

## Overview of Reviews

# The Cochrane Library and the Treatment of Chronic Abdominal Pain in Children and Adolescents: An Overview of Reviews

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**Background:** Chronic abdominal pain is a common, disabling and longstanding condition for children and their families that often involves lengthy treatment plans and regular re-evaluation. Chronic abdominal pain refers to both organic and functional pain, although for the majority of children and adolescents, the pain is functional in origin. Clinicians often feel pressure from parents to provide some type of treatment, and a large number of interventions are used in an attempt to decrease associated symptoms and functional impairment. Substantial variation in the treatment of childhood chronic abdominal pain currently exists.

**Objectives:** This overview of reviews aims to synthesize evidence from the Cochrane Database of Systematic Reviews (CDSR) on the efficacy and safety of various dietary, pharmacological and psychological interventions for the treatment of chronic abdominal pain in children and adolescents.

**Methods:** Issue 5, 2011 of the CDSR was searched for all reviews examining pharmacologic or non-pharmacologic treatments for chronic abdominal pain in children and adolescents. All relevant systematic reviews were included, and data were extracted, compiled into tables and synthesized using qualitative and quantitative methods.

**Main Results:** Five reviews containing 19 pediatric trials and 777 participants were included in this overview. In one small trial ( $n = 64$ ), post-treatment pain scores and school absences decreased significantly when children received combined cognitive behavioural therapy (CBT), biofeedback, parental support and fibre compared to fibre alone. In two small trials ( $n = 47$ ;  $n = 69$ ), internet CBT compared to standard pediatric care significantly decreased pain at follow-up and family CBT versus standard care significantly decreased school absences. In adolescents, two small trials ( $n = 33$ ;  $n = 90$ ) found that treatment with amitriptyline compared to placebo had a limited effect on some, but not all, measured outcomes. Data on adverse events were generally lacking for all dietary and psychological interventions; for pharmacological interventions, no differences in adverse events were reported, with only minor adverse events (i.e. fatigue, rash, headache) reported.

**Authors' Conclusions:** The successful management of chronic abdominal pain requires a comprehensive, multifaceted approach. The current evidence, albeit limited, suggests that CBT may be effective and that refocusing the patient and family on coping strategies as well as emphasizing normal childhood functioning can have positive results. As such, psychological treatments such as CBT look promising for the treatment of childhood chronic abdominal pain. If pharmacological interventions are considered, current evidence may support a trial of amitriptyline for adolescents with irritable bowel syndrome. However, both of these conclusions are based on a small number of short-duration trials that are at high or unclear risk of bias. Overall, conclusive evidence is lacking to support dietary, pharmacological and psychological interventions. Future high-quality, adequately powered trials are eagerly awaited.

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**Editors' Note:** Overviews of reviews, compiling evidence from multiple Cochrane reviews into one

accessible and usable document, are a regular feature of this journal. Our aim for each overview is to focus on the treatment question, 'which treatment should I use for this condition?', and to highlight the Cochrane reviews and their results in doing so. It is our hope

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*that the overview will serve as a 'friendly front end' to the Cochrane Library, allowing the reader a quick overview (and an exhaustive list) of Cochrane reviews relevant to the clinical decision at hand.*

## Plain Language Summary

Unfortunately, a number of children and teenagers experience pain in the abdomen that lasts for many months and does not go away. The current research suggests that changing a child's diet, on its own (e.g. by adding fibre to the diet), will not help the child get better. An antidepressant medication called amitriptyline might help some children, particularly teenagers, feel better, but there is not enough research to know if this medication is the right choice for most children. Current research suggests that a psychological treatment called 'cognitive behavioural therapy' (CBT) may help children with long-lasting abdominal pain. This treatment is designed to help replace upsetting thoughts about the pain with more positive ones, and even though the child's pain might not go away completely, treatment with CBT may help them return to some of his or her normal daily activities. Unfortunately, the studies we reviewed did not really examine the side-effects associated with these treatments, so we do not know if these treatments are safe. To be able to treat children with chronic abdominal pain properly, we need to have more high quality research, because there is currently very little information available.

## Background

### Description of the condition

Chronic abdominal pain was first described by Apley over 50 years ago and defined as a minimum of three episodes of pain over a period of three months, with the pain being severe enough to interfere with functioning (1). More recently, the American Academy of Pediatrics and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition suggest that abdominal pain that exceeds two months in duration can be considered chronic (2). These definitions include both organic and functional pain, where functional abdominal pain refers to pain with no evidence of pathology or anatomic, metabolic, infectious or inflammatory disease (2, 3). In the literature, several terms are used to describe populations with non-acute abdominal pain, and most reports use the terms 'recurrent abdominal pain' or 'functional abdominal pain'. In this overview we will use the term 'chronic abdominal pain' to refer to both organic and functional pain.

The majority of children who present with chronic abdominal pain experience functional pain (4), and the definition of functional abdominal pain has recently been updated in the Rome III criteria (3). The Rome III criteria recognize five types of chronic childhood

abdominal pain: functional dyspepsia, irritable bowel syndrome, abdominal migraine, childhood functional abdominal pain and childhood functional abdominal pain syndrome (Figure 1). The pathophysiologies of organic and functional chronic abdominal pain differ. Organic abdominal pain can be caused by various anatomic (e.g. malrotation), gastrointestinal (e.g. cholecystitis), genitourinary (e.g. ovarian cysts, renal calculi), infectious (e.g. helicobacter pylori infection), inflammatory (e.g. inflammatory bowel disease), metabolic (e.g. acute intermittent porphyria) or systemic disorders (e.g. food allergy, Henoch-Schönlein purpura) (5, 6). The pathophysiology of functional abdominal pain is often less clear, and may include enteric nervous system abnormalities, dysregulation of the brain-gut axis, decreased pain thresholds, low-grade intestinal inflammation, and abnormal bowel sensitivity to physiologic stimuli. However, the underlying pathology is often not sufficient to explain the severity of symptoms or level of impairment (7–9). Functional abdominal pain in children may also be influenced by psychological factors such as stressful family or psychosocial situations, or psychological conditions such as anxiety and depressive disorders (2, 8).

Differences in diagnostic criteria have led to some uncertainty around the reported prevalence of chronic abdominal pain. Most prevalence estimates range from 10% to 15% in school-aged children (10–13), with some estimates as low as 4% and as high as 25% (14, 15). Chronic abdominal pain is more common in girls, and as children grow older its prevalence decreases even further in boys (10, 16). Every year, approximately 8% of children visit a doctor with symptoms of chronic abdominal pain (17), accounting for 2% to 4% of all pediatric visits (18).

