	Diagnosed RAP	None listed	10 g F (control) × 8 wk F+BF F+BF+CBI F+BF+CBI+Parent	Parent satisfaction Child pain diary Parent pain observation Medications Medical services School attendance	None	RAP	General public
10	Kline et al ⁵⁴	N = 42 n = 21	n = 42 n = 21	8-12	Manning/Rome, pain × 2 wk	<8, <30 kg, medications, chronic disease	Peppermint oil × 2 wk	GI Symptom Rating Scale Severity of symptoms—(1-5) Change symptoms—(1-5) Daily pain diaries Other life variables	None	IBS	Tertiary care

GI indicates gastrointestinal; IBS, irritable bowel syndrome; GU, genitourinary; abnl, abnormal; PFS, pain frequency score; PSS, pain severity score; PIS, peptic index score; HA, headache; F, fiber; Lac Intol, lactose intolerance; Lac Tol, lactose tolerance; DD, developmental delay; VAS, visual analog scale; BF, biofeedback; CBI, cognitive behavioral intervention; RBPC, Revised Behavioral Problems Checklist; CBCL, Child Behavior Checklist; CTRS, Conner's Teacher Rating Scale.

abdominal pain severe enough to affect activity for at least 3 months' duration, and had dyspeptic symptoms.

Exclusion Criteria

Children were excluded when they had abnormal stooling patterns; evidence of a gastrointestinal disorder on history and physical examination; overt psychological, genitourinary, or other systemic problems; any abnormal laboratory results (complete blood count, erythrocyte sedimentation rate, biochemical profile, and liver function tests); positive stool examination for ova and parasites or *Giardia* antigen; occult blood in the stool; or received acid suppressive therapy for the month before beginning the trial.

Outcomes Measured

Two primary outcome measures were used to assess the therapeutic outcome, a quantitative scoring system and a global assessment. The quantitative scoring system, termed abdominal pain score, was obtained by patient report and composed of 3 separate subscores: pain frequency score, pain severity score, and the peptic index score. The peptic index score consisted of such symptoms as nausea, vomiting, chest pain, epigastric pain, decreased appetite, weight loss, and nocturnal awakening. These were obtained at baseline, after treatment period 1, and at the end of treatment period 2. This scoring system apparently had not been validated for this use in this population. The global assessment was completed by asking each patient at the end of each treatment phase of the study, "Since the trial began, have you felt: better/not better/worse?"

Results

Famotidine was found to be superior to placebo by the global assessment, with 68% of children reporting improvement after famotidine and only 12% of placebo-treated children reporting improvement (McNemar ratio for improvement: 5.67; 95% confidence interval: 1.64–30.18). However, when the pre- and posttreatment abdominal pain scores were compared, there was no statistically significant difference between the 2 treatment groups (famotidine versus placebo: 3.37 ± 3.53 vs 1.66 ± 2.7 ; $P = .16$ by paired t test). Because this medication was hypothesized to have its therapeutic effect primarily on the dyspeptic symptoms, a third, post hoc analysis was completed by comparing the change in the peptic index subscore by treatment group among children with high peptic index scores at baseline. Within this subgroup was a significant decrease in the peptic index score among children who received famotidine compared with placebo ($P = .01$).

Conclusion

These findings suggest that famotidine may be effective in children with RAP, especially when dyspeptic symptoms dominate the clinical presentation.

Pizotifen

Pizotifen, a serotonin antagonist, has been found to be effective in migraine prophylaxis in studies on adults.⁴¹ Although these results have not been duplicated in studies on children,⁴² clinical practice, nev-

ertheless, has found this drug to be effective for migraine in children.⁴³ Because of these clinical findings, this study was undertaken to evaluate its effectiveness in preventing abdominal migraines in children. Pizotifen was tested on 14 children in a randomized, double-blind, crossover trial.¹¹ The child was initially given 5 mL (0.25 mg) of pizotifen twice daily or the placebo for 1 month. If no improvement of symptoms were reported, then the frequency was increased to 3 times a day for the second month. Crossover occurred without a washout period in the third and fourth months.

Inclusion Criteria

Children who were eligible for the study were 5 to 13 years of age, had recurrent central abdominal pain with radiation present for at least 6 months, had pain occurring at least twice monthly, with attacks lasting at least 2 hours. In addition, abdominal pain had to be accompanied by facial pallor, and the patient had to have either 1 first-degree relative or 2 second-degree relatives with a history of migraine or recurrent throbbing headache. There were no features to suggest structural disease.