Chronic abdominal pain can be associated with other functional symptoms such as headaches, nausea, vomiting, anorexia, arthralgia, eye problems, excessive gas, altered bowel movements, constipation or diarrhoea (2, 4). Patients with chronic abdominal pain often have co-morbid symptoms of depression and anxiety in childhood (4, 19, 20), which can progress to one or more psychiatric diagnoses in adulthood (21). Although many children with chronic abdominal pain will improve with time, between 24% and 45% of children will continue to experience abdominal symptoms after five years (22, 23), necessitating ongoing treatment and re-evaluation.

### Description of the interventions

The current treatment of chronic abdominal pain is controversial. While functional abdominal pain is neither life-threatening nor associated with significant organic pathology, the symptoms cause considerable discomfort, pain, distress and functional impairment. It is also frequently accompanied by significant parental worry and clinician concern (2, 24). There is substantial variation in the management of chronic abdominal

<b>Functional dyspepsia</b>	<b>Irritable bowel syndrome</b>	<b>Abdominal migraine</b>	<b>Childhood functional abdominal pain</b>	<b>Childhood functional abdominal pain syndrome</b>
<p>1. Persistent or recurrent pain or discomfort centred in the upper abdomen (above the umbilicus);</p> <p>2. Not relieved by defecation or associated with the onset of a change in stool frequency or stool form.</p>	<p>Abdominal discomfort or pain associated with two or more of the following at least 25% of the time:</p> <ol style="list-style-type: none"> <li>1. Improvement with defecation;</li> <li>2. Onset associated with a change in frequency of stool;</li> <li>3. Onset associated with a change in form (appearance) of stool.</li> </ol>	<p>1. Paroxysmal episodes of intense, acute, periumbilical pain that last for one hour or more; Intervening periods of usual health lasting weeks to months;</p> <p>2. The pain interferes with normal activities;</p> <p>3. The pain is associated with two of the following: anorexia/weight loss, nausea, vomiting, headache, photophobia and pallor.</p> <p>No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the child's symptoms.</p>	<p>1. Episodic or continuous abdominal pain;</p> <p>2. Insufficient criteria for other functional gastrointestinal disorders.</p>	<p>Must satisfy criteria for childhood functional abdominal pain and have one or more of the following at least 25% of the time:</p> <ol style="list-style-type: none"> <li>1. Some loss of daily functioning</li> <li>2. Additional somatic symptoms such as headache, limb pain or difficulty sleeping.</li> </ol>
Criteria fulfilled at least once per week for at least two months prior to diagnosis.	Criteria fulfilled two or more times in the preceding 12 months.	Criteria fulfilled at least once per week for at least two months prior to diagnosis.	Criteria fulfilled at least once per week for at least two months prior to diagnosis.	The above information has been modified from Rome III: The Functional Gastrointestinal Disorders, Third Edition

**Figure 1.** Rome III diagnostic criteria for functional abdominal pain disorders in children

pain. Clinicians often feel pressure from parents to provide some type of treatment, and a large number of interventions are tried in an attempt to decrease associated symptoms and functional impairment. This overview of treatment strategies examines evidence for various dietary, pharmacological and psychological interventions for chronic abdominal pain in children and adolescents.

### How the interventions might work

#### Dietary interventions

Dietary changes might be advocated for children with chronic abdominal pain so as to modulate exposure to foods that might alleviate or exacerbate symptoms. Because *fibre supplements* have potentially beneficial effects on intestinal transit time and may decrease pain in adults with irritable bowel syndrome (25, 26), it is postulated that they might confer an equivalent clinical benefit in children. The probiotic *Lactobacillus* is a non-pathogenic micro-organism that possesses anti-inflammatory properties through modulation of gut microbiota, and it is thought that its dietary supplementation might help relieve abdominal pain and distension, improve lactose tolerance, increase intestinal peristalsis, accelerate bowel evacuation and alter the volume and composition of stool and gas (27–29). Research has also examined *lactose-free diets*, which are postulated to alleviate excessive bloating, cramping, gas production and diarrhea (30, 31).

#### Pharmacological interventions

Pharmacological interventions for the treatment of childhood chronic abdominal pain often focus on symptom relief and regulation of gastro-intestinal function. The tricyclic antidepressant *amitriptyline* inhibits reuptake of both serotonin and norepinephrine and has the potential to regulate the bidirectional communication of the brain-gut axis and modify intestinal motility (32, 33). H<sub>2</sub>-receptor antagonists, including *famotidine*, inhibit gastric acid production and are commonly used to prevent and heal esophagitis and gastritis. *Peppermint oil* promotes relaxation of gastrointestinal smooth muscle, has carminative and antispasmodic effects, and has been used for irritable bowel syndrome (34, 35). Lastly, *pizotifen* is a serotonin antagonist that is commonly used for migraine prophylaxis. It might confer a similar benefit in children with abdominal pain given the postulated similar pathophysiology of migraine headaches and abdominal migraines (36).

#### Psychological interventions

Due to our better understanding of the complex pathophysiology of chronic pain, treatment approaches for childhood chronic abdominal pain are increasingly moving toward a biopsychosocial approach.

*Biofeedback* is based on the premise that ‘physiological changes result in symptom changes’ (37) and trains patients to control certain physiological processes that normally occur involuntarily. *Hypnotherapy* is characterized by focussed concentration and heightened suggestibility; it aims to relieve anxiety and promote short-term analgesia and long-term pain cessation (38). High parental anxiety sometimes precedes the development of childhood chronic abdominal pain, and *parental support* might successfully decrease parental anxiety and facilitate treatment (39). Lastly, *cognitive behavioural therapy* (CBT) attempts to manage symptoms and restore functioning by incorporating elements of cognitive therapy (e.g. stress management, cognitive restructuring) and behavioural therapy (e.g. relaxation training, behaviour management). It can be directed toward either individuals or families and can be provided in person or via alternate modalities (e.g. the internet).

#### Why it is important to do this overview

Chronic abdominal pain in children is of considerable interest to the medical community due to its high prevalence and the large number of resultant healthcare presentations. The exact cost of childhood chronic abdominal pain in the USA is unknown but is likely substantial, given that the cost for adults with functional gastrointestinal disorders (including irritable bowel syndrome) is an estimated \$8 to \$33 billion per annum (40–43). Total direct costs for adults (e.g. medical services, diagnostic tests, rehabilitation) are thought to range from \$348 to \$8750 per person per year, while indirect costs (e.g. absence from school or work, long-term disability) are estimated at \$355 to \$3344 (44). Clinicians must make difficult treatment decisions when managing a child with chronic abdominal pain, and this overview of reviews aims to present the current body of evidence on the efficacy and safety of various interventions.

#### Objectives

This overview of reviews aims to synthesize the most current evidence in the *Cochrane Database of Systematic Reviews* (CDSR) on the efficacy and safety of dietary, pharmacological and psychological therapies for the treatment of chronic abdominal pain in children and adolescents up to 18 years of age. Treatments could be compared to placebo, no treatment or other active interventions.