Exclusion Criteria

Children were excluded when there were any abnormal laboratory results (complete blood count, erythrocyte sedimentation rate, biochemical screen, urine culture) or findings on physical examination.

Outcomes Measured

Two primary indices were used to assess the effects of the drug on the severity of the pain attacks: the index of severity and the index of total misery. The index of severity was calculated by assigning 1 point for a "mild attack," 2 points for a "moderate attack," or 3 points for a "severe attack." This index was the summation for all attacks during the treatment trial. The index of total misery was the product of the severity index and the duration of the pain attacks totaled over the duration of the treatment trial.

Results

Patients who received pizotifen had fewer days of abdominal pain (4.29 vs 12.5; $t = 3.37$, $P < .005$), a lower index of severity (7.29 vs 23.5; $t = 3.4$, $P < .005$), and a lower index of misery (25.43 vs 81.5; $t = 3.19$, $P < .007$) as compared with placebo. The only side effects noted while taking pizotifen were slight drowsiness and slight weight gain (1.25 kg vs 0.38 kg placebo; $P = .039$).

Conclusion

Despite the small sample size, these findings suggest that pizotifen might be an effective treatment when used prophylactically in children specifically with abdominal migraine. Pizotifen, available worldwide but not approved for use in the United States, has known side effects of drowsiness, change in appetite, and gastrointestinal disturbances.¹⁰

Diet

Four studies that used dietary interventions as treatment for children with RAP were identified. Two assessed the effectiveness of added fiber, and 2 assessed the effects of a lactose-free diet. Studies

have shown that adults with IBS tend to experience relief of symptoms when on a high-fiber diet.⁴⁴ Symptom resolution was not guaranteed, however, for those placed on a lactose-free diet,⁴⁵ thus the interest in evaluating these therapies in children.

Dietary Fiber: Feldman et al

The addition of 10 g of insoluble dietary corn fiber in a cookie form was tested on 52 children in a randomized, double-blind, placebo-controlled trial.⁴⁶ Children received either the 5-g high fiber cookie or a placebo cookie twice daily for 6 weeks.

Inclusion Criteria

Children who were eligible for the study were between 5 and 15 years of age, had at least 1 attack of unexplained abdominal pain per week over at least 2 months, and had pain that was severe enough to affect activity.

Exclusion Criteria

A child was excluded when there had been weight loss since the onset of pain; the child had abnormal laboratory results (hemoglobin, erythrocyte sedimentation rate, urinalysis); or the child had obvious developmental, emotional, or behavioral problems.

Outcomes Measured

The primary outcomes measured were the frequency of pain attacks—specifically, a 50% decrease—and change in pain intensity as rated on a 5-point scale.

Results

Feldman et al⁴⁶ reported that their results showed a significant difference between the fiber and placebo groups. The percentage of those with the fiber intervention having at least a 50% decrease of pain episodes was 50% compared with only 27% in the placebo group ($P < .05$). Less severe pain was noted in the fiber group; however, the differences between the 2 groups were not significant. The degree of compliance and incidence of side effects between the 2 groups were similar. Although not mentioned in the original study, it was recently reported that the P value was calculated from a 1-sided statistic.⁴⁷ Reanalysis of the same data found no difference between the 2 treatment groups.

Dietary Fiber: Christiansen

Forty children received either ispaghula husks or placebo, given in the form of cereal, 250 g twice daily for 7 weeks.^{47,48} The ispaghula husks had a fiber content of 66% (165 g per serving), and the placebo had only 2% (5 g per serving). This was stated to be a randomized, double-blind, controlled study, although randomization was not clear.

Inclusion Criteria

Children who had recently been discharged from the hospital with a diagnosis of RAP and were aged 3 to 15 years were included. They had had at least 2 pain episodes in the preceding 6 weeks sufficient enough to affect activity.

Exclusion Criteria

Those children evaluated and found to have an organic disease.

Outcomes Measured

The primary outcome measured was the number of pain episodes, as reported by parents, in the final 6 weeks of the 7-week intervention.

Results

Thirty-one children completed the investigation: 15 in the active group and 16 in the placebo group. Nine were excluded for failure to complete the interventions or the outcome data. The mean number of pain episodes in the active group was 13.5 during those 6 weeks and 13 in the placebo group. No standard deviations or baseline data were reported, limiting comparisons in this study.

Conclusion

The evidence supporting the use of fiber in RAP is, at best, weak and, at worse, inconclusive. Nevertheless, the addition of fiber each day seems to be a simple and inexpensive intervention that might benefit some children with RAP. Furthermore, insoluble fiber can be obtained through the diet with high-fiber cereals; bran muffins; whole-grain products; and fruits, vegetables, and legumes to approximate 10 g/d.

Lactose Avoidance: Lebenthal et al

Sixty-nine children who had a diagnosis of RAP and had lactose tolerance testing were admitted to the diet trial that consisted of 3- to 6-week segments.⁴⁹ Subjects completed these 3 trials in a random order: trial 1, normal diet that included lactose (considered baseline); trial 2, lactose-free diet plus 400 mL/d a lactose-containing formula; and trial 3, lactose-free diet plus 400 mL/d lactose-free formula. In addition, many of these children were maintained on a lactose-free diet for 12 months and followed to assess for ongoing pain.

Inclusion Criteria

Children who were aged 6 to 14 years and of Anglo-Saxon, Irish, Italian, and Polish extraction were included in the study. Diagnosis of RAP was determined by the history of intermittent episodes of abdominal pain of at least 4 months' duration, severe enough to interfere with activities, and no evidence of organic disease.

Exclusion Criteria

Evidence of abnormal laboratory tests: hemoglobin, urinalysis with culture, sedimentation rate, stool for occult blood.

Outcomes Measured

Pain episodes, as recorded by the parents, were recorded for each 6-week period with baseline being the trial of normal eating patterns. The frequency of abdominal pain was considered increased when the number of episodes was 20% greater than the baseline value.

Results

Only 38 subjects completed the study satisfactorily; 31 had been eliminated because of poor compliance. Of those 38, 21 were identified by lactose tolerance testing as being lactose malabsorbers and 17 as lactose absorbers. Ten (47.6%) of the 21 malabsorbers reported increased pain with the lactose formula, and 7 (33.3%) of 21 reported increased pain with the

nonlactose formula. In the lactose absorbers, 4 (23.5%) of 17 reported increased pain with lactose formula, and 4 (23.5%) of 17 reported increased pain with the nonlactose formula. For those who were followed for 12 months on a lactose-free diet, 6 (40%) of 15 malabsorbers were pain-free and 5 (38%) of 13 lactose absorbers were pain-free.

Lactose Avoidance: Dearlove et al

A total of 2 g/kg lactose or placebo tonic were given to 21 children for 2 weeks.⁵⁰ This followed a 2-week baseline period of the child's regular diet and a 2-week period of a lactose-free diet, which was maintained during the intervention. The lactose and placebo were allocated at random using a double-blind, single crossover design. Eighteen children with RAP received no intervention and served as controls.

Inclusion Criteria

Children who were older than 3 years and had abdominal pain more than once every 4 days for at least 3 months were included.

Exclusion Criteria

None listed.

Outcomes Measured

Global outcome was assessed after 3 months to the question of whether the child's symptoms were better, worse, or the same. Children in the intervention group were categorized as lactose intolerant or lactose tolerant and compared with children in the control group.

Results

During the diet trials, there were no differences in the number of children who claimed relief, whether they were lactose intolerant or tolerant or whether they received lactose or lactose-free tonic. After 3 months, 9 (44%) of 21 children in the intervention group improved and 8 (44%) of 18 in the control group improved.

Conclusion

There seems to be no association between recurrent abdominal pain in children and lactose intolerance, and a lactose-free diet is unlikely to improve the symptoms of RAP.

Behavioral Interventions Only

Behavioral techniques have been used with the idea that pain behaviors produce secondary gain (special attention, school avoidance, etc.) that reinforces the pain behaviors.⁴ Two methodologically strong studies evaluated the use of cognitive-behavioral interventions among children with RAP.^{4,51} Both studies were completed by the same group of researchers and used a similar intervention. The first study used a smaller sample size and a wait-list control group, whereas the second study included a larger sample size and compared the intervention with standard pediatric care (SPC).