#### Methods

##### Criteria for considering reviews for inclusion

Reviews were included if the full-length article was published in the *Cochrane Database of Systematic Reviews* (CDSR) and examined pharmacologic or nonpharmacologic interventions for the

treatment of chronic abdominal pain in children. Reviews examining a broader diagnosis (e.g. 'chronic pain') were included only if there was data related to abdominal pain that could be extracted separately. Reviews containing both adult and pediatric data were included provided the pediatric data could be extracted separately.

### Search methods for identification of reviews

Issue 5, 2011 of the CDSR was searched for all reviews examining the pharmacologic or non-pharmacologic treatment of chronic abdominal pain in children and adolescents. The complete search strategy can be found in Figure 2. We also consulted *The Cochrane Developmental, Psychosocial and Learning Problems Group*, as well as *The Cochrane Pain, Palliative and Supportive Care Group* to ensure that we did not miss any relevant reviews.

### Outcome measures

The following *a priori* outcomes were pre-specified for inclusion in this overview:

- Associated signs and symptoms: pain, vomiting, weight loss, bloating, headache, constipation, diarrhoea, stool frequency and early satiety.
- Improvement (as defined by review authors and trialists).
- Functional disturbances: disability, quality of life, days off work or school and psychosocial symptoms and disorders.
- Administrative outcomes: use of additional medication, health service utilization, treatment satisfaction and number and cost of investigations.
- Adverse events

### Data collection and analysis

#### Inclusion criteria

For this overview, one reviewer (MF) extracted the inclusion criteria (i.e. population, interventions, comparisons and outcomes) and review characteristics (i.e. number of trials, sample sizes) from all included reviews. Two included reviews (45, 46) examined the same intervention, and because they had similar inclusion criteria the reviews contained five overlapping trials (47–51). Both reviews extracted different data from the overlapping trials, therefore all available data are reported in this overview.

#### Methodological quality assessments

All reviews except one (46) used the Cochrane Risk of Bias tool to assess methodological quality of trials. The Cochrane Risk of Bias tool assesses trial quality based on sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other sources of bias (e.g. study design, inappropriate influence of funder or stopping early) (52). According to the Cochrane Risk of Bias tool, each dimension is given a rating of adequate, unclear or inadequate based on the trial characteristics. A trial is rated as having a high risk of bias if it receives one or more ratings of 'inadequate' and is rated as having an unclear risk of bias if it receives one or more ratings of 'unclear' (but no ratings of 'inadequate'). If all dimensions are rated as 'adequate', the trial is assessed as having a low risk of bias.

One reviewer (MF) extracted Risk of Bias assessments from the first review (53). Three reviews (45, 54, 55) provided partial Risk of Bias assessments, therefore the reviewer and a research assistant used the available information to independently score the

Search term	Results
#1 MeSH descriptor Irritable Bowel Syndrome explode all trees	303
#2 MeSH descriptor Constipation explode all trees	726
#3 MeSH descriptor Abdominal Pain explode all trees	820
#4 MeSH descriptor Colonic Diseases, Functional explode all trees	636
#5 "irritable bowel syndrome":ti,ab,kw OR "constipation":ti,ab,kw OR "abdominal pain":ti,ab,kw OR "functional abdominal pain":ti,ab,kw	5142
#6 "recurrent abdominal pain"	56
#7 MeSH descriptor Dyspepsia explode all trees	864
#8 "functional dyspepsia":ti,ab,kw	383
#9 "non?organic abdominal condition":ti,ab,kw	0
#10 "abdominal cramp":ti,ab,kw	45
#11 "gastric pain":ti,ab,kw OR "epigastric pain":ti,ab,kw	483
#12 MeSH descriptor Somatoform Disorders explode all trees	344
#13 "somatoform disorder":ti,ab,kw	30
#14 "apley criteria" OR "rome ? criteria"	40
#15 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14)	130

Figure 2. Search strategy for Issue 5, 2011 of the CDSR

methodological quality of all included trials using the full Risk of Bias criteria. A review by Eccleston *et al.* (46) used the Yates scale to assess methodological quality of trials (56), and to maintain consistency with the other included reviews, the researcher and a research assistant independently scored the trials of this review using the Cochrane Risk of Bias tool. For all methodological quality assessments, discrepancies were resolved through discussion.

#### **Quantitative and qualitative results**

One reviewer (MF) extracted quantitative and qualitative results from all included reviews, and a research assistant subsequently verified data accuracy. Qualitative data were reported in tables with corresponding *p*-values (when available), and quantitative data were reported using effect estimates and 95% confidence intervals (CI). Random effects modelling was used for all quantitative data to determine the most conservative estimate, and when data were presented in the reviews using fixed effects modelling, Review Manager 5 (57) was used to re-analyse the data using random effects modelling.

In this overview, all dichotomous data were summarized using relative risks (RR) with 95% CIs, and were interpreted as statistically significant if the 95% CI did not cross 1. Continuous data were summarized using mean differences (MD) with 95% CIs, and were interpreted as statistically significant if the 95% CI did not cross 0. For all pooled effect estimates, the accompanying  $I^2$  values were reported and represent the degree of statistical heterogeneity between the trials. An  $I^2$  value close to 0% indicates minimal or no heterogeneity of trials, whereas an  $I^2$  of 50% or greater represents substantial heterogeneity (58).  $I^2$  values of 50% or greater were included in the text along with the effect sizes.

## **Results**

### **Results of the search**

The search strategy returned 130 reviews (see Figure 2). Twenty-five of these reviews contained one or more terms in their title which were included in our search strategy, and were therefore deemed potentially relevant. Ten reviews (59–68) and four protocols (69–72) were excluded because they examined the treatment of chronic abdominal pain in adults. One review (73) was excluded because it was withdrawn from *The Cochrane Library* for being out of date, and another review (74) was excluded because it examined a treatment (Tegaserod) that is not approved for sale in Europe or North America.

Four reviews and five protocols examined interventions for chronic abdominal pain in children. The four reviews were included in this overview (45, 46, 54, 55). One protocol (53) was also included because the authors provided us with a peer-reviewed,

pre-publication version of the completed manuscript. The last four protocols (antibiotics, calcium channel blockers, probiotic agents and prokinetic drugs) were excluded because the manuscripts were not yet complete (53, 75–78). Therefore, a total of five reviews were included in this overview (45, 46, 53–55).

### **Description of included reviews**

The included reviews examined three different types of interventions: dietary (55), pharmacological (53, 54) and psychological (45, 46). All included reviews were published between 2009 and 2011 and the searches for the primary trials included in the reviews were conducted between 2006 and 2010. Most trials included in the reviews were randomized controlled trials (RCTs), but two reviews (54, 55) also included a total of five cross-over RCTs (36, 79–82). One trial (81) was published only as an abstract.

Each review contained between two and seven trials, and the number of participants in each review ranged from 89 (54) to 356 (46). Sample sizes of individual trials were generally very small, with the smallest trial containing only 12 participants (81) and the largest trial containing 104 (83). In total, this overview contains 19 pediatric trials with a modest total of 777 participants. Table 1 presents additional characteristics of the included reviews.

### **Search methods**

The search strategies used to identify potentially relevant trials were comparable across reviews. All reviews searched CENTRAL, EMBASE, MEDLINE and PsycINFO, and all but one review (46) searched CINAHL, SIGLE, dissertation abstracts and reference lists. Three reviews searched ERIC, LILACS and contacted experts (45, 54, 55), and two reviews searched clinical trials registries (53, 54).

### **Participants**

The children and adolescents included in all reviews were between 5–18 years of age and had fairly similar diagnoses. Three reviews (45, 54, 55) included participants with recurrent abdominal pain (diagnosed using the Apley criteria) or functional gastrointestinal disorders (diagnosed using the Pediatric Rome II criteria), and one review (53) included children with any functional gastrointestinal disorder (as defined by trialists). The Eccleston *et al.* review on chronic and recurrent pain (46) included children with persistent, recurrent or episodic pain in any body site not due to cancer or another malignant disease; the relevant trials on abdominal pain were extracted and included participants with recurrent abdominal pain, irritable bowel syndrome and functional abdominal pain.

### **Interventions**

Three reviews (53–55) compared an active treatment to placebo, three (45, 46, 55) compared an active

**Table I.** Characteristics of included reviews

Review title	Number of trials (children only)	Pooled sample size (range)	Definition of chronic abdominal pain	Intervention	Comparison	Outcomes for which data are reported	Authors' conclusions
Antidepressants for the treatment of abdominal pain-related functional gastrointestinal disorders in children and adolescents (in press) Kaminski A, Kamper A, Thaler K, Chapman A, Gartlehner G August 2010	2	123 (33–90)	Abdominal pain-related FGIDs.	Commonly prescribed antidepressant agents including tricyclic antidepressants, SSRI's, SSNRI's and antidepressants with other mechanisms of action.	Placebo or other active treatment.	Improvement, feeling better or worse, pain, overall symptoms, quality of life, treatment satisfaction and adverse events.	'The existing randomized controlled evidence on amitriptyline revealed no statistically significant differences between amitriptyline and placebo for most efficacy outcomes.'
Dietary interventions for recurrent abdominal pain (RAP) and imitable bowel syndrome (IBS) in childhood Huertas-Ceballos AA, Logan S, Bennett C, Macarthur C November 2006	7 (6)	All trials: 362 (12–104) Children only: 298 (12–104)	RAP, IBS, abdominal migraine, functional dyspepsia or functional abdominal pain (as defined by the Pediatric Rome II criteria).	Any dietary intervention (e.g. fibre, lactose-free diet, <i>Lactobacillus</i> supplementation).	Placebo or no treatment.	Improved on treatment, improved versus not improved and pain.	'This review provides no evidence that fibre supplements, lactose free diets or <i>Lactobacillus</i> supplementation are effective in the management of children with RAP.'
Pharmacological interventions for recurrent abdominal pain (RAP) and imitable bowel syndrome (IBS) in childhood Huertas-Ceballos AA, Logan S, Bennett C, Macarthur C October 2006	3	89 (14–50)	RAP, IBS, abdominal migraine, etc., as long as participants meet the standard criteria for a diagnosis of RAP (as defined by Apley or the Rome II criteria for gastrointestinal diseases).	Any drug intervention (e.g. pizotifen, peppermint oil, famotidine).	Placebo or no treatment.	Improved versus not improved and global improvement in symptoms.	'Although the authors of the original trials suggested that pizotifen and famotidine were effective treatments, the reviewers conclude that this review provides only weak evidence for the use of drugs in the treatment of RAP'.

**Table 1. (Continued)**

Review title	Number of trials (children only)	Pooled sample size (range)	Definition of chronic abdominal pain	Intervention	Comparison	Outcomes for which data are reported	Authors' conclusions
Psychosocial interventions for recurrent abdominal pain (RAP) and irritable bowel syndrome (IBS) in childhood	6 167 (16–69)	RAP or a non-organic abdominal condition (as defined by Apley or the Rome II criteria for gastrointestinal diseases).	Any psychosocial intervention (e.g. CBFT, CBT, biofeedback, parental support).	Standard care, wait list or no treatment.	Pain free post-treatment and pain free at follow-up.	'In spite of methodological weaknesses and clinical heterogeneity, the consistency and magnitude of the effects reported provides some evidence that cognitive behavioural therapy may be a useful intervention for children with recurrent abdominal pain.'	
Eccleston C, Palermo TM, Williams ACDC, Lewandowski A, Morley S	All studies: 29 Abdominal pain only: 7§	Persistent, recurrent or episodic pain in any body site that is not due to cancer or other life threatening malignant disease. Diagnoses of RAP and IBS were included.	A credible psychological treatment (e.g. CBFT, CBT, biofeedback, parental support, hypnotherapy).	Placebo, other active treatment, treatment as usual or waiting list control.	Pain, mood and disability (i.e. school absences).	'Psychological treatments may improve pain control for children with recurrent abdominal pain. There is little evidence available to estimate effects on disability and mood'.	
January 2009	1,432 (26–136) Abdominal pain only: 356 (32–69)						

CBFT: cognitive behavioural family therapy; CBT: cognitive behavioural therapy; FGID: functional gastrointestinal disorder; IBS: irritable bowel syndrome; RAP: recurrent abdominal pain; SSRI: selective serotonin reuptake inhibitor; SSNRI: selective serotonin-norepinephrine reuptake inhibitor.

\* This review only included trials that had ten or more children in each arm post-treatment; § One trial (49) included children with abdominal pain and/or headaches.

treatment to another active treatment (standard pediatric care, fibre and lactose-containing diets) and two (45, 46) compared an active treatment to wait lists (no treatment). Specifically, the reviews examined 12 interventions that contributed data to this overview:

#### Dietary interventions:

- Fibre supplements versus placebo (two trials) (84, 85)
- *Lactobacillus* versus placebo (two trials) (81, 83)
- Lactose-free versus lactose-containing diet (two trials) (79, 80)

#### Pharmacological interventions:

- Amitriptyline versus placebo (two trials) (86, 87)
- Famotidine versus placebo (one trial) (82)
- Peppermint oil versus placebo (one trial) (88)
- Pizotifen versus placebo (one trial) (36)

#### Psychological interventions:

- Hypnotherapy versus standard pediatric care (one trial) (89)
- Family CBT versus standard pediatric care (three trials) (47, 50, 51)
- Individual CBT versus wait list (one trial) (90)
- Internet CBT versus standard pediatric care (one trial) (49)
- Individual CBT, biofeedback, parental support and fibre versus fibre alone (one trial) (48).