Cognitive-Behavioral Therapy: Sanders et al First Study

A multicomponent treatment program was used on 16 children and consisted of reinforcement of well behavior, distraction, and cognitive coping skills

training (self-efficacy statements, self-induced relaxation, self-administration of rewards).⁵¹ This was done in a randomized, wait-list control trial that lasted 8 weeks. The control group was asked to manage the child's pain complaints in their usual manner. No methods of blinding or the attempts thereof were mentioned in the study.

Inclusion Criteria

Children who were 6 to 12 years of age, had periodic abdominal pain of >3 episodes during 3 months' time, and had pain severe enough to interfere with the child's daily activities were included in the study. Each child was evaluated, but none met the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition*, criteria for major psychopathology, ie, major depression, anxiety disorder, conduct disorder, or specific learning disabilities.

Exclusion Criteria

Children were excluded when they had had major surgery, a major medical illness, lactose intolerance, constipation, a recent viral illness, or persistent diarrhea.

Outcomes Measured

Daily pain diaries done by the patient were used to assess pain frequency, and a visual analog scale was used to measure pain intensity. Parent pain observation recorded the presence or absence of pain behavior while the child was at home. A teacher's pain observation diary recorded the child's verbal complaints of pain while the child was at school. Parent-child interactions were observed by researchers in the home to assess oppositional child behavior and aversive parent behavior. The Revised Behavioral Problem Checklist and Conner's Teacher's Rating Scale were also used.

Results

A decrease in pain reports of the treatment group was significant for both the child's reports ($F[1,12] = 8.57; P < .01$) and parent observation ($F[1,12] = 5.53; P < .04$) when compared with the treatment group at the end of the treatment phase. There continued to be a significant decrease of pain reports by the child at 2 weeks posttreatment ($F[1,12] = 6.47; P < .02$). At posttreatment, the number of pain-free children in the treatment group was 75%, which increased to 87.5% by follow-up 3 months later. The corresponding figures for the control group were 25% and 37.5%. Furthermore, teachers observed an improvement in the treatment group at the 3-month follow-up in comparison with pretreatment measures and noted a slight deterioration in the control group ($F[1,13] = 5.21; P < .05$). Parent-child interaction, problem behaviors in the Revised Behavioral Problem Checklist, and teachers' ratings on the Conner's Teacher's Rating Scale showed no significant differences between groups. There was no evidence that this treatment resulted in any negative side effects.

Cognitive-Behavioral Therapy: Sanders et al Second Study

Cognitive-behavioral family intervention (CBFI) was compared with SPC in 44 children who were randomly allocated to these 2 groups and followed over time.⁴ The CBFI in this study included 6 ses-

sions with a practitioner who provided an explanation of RAP with rationale for pain management procedures, contingency management training for parents, and self-management training for children. SPC consisted of 4 to 6 sessions with a physician to develop a caring, supportive therapeutic relationship and to offer reassurance that no serious organic disease was present even though the pain was real; that most children grow out of it; and that children must learn to cope with the pain themselves. No mention of attempts for blinding was mentioned.

Inclusion Criteria

Children who were eligible for the study were 7 to 14 years of age and had paroxysmal abdominal pain that occurred at least 3 times during a 3-month period with pain severe enough to interfere with the child's daily activities.

Exclusion Criteria

Children were excluded when they had had major surgery or a major medical illness; were on medication or receiving medical treatment elsewhere; or had lactose intolerance, constipation, a recent viral illness, persistent diarrhea, or a diagnosis of a specific learning disability. Also excluded were those who met diagnostic criteria for affective disorder, conduct disorder, oppositional defiant disorder, psychosis, or developmental disorder or those who were suspected of being sexually abused and had been assessed via a structured intake interview. None of the children who were referred to the project was excluded on these grounds.

Outcomes Measured

The main outcomes measured in this study were the patient's report of pain intensity using a visual analog scale recorded on a daily diary, parent observation of pain behavior, assessment of maternal caregiving, assessment of children's self-coping, measures of child adjustment, measures of treatment expectancies of the parent, measures of relapse, and measures of parent satisfaction with the treatment. Each was measured at pretreatment, posttreatment (which was approximately 8 weeks), and follow-up at 6 months and 12 months.