#### Outcome measures

All but one review pre-specified primary outcome measures, and primary outcomes were fairly homogeneous between reviews. There were a total of three pre-specified primary outcomes (intensity of pain, frequency of pain and ‘improvement’) and five pre-specified secondary outcomes (school performance, social/psychological functioning, quality of life, parental anxiety/depression and adverse effects). The review that did not pre-specify primary outcomes (46) presented data on pain, disability and mood. In this overview, data on pain are reported at three time points (during treatment, post-treatment and at follow-up) based on information stated directly in the reviews.<sup>1</sup> No reviews included assessments of health care utilization such as visits to the emergency department or inpatient admissions.

The review authors and trialists defined ‘improvement’ in a variety of ways. Often, data on ‘improvement’ were actually data on pain (e.g. ‘improvement in frequency of pain’), and this overview reports these data as ‘pain’ outcomes whenever possible. Otherwise, ‘improvement’ was defined in a variety of ways, including ‘improvement in symptoms’, ‘feeling better’ and ‘change in frequency and severity of gastrointestinal symptoms’.

<sup>1</sup> We had to refer to one trial (91) to determine the timing of the pain measurement.

**Table II.** Breakdown of Risk of Bias assessments for all included trials

Risk of Bias dimension	Adequate (%)	Unclear (%)	Inadequate (%)
Sequence generation	32	63	5
Allocation concealment	37	63	0
Blinding	37	21	42
Incomplete outcome data	58	10.5	31.5
Selective outcome reporting	84	16	0
Other sources of bias	68.5	5	26.5

#### Methodological quality of included trials

All trials in the included reviews were assessed for methodological quality using the Cochrane Risk of Bias tool (52), and these ratings are summarized in Table 2. Incomplete outcome data, selective outcome reporting and ‘other sources of bias’ were each judged as adequate over 50% of the time, while sequence generation, allocation concealment and blinding were each judged as adequate less than 50% of the time. Based on the Risk of Bias criteria, 79% of the trials in the five reviews were assessed as high risk of bias, 10.5% as unclear and 10.5% as low risk of bias.

Most trials were generally of short duration: the intervention periods for all trials assessing dietary and pharmacological interventions lasted between two and eight weeks, while the intervention periods for most trials assessing psychological interventions lasted between seven weeks and four months (with one trial lasting ten months). Unfortunately, the lengths of the follow-up periods were generally unclear or not reported in the included reviews.

#### Effect of interventions

##### Pain

Tables 3 and 4 present quantitative and qualitative data on pain outcomes measured at three different time points: during treatment, post-treatment and at follow-up.

*During treatment:* No quantitative data were reported for this time-point. A review reporting qualitative data from one small trial at high risk of bias reported mixed results: children receiving family CBT versus standard pediatric care showed a decrease in episodes, but not intensity, of pain ( $p = 0.001$ ) (47). Lactose-free versus lactose-containing diets did not impact pain scores (80).

*Post-treatment:* In one small trial at high risk of bias, children treated with a combination of individual CBT, biofeedback, parental support and fibre recorded an average of 50% less pain in a pain diary compared to children receiving fibre alone (MD: -3.52; 95% CI: -5.02, -2.03) (48). However, there were no significant differences in pain scores for children receiving family CBT or internet CBT compared to standard pediatric care (49, 50), or individual CBT compared to wait list (90). *Lactobacillus* (81, 83), famotidine (82),

**Table III.** Quantitative data: pain

Outcome	Comparison	Number of subjects (trials)	Measure of effect (95% CI)
Pain (post-treatment)	<b>Lactobacillus versus placebo</b>	120 (2)	<b>RR: 0.82 (0.69, 0.98)<sup>a</sup></b>
	Fibre supplement versus placebo	83 (2)	RR: 1.16 (0.47, 2.87) <sup>§</sup>
	Family CBT versus standard pediatric care	61 (1)	MD: -3.53 (-8.09, 1.03)
	<b>Individual CBT, biofeedback, parental support and fibre versus fibre alone<sup>†</sup></b>	61 (1)	<b>MD: -3.52 (-5.02, -2.03)<sup>b</sup></b>
	<b>Hypnotherapy versus standard pediatric care</b>	52 (1)	<b>MD: -6.40 (-8.98, -3.82)<sup>c</sup></b>
	Internet CBT versus standard pediatric care	37 (1)	MD: -1.30 (-2.79, 0.19)
	<b>Famotidine versus placebo</b>	25 (1)	<b>RR: 0.39 (0.17, 0.91)<sup>d</sup></b>
	Individual CBT versus wait list	16 (1)	RR: 0.33 (0.09, 1.18)
	<b>Pizotifen versus placebo<sup>‡</sup></b>	14 (1)	<b>MD: -8.21 (-13.48, -2.93)<sup>e</sup></b>
	<b>Internet CBT versus standard pediatric care</b>	32 (1)	<b>MD: -2.00 (-3.19, -0.81)<sup>f</sup></b>
Pain (follow-up)	Individual CBT versus wait list	16 (1)	RR: 0.20 (0.03, 1.35)

CBT: cognitive behavioural therapy; CI: confidence interval; MD: mean difference; RR: risk ratio.

<sup>a</sup> Significantly favours *Lactobacillus*; <sup>b</sup> Significantly favours individual CBT, biofeedback, parental support and fibre; <sup>c</sup> Significantly favours hypnotherapy;

<sup>d</sup> Significantly favours famotidine; <sup>e</sup> Significantly favours pizotifen; <sup>f</sup> Significantly favours internet CBT.

\* I<sup>2</sup>: 0%; § I<sup>2</sup>: 70%; <sup>†</sup> This continuous outcome was also reported as dichotomous data, and the effect estimate remained significant in favour of the active treatment (RR: 0.30; 95% CI: 0.19, 0.49); <sup>‡</sup> This was a cross-over trial that combined data from both phases of the study.

**Table IV.** Qualitative data: pain

Outcome	Comparison	Number of subjects (trials)	Statistically significant in favour of treatment (as stated in review)?
Pain (during treatment)	Lactose-free versus lactose-containing diet	69 (1)	No
	Family CBT versus standard pediatric care	32 (1)	Unclear <sup>a</sup>
Pain (post-treatment)	Amitriptyline versus placebo	123 (2)	No
	<b>Peppermint oil versus placebo</b>	42 (1)	<b>Yes<sup>b</sup></b>
	Lactose-free versus lactose-containing diet	21 (1)	No
Pain (follow-up)	Family CBT versus standard pediatric care	36 (1)	Unclear <sup>c</sup>

CBT: cognitive behavioural therapy.