Results

A total of 55% of the CBFI children were pain-free compared with only 23.8% in the SPC group at posttreatment ($\chi^2[1, N = 39] = 4.02; P = .04$) with those percentages increasing to 66.7% and 27.8%, respectively, at the 6-month follow-up ($\chi^2[1, N = 39] = 5.31; P = .02$). On the parent observation report of pain behavior, there were significantly more pain-free children in the CBFI group (70%) compared with SPC (38.1%) at posttreatment ($\chi^2[1, N = 38] = 3.87; P = .05$) and at 12 months (82.4% vs 42.1%; $\chi^2[1, N = 36] = 5.96; P = .01$). In terms of expectancies for change, mothers in both groups were moderately confident of a favorable outcome. A 2×2 analysis of variance showed no significant differences in mothers' expectations. Mothers in the CBFI group had a significantly higher rating of both the quality of service received ($t[22] = -2.34; P = .02$) and overall satisfaction ($t[22] = -2.36; P = .03$) than mothers in the SPC group. Children and parents in the CBFI

group reported lower levels of relapse (child: $P = .03$; parent: $P = .05$) and pain interfering with child's daily activity (child: $P = .003$; parent: $P = .04$) when compared with the SPC group at the 12-month follow-up.

Conclusion

These results show the value of using cognitive-behavioral therapy to reduce or eliminate pain in children with RAP. It also highlights the usefulness of involving the parent in supporting their child's self-management behavior. Furthermore, there were no negative side effects or symptom substitution with these interventions.

Behavioral Intervention with Fiber Control

One study used behavioral interventions along with fiber as the control. Because dietary fiber had been shown to be more effective than placebo in a previous study,⁴⁶ a fiber-only comparison group was used as the minimal treatment condition (control).

Behavioral Intervention

A total of 61 children were randomized into 1 of 4 groups: 1) fiber only—10 g/d—control group; 2) fiber plus biofeedback (BF); 3) fiber, BF, and cognitive-behavioral intervention (CBI); or 4) fiber, BF, CBI, and parental support.⁵² The treatment period was for 8 weeks. CBI included relaxation training, self-management techniques, and coping skills, and parental support included distraction techniques and caregiving strategies.

Inclusion Criteria

Eligible children were between 4 and 18 years of age and had the medical diagnosis of RAP—not specifically characterized to a functional gastrointestinal disorder outlined by Rome II.

Exclusion Criteria

Anyone unwilling to take the 10 g/d dietary fiber. No other exclusion criteria were mentioned.

Outcomes Measured

The main outcome measures included self-reported pain, parent observation, medication use, health care utilization, and school attendance. These were measured at baseline (pretreatment) and at the end of the treatment period.

Results

The main effects for pre- versus posttreatment were found for self-reported pain ($F[1,43] = 117.19; P < .001$), parent's observation of the child asking for help ($F[1,43] = 7.64; P < .01$), child's report of pain to parents ($F[1,43] = 22.83; P < .001$), RAP medication reduction use ($F[1,43] = 11.86; P < .001$), and school absences ($F[1,43] = 8.53; P < .01$) indicating improvement in all groups. Comparisons were then done between the combination treatment groups and the fiber-only group to evaluate the effects of active treatment versus control. The combined groups showed more improvement than the fiber-only group on self-reported pain ($F[1,59] = 10.20; P = .002$). A total of 72% of the treatment participants reported elimination of pain compared with only 7% in the fiber-only comparison group.

Conclusion

The results of this study suggest that the combination of self-regulation and cognitive-behavioral therapies along with fiber intervention may be more effective for treating RAP rather than using fiber alone.

Botanicals

One study evaluated the use of peppermint oil for the treatment of IBS. Other studies in the literature have assessed the benefits of botanicals in functional gastrointestinal disorders^{30,53}; however, this was the first conducted in children.

Peppermint Oil

Peppermint oil in the form of a pH-dependent, enteric-coated capsule was used against placebo in a randomized, double-blind, controlled trial in 50 children with IBS.⁵⁴ Each capsule contained 187 mg of peppermint oil. Subjects >45 kg were given 2 capsules of either the peppermint or placebo 3 times a day for 2 weeks. For those children 30 to 45 kg, only 1 capsule was given 3 times a day.

Inclusion Criteria

All children had a previous diagnosis of IBS by either the Manning or Rome criteria and were 8 to 12 years of age with symptoms and pain in the preceding 2 weeks before entering the study.

Exclusion Criteria

Children were excluded when they were younger than 8 years, weighed <30 kg, had another chronic disease, or were on medication for IBS or one that could potentially affect abdominal symptoms.