<sup>a</sup> The treatment group showed a significant decrease in episodes of pain ( $p = 0.001$ ) but not intensity of pain; <sup>b</sup>  $p < 0.03$ ; <sup>c</sup> Significantly more children were pain free in the treatment versus control group, but pain scores did not differ between groups (no  $p$ -values reported).

peppermint oil (88), pizotifen (36) and hypnotherapy (89) all led to decreases in abdominal pain (RR: 0.82; 95% CI: 0.69, 0.98; RR: 0.39; 95% CI: 0.17, 0.91;  $p < 0.03$ ; MD: -8.21; 95% CI: -13.48, -2.93; MD: -6.40; 95% CI: -8.98, -3.82). However, all trials had small sample sizes, one was a cross-over trial at high risk of bias that combined data from both phases of the study (36), and one was a high risk of bias trial published only as an abstract (81). There was no significant difference in pain scores for children receiving fibre supplements versus placebo (84, 85) or lactose-free versus lactose-containing diets (79). There was also no difference in pain scores for adolescents receiving amitriptyline versus placebo (86, 87).

**Follow-up:** At follow-up, one small trial at high risk of bias found that children randomized to internet CBT versus standard pediatric care scored an average of 20% less on a pain scale (MD: -2.00; 95% CI: -3.19, -0.81) (49). Children receiving individual CBT compared to wait list showed no difference in pain (90). Qualitative data in one review reported mixed findings: in one small trial at high risk of bias, more children receiving family CBT compared to wait list were pain free post-treatment, even though pain scores did not differ between groups (51).

#### Other abdominal pain-related outcomes

Tables 5 and 6 present quantitative and qualitative data on other abdominal pain-related outcomes, including associated signs and symptoms, improvement, functional disturbances and administrative outcomes.

**Associated signs and symptoms:** There were no quantitative data reported for this outcome. Qualitative data showed no significant benefit of amitriptyline versus placebo for decreasing 'overall symptoms' (86) or peppermint oil versus placebo for decreasing 'gastrointestinal symptoms' (88).

**Improvement:** When *Lactobacillus* (83), peppermint oil (88) and pizotifen (36) were compared to placebo, only pizotifen led to improvement on an 'index of severity' (MD: -16.21; 95% CI: -26.51, -5.90), but this result was based on one small, high risk of bias, cross-over trial that combined data from both phases of the study. Two small trials at unclear and high risk of bias compared amitriptyline treatment with placebo (86, 87): one trial of 90 participants reported no difference between groups while another with 33 participants reported more improvement in the treatment group (week 10:  $p = 0.007$ ; week 13:  $p = 0.002$ ).

**Table V.** Quantitative data: other abdominal pain-related outcomes

Outcome	Comparison	Number of subjects (trials)	Measure of effect (95% CI)
Improvement	Lactobacillus versus placebo	104 (1)	RR: 1.09 (0.72, 1.65)
	Amitriptyline versus placebo	90 (1)	RR: 1.12 (0.77, 1.63)
	Peppermint oil versus placebo	42 (1)	RR: 1.67 (0.95, 2.93)
	<b>Pizotifen versus placebo*</b>	<b>14 (1)</b>	<b>MD: -16.21 (-26.51, -5.90)<sup>a</sup></b>
Disability	Family CBT versus standard pediatric care	66 (1)	MD: -1.50 (-4.22, 1.22)
School absences (days)	<b>Individual CBT, biofeedback, parental support and fibre versus fibre alone</b>	<b>30 (1)</b>	<b>MD: -0.70 (-1.35, -0.05)<sup>b</sup></b>
Treatment satisfaction	Amitriptyline versus placebo	90 (1)	MD: 1.10 (0.71, 1.70)
Withdrawal due to minor adverse events	Amitriptyline versus placebo	90 (1)	RR: 1.91 (0.18, 20.35)

CBT: cognitive behavioural therapy; CI: confidence interval; MD: mean difference; RR: risk ratio.

<sup>a</sup> Significantly favours pizotifen; <sup>b</sup> Significantly favours individual CBT, biofeedback, parental support and fibre.

\* This was a cross-over trial that combined data from both phases of the study.

**Table VI.** Qualitative data: other abdominal pain-related outcomes

Comparison	Outcome	Number of subjects (trials)	Statistically significant in favour of treatment (as stated in review)?
Amitriptyline versus placebo	Disability	123 (2)	No
	<b>Anxiety</b>	<b>90 (1)</b>	<b>Yes</b>
	Depression	90 (1)	No
	Somatization	90 (1)	No
	Discontinuation due to adverse events	90 (1)	No
	<b>Dysphoria</b>	<b>33 (1)</b>	<b>Yes<sup>a</sup></b>
	<b>Improvement</b>	<b>33 (1)</b>	<b>Yes<sup>b</sup></b>
	<b>Quality of life</b>	<b>33 (1)</b>	<b>Yes<sup>c</sup></b>
	Overall symptoms*	33 (1)	No
	Weight gain (adverse event)	33 (1)	No
	Health services utilization	30 (1)	No
	Use of medication	30 (1)	No
	Health service utilization	77 (1)	No
Individual CBT, biofeedback, parental support and fibre versus fibre alone	<b>School absences</b>	<b>77 (1)</b>	<b>Yes<sup>d</sup></b>
Family CBT versus standard pediatric care	Gastrointestinal symptoms (unspecified)	42 (1)	No
Peppermint oil versus placebo			

CBT: cognitive behavioural therapy.

<sup>a</sup>  $p = 0.003$  on week 10; <sup>b</sup>  $p = 0.007$  on week 10 and  $p = 0.002$  on week 13; <sup>c</sup>  $p = 0.019$  on week 6,  $p = 0.004$  on week 10 and  $p = 0.013$  on week 13; <sup>d</sup> 9.0 absences in treatment group versus 14.5 in control group (no  $p$ -value reported).

\* Constipation, diarrhoea, tenesmus, abdominal distension and diffuse abdominal pain.