Outcomes Measured

The primary outcome was to assess changes in the severity of symptoms that included abdominal pain, stool patterns, abdominal rumbling, gas, nausea, belching, urgency for defecation, heartburn, and abdominal distention. A change of symptom scale from "much worse" to "no effect" to "much better" was used to rank these symptoms. Pretreatment and posttreatment measures of symptoms using this scale and daily pain diaries were obtained and compared.

Results

Of the 50 recruited, 42 completed the study. Reasons for withdrawal were travel limitations, use of erythromycin, and inability to swallow pills. At the conclusion of the 2-week trial, 76% of patients who received peppermint oil reported decreases in the severity of symptoms compared with only 19% who received placebo ($\chi^2[6, N = 42] = 12.6; P < .001$). Improvements in the change of symptom scale were reported in 71% of the peppermint oil group versus 43% in the placebo group ($\chi^2[6, N = 42] = 9.5; P < .002$). The daily pain diaries recorded by the patients showed that the mean severity of pain was significantly lower for the peppermint oil group than for the placebo group ($t[60] = 1.99; P < .03$). The peppermint oil did not alter other symptoms, eg, heartburn, gas, stool patterns, consistency.

Conclusion

The use of a pH-dependent peppermint oil capsule seemed to reduce the pain that children experienced during the acute phases of RAP/IBS. The mechanism of action is thought to be from the menthol component of peppermint that causes inhibition of smooth muscle contractions by blocking calcium channels.⁵⁵ Peppermint also has a mild topical anesthetic affect and so, presumably, reduces pain locally as it is released and coats the lower intestine.⁵⁴

Effect Sizes

We calculated effect sizes for four double-blinded, placebo-controlled trials (Table 2). Effect size is an important tool for judging the effectiveness of a therapy. It tells us the standardized mean difference between the treatment and control groups. The larger the effect size, the greater the difference between the 2 groups. We chose these studies because all of the information needed for effect size calculations was available. The 13 outcomes in these studies were coded for outcome type (frequency of pain, intensity of pain, or medical occurrences) and rater (parent, child, or clinician). Intensity of stomach pain was used as the outcome measure more than half of the time. Of the 13 outcomes, 3 were reported as nonsignificant. For summary statistics, we estimated

TABLE 2. Effect Sizes for Randomized Placebo-Controlled Studies

First Author	Intervention	Treatment Sample Size	Control Sample Size	Effect Size	Method	Rater	Outcome*
Feldman	Fiber	26	26	0.55	Frequency	Child	Frequency of pain
Feldman	Fiber	26	26	NS	Intensity	Child	Intensity of pain
Kline	Peppermint	21	21	1.31	Intensity	Clinician	Change in severity of symptoms
Kline	Peppermint	21	21	1.08	Intensity	Clinician	Change of symptom scale
Kline	Peppermint	21	21	NS	Intensity	Clinician	GSRs
Kline	Peppermint	21	21	2.25	Intensity	Child	Severity of pain symptoms
Kline	Peppermint	21	21	NS	Medical	Child	Life variables
See	Famotidine	25	25	0.54	Frequency and Intensity	Parent and child	Change in abdominal pain score
See†	Famotidine	13	13	0.99	Frequency and Intensity	Parent and child	Change in abdominal pain score
See	Famotidine	25	25	0.42	Intensity	Child	Global improvement outcome
Symond	Pizotifen	14	14	0.90	Frequency	Parent and child	Frequency of pain
Symond	Pizotifen	14	14	0.91	Intensity Frequency	Parent and child	Intensity of pain
Symond	Pizotifen	14	14	0.85	Frequency and Intensity	Parent and child	Index of misery

GSRs indicates GI Symptom Rating Scale.

* Each study had more than 1 outcome variable.

† Subset of children with high PIS.

these nonsignificant effect sizes at 0. The average effect size for the 13 outcome measures in the 4 double-blinded, placebo-controlled studies was 0.75 (standard deviation: 0.62). We also estimated outcomes for the studies without placebo control groups and found a similar effect size.

DISCUSSION

This literature review identified a small number of methodologically sound investigations of various therapies for children with functional gastrointestinal disorders. It is interesting that the types of interventions found to be efficacious varied widely, including histamine and serotonin antagonists, dietary management, behavioral interventions, and botanicals. Although the underlying biological mechanism for each therapy is not fully understood, each mechanism is likely different from one another.