**Functional impairment:** Neither amitriptyline versus placebo nor family CBT versus standard pediatric care (50) led to significant reductions in measures of disability. Qualitative data in one review reported that treatment with amitriptyline versus placebo significantly increased childhood quality of life at three measured time points (week 6:  $p = 0.019$ ; week 10:  $p = 0.004$ ; week 13:  $p = 0.013$ ), but this trial had a high risk of bias (86). In one small trial, school absences decreased by 0.7 days in children receiving a combination of individual CBT, biofeedback, parental support and fibre compared to fibre alone ( $MD: -0.70$ ; 95% CI:  $-1.35, -0.05$ ) (48), and qualitative data from another small trial at high risk of bias reported a decrease in school absences for children receiving family CBT versus standard pediatric care (9.0 vs. 14.5 absences; no  $p$ -value reported) (50). Lastly, qualitative data on psychosocial symptoms reported that amitriptyline compared to placebo significantly decreased levels of dysphoria ( $p = 0.003$ ) (86)

and anxiety (no  $p$ -value reported) (87) but did not have an impact on measures of depression or somatization (87).

**Administrative outcomes:** There was no difference between groups for any administrative outcome (treatment satisfaction, health services utilization or medication use) for participants receiving amitriptyline versus placebo (87), individual CBT, biofeedback, parental support and fibre compared to fibre alone (48) or family CBT versus standard pediatric care (50).

#### Adverse events

The reviews assessing dietary and psychological interventions did not report on adverse events. When pharmacological interventions were compared to placebo treatments, one trial on peppermint oil reported no adverse events in either group (88) and one trial on pizotifen (36) asked participants to record side-effects on symptom cards but the data were not reported in the review. One trial examining amitriptyline (86)

reported no adverse events and no difference in mean weight gain between groups; a second (87) reported no difference in withdrawals due to adverse events, with two dropouts in the treatment group (one due to fatigue and another due to rash and headache) and one dropout in the control group (due to dizziness). No trials included in this overview reported any serious adverse events.

## Discussion

This overview of reviews presents the most current evidence in *The Cochrane Library* regarding the efficacy of dietary, pharmacological and psychological interventions for chronic abdominal pain in children and adolescents. The trials in this area are challenged by the fact that the definition of the clinical syndrome of chronic abdominal pain encompasses a number of clinical entities. Nevertheless, most of the clinical descriptions of this condition include the experience of pain and functional impairment for the patient as well as the lack of significant organic pathology. The primary outcome measures were homogenous between reviews and described the impact of the interventions on qualities of pain such as intensity, frequency and 'improvement', noting that improvement was often related to a change in pain qualities. Of the trials included in this overview of reviews, 79% of trials had a high risk of bias. Sequence generation, or randomization, was unclear or inadequate in 68% of the trials. Blinding of participants, parents and outcome assessors was unclear or inadequate 63% of the time. Furthermore, the outcome data were unclear or inadequate for 42% of the trials, meaning that substantial numbers of participants often dropped out or withdrew from the trials for reasons that were not adequately explained. These participants were often excluded from the trials' outcome analyses, and studies have shown that chronic pain trials with incomplete outcome data often lead to biased overestimates of treatment effects (92). It is possible that even the trials with no incomplete outcome data did not use proper imputation methods or true intention-to-treat analyses. The evidence presented in this overview must therefore be interpreted within the context of the above listed methodological limitations, which clearly impact the strength of the conclusions that can be drawn from the available data.

## Summary of main results

### Dietary interventions

The success in management of children with chronic functional abdominal pain rests in a comprehensive, multifaceted approach. Perhaps one of the relatively benign approaches is to target the diet. The main dietary interventions studied in children were lactose-free diets, probiotic administration and fibre supplementation. Although no difference in pain scores were

reported for children randomized to lactose-free versus lactose-containing diets (80), supplementation with the *Lactobacillus* probiotic ( $3 \times 10^9$  colony forming units twice per day for four weeks; dosage unspecified in second trial) slightly decreased abdominal pain (81, 83). Of note, additional randomized, double-blind, placebo-controlled trials on probiotics for chronic abdominal pain have recently been published but are not included in this overview. A study by Bausserman *et al.* (91) utilized *Lactobacillus* GG in children with irritable bowel syndrome and did not show any reduction in pain, while more recent trials showed benefit when *Lactobacillus* GG (93) and the polymicrobial probiotic supplement VSL#3 (94) were used to treat children with functional abdominal pain and irritable bowel syndrome. With regards to fibre supplementation, two trials showed no difference in pain scores for children receiving fibre supplements versus placebo (84, 85). Another study examined the effect of combined individual CBT, biofeedback, parental support and fibre (eight treatment sessions and 10 g of fibre per day) versus fibre alone (10 g per day) and showed that combination therapy appears superior to fibre alone (48). This trial emphasizes the importance of a comprehensive approach to the management of children with chronic abdominal pain.

### Pharmacological interventions

In clinical practice, a wide variety of medications are used in children with chronic abdominal pain, including antidepressant, antispasmodic, anticholinergic and antisecretory agents. The majority of these drugs have not been subject to extensive investigation, however, pharmacologic interventions were examined in five reviewed trials and included evaluations of amitriptyline, famotidine, peppermint oil and pizotifen. Two small trials enrolling a total of 116 children compared amitriptyline with placebo and found no significant differences between amitriptyline and placebo for most outcomes (86, 87), but the trials did reveal efficacy of amitriptyline for limited outcomes in adolescents with irritable bowel syndrome. A trial of famotidine was performed in 25 children with chronic abdominal pain and found that famotidine resulted in symptom improvement as reported by a subjective global evaluation; however, only a subset of patients with dyspeptic symptoms demonstrated benefit with famotidine when objective outcomes were applied (82). Another trial enrolling 50 children with irritable bowel syndrome examined the efficacy of three doses of peppermint oil per day for two weeks compared to placebo and found that the use of peppermint oil led to a slight decrease in post-treatment abdominal pain severity (88). In this short-term study, peppermint oil did not reduce associated symptoms (e.g. heartburn, diarrhea) and a validated clinical rating scale for IBS showed no difference between peppermint oil and placebo. Pizotifen, a serotonin antagonist used for migraine headaches, demonstrated benefit post-treatment pain in

a double-blind cross-over trial involving 14 children with abdominal migraine (36); however, this study population was not defined by the Rome criteria, and as such, the results may not be generalizable. Overall, there are a very small number of pharmacologic trials conducted for children with chronic abdominal pain, and those that have been published were conducted with very small numbers of participants. Evidence supporting the use of pharmacologic interventions for children with chronic abdominal pain is minimal, but certain drugs may be beneficial when directed at specific subsets of children.

### **Psychological interventions**

In general, cognitive behaviour therapy (CBT) was the most commonly studied intervention. CBT focuses on examining and replacing distressing thoughts and feelings, and it was often reported as beneficial when compared to the control groups in our included trials. While bearing in mind the methodological limitations of the trials, it is interesting to note that five out of six trials included in this overview suggested that CBT was effective in the management of chronic abdominal pain. An additional, recently published trial enrolling 200 children with chronic abdominal pain evaluated the efficacy of CBT compared to an educational program of equivalent duration, and the cognitive behavioural intervention showed greater reduction of reported abdominal pain and solicitous responses from parents (95). In this overview, one small trial of 53 children found that hypnotherapy compared to standard medical therapy prescribed by a pediatric gastroenterologist also reduced pain post-treatment (89). Adult trials have also shown that hypnotherapy can relieve symptoms of irritable bowel syndrome, and the beneficial effects may be long-term (96, 97).

Psychological interventions draw attention to the value of involving the family or parents in treatment. They help to actively engage the patient and parents in recovery, thus possibly reducing parental helplessness. The general goal of psychological interventions is to manage the disabling effects of the cognitive preoccupation with pain in the patient and family. In fact, clinical experience suggests that refocusing the patient and family on coping strategies with an emphasis on supporting their child's functioning (mobilization, school attendance and social events) can have positive effects even if the experience of pain is not reduced. The results of this overview suggest that psychological interventions, specifically cognitive behavioural therapy targeting both individuals and their families, may be effective treatments for childhood chronic abdominal pain.

### **Limitations**

The limitations of this overview are primarily related to the degree of bias in the included trials, which

limits the conclusions that can be made. This overview contains a small number of underpowered trials, most of which are at high risk of bias. The small sample sizes are particularly noteworthy, given that it has been suggested that, for pain research, nearly 500 participants are required before results from meta-analyses become clinically relevant (98). Small sample sizes can lead to an increased likelihood of selection bias, as subjects with more severe symptoms are likely to be selected for participation in the trials. In addition to small sample sizes, follow-up was relatively short for the majority of included trials, which tends to overestimate the likelihood of the intervention being beneficial and increase the likelihood of publication bias. Publication bias is also particularly relevant when evaluating few trials with small sample sizes as the inclusion of more negative studies (less likely to be submitted for review and accepted for publication) would reduce the likelihood of a positive aggregate effect. Lastly, data on adverse events was also lacking, which is worrisome because lack of data does not necessarily equate with safe interventions. For most interventions assessed in this overview, there was a lack of high-quality, adequately powered randomized controlled trials using standardized tools to measure clinically important outcomes over adequate periods of time. Therefore, all results presented in this overview should be interpreted with caution.

The conclusions that can be drawn from the data in this overview are limited by an overall lack of generalizability. There is general difficulty in defining chronic abdominal pain, and children with chronic functional abdominal pain are a heterogeneous population; however, the trials included in this overview over-represent children with irritable bowel syndrome, meaning that the findings are most relevant to this subset and may not be generalizable to the entire group of children with chronic abdominal pain. Further, a variety of pain scales were used across trials, which limits our ability to draw meaningful comparisons both within and across treatments. There was also a lack of clarity regarding the specific nature of the psychological interventions (primarily under the cognitive behavioural therapy umbrella); thus, specific treatment protocols cannot be recommended at this time. The limitations of this overview highlight the need for well-designed, robust clinical trials in children with chronic abdominal pain.

### **Authors' Conclusions**

#### **Implications for practice**

Chronic abdominal pain is a distressing and long-term problem for children and their families, and it is not uncommon to see such children undergo trials of multiple varying therapies in an attempt to achieve a manageable level of pain and reasonable level of functioning. Despite a general lack of evidence,

clinicians and families often look to dietary and pharmacological interventions when treating a child with chronic abdominal pain. While clinical trials suggest no benefit or limited effect of the dietary and pharmacological interventions studied to date, future trials are eagerly awaited to enhance our current understanding of the effects of such interventions.

A small number of trials with very limited sample sizes exist for pharmacological interventions. At present, they would suggest that, in the subset of adolescent patients with irritable bowel syndrome, amitriptyline may be a reasonable drug to trial with a patient. Beyond the two trials that provide some support for amitriptyline treatment, the quality, sample size and degree of bias in the other pharmacological trials preclude any definitive conclusions from being made.

The most notable improvements involved relatively intensive psychological support (e.g. cognitive behavioural therapy) with a focus on functional improvement rather than an exclusive focus on pain. Some family physicians and pediatricians may not be comfortable managing the mental health aspects of children and adolescents with chronic abdominal pain. Nevertheless, these clinicians are often the 'safety net' for parents who care for children with chronic abdominal pain, when mental health services and specialist access are limited. Through cooperation and collaboration between primary care physicians and mental health specialists, efforts should be made to make psychological therapies more accessible to patients with chronic abdominal pain. This may involve further training for primary care physicians or greater accessibility to formally trained mental health professionals.

Sometimes, patients and families are not accepting of mental health interventions, despite the fact that psychological interventions seem to be more effective than standard medical treatment in several clinical trials. This can be related to the societal stigma associated with treating a medical condition with 'psychological' treatments, and efforts should be made to de-stigmatize psychological interventions for patients, families and the greater general community.

### Implications for research

As outlined above, chronic abdominal pain is a common and disabling condition for children and their families, and yet, evidence examining the use of dietary and pharmacological interventions is surprisingly limited. Additional clinical trials, powered to examine subsets of patients, are needed to investigate dietary supplements (e.g. probiotics) and exclusion diets (e.g. fermentable substrates), as well as pharmacological interventions commonly used in clinical practice (e.g. amitriptyline, antidepressants, H<sub>2</sub> receptor antagonists). While CBT seems to hold promise, further trials are also required to confirm this possible benefit.

While dietary intervention studies have begun to be explored, the paucity of the current data remains a concern. There are a limited number of trials which generally lack homogeneity, as many of the individual trials have distinctly different protocols, with different dietary supplements, type and dosing of supplements, durations of administration and outcome measures, making it difficult to draw firm conclusions. Standardized regimens of therapy and outcomes measures would make inter-study comparisons feasible, thereby improving our ability to draw clinical conclusions for our patients.

With regards to pharmacological interventions, more research examining selective serotonin reuptake inhibitors, which target anxiety and somatoform disorders, may be helpful. These medications have shown promise in adult populations with chronic abdominal pain (99), and may confer an equivalent benefit in children and adolescents.

Interventions that target a change in function as opposed to the symptom of pain may also be a fruitful area of inquiry. The current research is increasingly focusing on rehabilitation, and improving function as opposed to reducing pain may be a useful goal for children with chronic abdominal pain. Standardizing the measurement of pain outcomes will aid in comparisons between trials. Further, clearer definitions of terms and specific descriptions of interventions and outcome variables will enable research to help guide the care of these children and their families.

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### Contributions of Authors

All authors contributed to this overview. MF extracted all data and wrote the Background, Objectives, Methods and Results sections. SA, RG, MW, SM and KT wrote the Discussion and Authors' Conclusions sections. MF is the primary author of this overview. All authors contributed to editing all sections of the overview and take responsibility for the manuscript.

### Declarations of Interest

No declarations of interest are noted.

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