The studies that had the largest effect sizes were those therapies that targeted specific functional gastrointestinal disorders (famotidine for dyspepsia, pizotifen for abdominal migraine, peppermint oil for IBS). The patients in the dietary and behavioral studies were not fully characterized by symptoms, but it is likely that the studies had a mixture of the various subgroups of functional gastrointestinal disorders in their study populations, thereby imparting more generalized effects. Identifying specific functional disorders using the Rome II classifications may be helpful to clinicians who treat children with RAP by targeting therapy that is most effective for their symptoms.

The behavioral studies reviewed used self-monitoring, relaxation training, coping skills, and positive imagery skills that benefited children with RAP. From what we now know about the brain-gut interactions, it makes sense that “mind-body” therapies—those therapies that encourage self-regulation—could be efficacious in the treatment of RAP. Mind-body therapies have been found to be beneficial in children with other chronic disorders, such as migraine, pain associated with medical procedures, and cystic fibrosis.^{56–58} One recent case series described the successful use of self-hypnosis in 4 of 5 children with functional abdominal pain.³⁵ Nevertheless, such techniques have not been vigorously tested in large numbers of children with functional abdominal disorders.

CBIs, with and without dietary management, were found to be beneficial in the treatment of children with RAP. These studies, published in psychological journals, likely were not read by practicing pediatricians as a means to expand their repertoire of treatments for RAP. This is important because a recent survey of practicing pediatricians found that pediatricians rarely consulted mental health professionals in the management of RAP.⁵ The primary reasons cited for the lack of referrals were concerns about cost, family resistance, and personal beliefs about the natural course of the disorder. Unfortunately, these barriers could potentially impede the process of finding appropriate and cost-effective therapy for children with RAP. There is evidence in the adult literature that management of functional disorders by the

physician in collaboration with a mental health professional may reduce health care costs.⁵⁹ Incorporating mental health evaluations and treatments early in the management of children with RAP could facilitate symptom resolution by integrating the coping and self-management skills with other interventions, such as dietary, pharmaceutical, or botanical therapies.

Completing a systematic review of therapies for RAP was challenging because of few RCTs, the lack of standardization of inclusion/exclusion criteria used for the studies, and varying criteria for ruling out organic disease. Rather than strictly using Apley’s criteria, various interpretations of the definition and classification of RAP also lead to discrepancies in sample selections across studies. More good quality studies with larger populations need to be conducted to further our understanding and thus treatments of RAP. Using the recommendations outlined in Rome II may help in the design of future research studies so as to bring clarity to the selection of subjects, target therapies that would be more specific to the functional groups, and facilitate the formulation of more specific measures of outcomes.

Having multiple outcomes measured in the various studies was an additional challenge to doing this review. Thirty-nine treatment outcomes were reported in the 10 articles included in this review. Having standardized outcomes would lend itself to understanding the effects of various interventions used in studying RAP so that one could more effectively compare treatments across studies. Although the Rome II panel identified the need for standardized outcome measures, they could not agree on what specific outcomes should be used.⁶⁰ Nevertheless, they did agree that outcomes should be reported by the patient rather than by the clinician or the researcher; a standardized scale should be used to measure pain episodes; and a predefined criterion of clinical significance should be used with efficacy on the basis of the percentage of patients who meet that criterion. In addition, because Apley’s original definition of RAP referred to painful episodes that interfere with normal activities, we believe that some measure of disability, such as school absences, should also be reported. The majority of the studies reviewed here did not include a measure of disability.

Despite the many outcomes measured in these reviewed studies, there also was a general lack of psychological measures, which was surprising given previous studies that show children with RAP, when compared with well children, have higher levels of anxiety, depression, and somatization symptoms.^{3,61,62} These comorbid states need to be consistently evaluated in an objective way in children with RAP as these states might affect the response to therapy and vice versa.

Despite these identified methodologic challenges, evidenced-based therapies, although weak as a result of the small numbers, were identified for RAP. The rather diverse group of therapies most likely reflects the heterogeneous group of functional disorders that present as recurrent abdominal pain during child-

hood. It is expected that greater use of the Rome II diagnostic criteria will help with the diagnosis as well as the treatment of this disorder. It is also apparent that pediatricians will probably be required to expand their comfort level beyond the use of conventional modalities to care optimally for this group of children.

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