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Antidepressants for functional abdominal pain disorders in children and adolescents (Review)

de Bruijn CMA, Rexwinkel R, Gordon M, Benninga M, Tabbers MM

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Antidepressants for functional abdominal pain disorders in children and adolescents.
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TABLE OF CONTENTS

[Intervention Review]

Antidepressants for functional abdominal pain disorders in children and adolescents

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ABSTRACT

Background

Functional Abdominal Pain Disorders (FAPDs) present a considerable burden to paediatric patients, impacting quality of life, school attendance and causing higher rates of anxiety and depression disorders. There are no international guidelines for the management of this condition. A previous Cochrane Review in 2011 found no evidence to support the use of antidepressants in this context.

Objectives

To evaluate the current evidence for the efficacy and safety of antidepressants for FAPDs in children and adolescents.

Search methods

In this updated review, we searched the Cochrane Library, PubMed, MEDLINE, Embase, PsycINFO and two clinical trial registers from inception until 03 February 2020. We also updated our search of databases of ongoing research, reference lists and 'grey literature' from inception to 03 February 2020.

Selection criteria

We included randomised controlled trials (RCTs) comparing antidepressants to placebo, to no treatment or to any other intervention, in children aged 4 to 18 years with a FAPD diagnosis as per the Rome or any other defined criteria (as defined by the authors). The primary outcomes of interest included treatment success (as defined by the authors), pain severity, pain frequency and withdrawal due to adverse events.

Data collection and analysis

Two review authors checked all citations independently, resolving disagreement with a third-party arbiter. We reviewed all potential studies in full text, and once again made independent decisions, with disagreements resolved by consensus. We conducted data extraction and 'Risk of bias' assessments independently, following Cochrane methods. Where homogeneous data were available, we performed meta-analysis using a random-effects model. We conducted GRADE analysis.

Main results

We found one new study in this updated search, making a total of three trials (223 participants) eligible for inclusion: two using amitriptyline (AMI) and one using citalopram.

For the primary outcome of treatment success, two studies used reports of success on a symptom-based Likert scale, with either a two-point reduction or the two lowest levels defined as success. The third study defined success as a 15% improvement in quality of life (QOL) ratings scales. Therefore, meta-analysis did not include this final study due to the heterogeneity of the outcome measure. There is low-certainty evidence that there may be no difference when antidepressants are compared with placebo (risk ratio (RR) 1.17, 95% confidence interval (CI) 0.87 to 1.56; 2 studies, 205 participants; I^2 = 0%). We downgraded the evidence for significant imprecision due to extremely sparse data (see Summary of findings table 1).

The third study reported that participants receiving antidepressants were significantly more likely than those receiving placebo to experience at least a 15% improvement in overall QOL score at 10 and 13 weeks (P = 0.007 and P = 0.002, respectively (absolute figures were not given)).

The analysis found no difference in withdrawals due to adverse events between antidepressants and placebo: RR 3.17 (95% CI 0.65 to 15.33), with very low certainty due to high risk of bias in studies and imprecision due to low event and participant numbers. Sensitivity analysis using a fixed-effect model and analysing just for AMI found no change in this result. Due to heterogeneous and limited reporting, no further meta-analysis was possible.

Authors' conclusions

There may be no difference between antidepressants and placebo for treatment success of FAPDs in childhood. There may be no difference in withdrawals due to adverse events, but this is also of low certainty. There is currently no evidence to support clinical decision making regarding the use of these medications. Further studies must consider sample size, homogenous and relevant outcome measures and longer follow up.

PLAIN LANGUAGE SUMMARY

Antidepressants for the treatment of children and adolescents with functional abdominal pain disorders

What is the aim of this review?

The aim of this Cochrane Review was to find out whether antidepressants can improve symptoms in children and adolescents with functional abdominal pain disorders (FAPDs). We collected and analysed data from three studies with a total of 223 children and adolescents to answer this question.

Key messages

The question of whether antidepressants can improve symptoms in children and adolescents with FAPDs remains unanswered. There were no serious adverse events when compared with placebo (dummy treatment). The number of studies was low, and the number of people in them was also low, meaning that more studies are needed to answer the question.

What was studied in the review?

FAPDs are common in childhood and adolescence. In most cases, no medical reason for the pain can be found. There are various drug treatment approaches for the different types of FAPDs. Antidepressants have been shown to be effective in some studies of adults with FAPDs. Consequently, children and adolescents with similar complaints are sometimes treated with antidepressants.

What are the main results of the review?

We searched for randomised controlled trials (RCTs; clinical studies where people are randomly put into one of two or more treatment groups) comparing antidepressants with placebo (dummy treatment).

We found three studies eligible for inclusion: two using amitriptyline (AMI) and one using citalopram, involving a total of 223 young people.

1. It is uncertain whether there is a difference in the number of people who had successful treatment when on antidepressants compared with placebo.

2. It is uncertain whether there is a difference in the number of people who withdraw from treatment due to adverse events when on antidepressants compared with placebo.

Conclusion

We are uncertain whether antidepressants can improve symptoms in children and adolescents with FAPDs. This is because the studies had very few participants and were not conducted using reliable methods. With the evidence presented in these studies, we are unable to draw strong conclusions about the effectiveness of antidepressants for this problem; better-designed studies with more participants are needed.

How up-to-date is this review?

This review is up-to-date as of February 2020.

SUMMARY OF FINDINGS

Summary of findings 1. Antidepressant compared to placebo for the treatment of functional abdominal pain disorders in children and adolescents

Antidepressant compared to placebo for the treatment of functional abdominal pain disorders in children and adolescents

Patient or population: Children and adolescents with functional abdominal pain disorder
Setting: Outpatient
Intervention: Antidepressant
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with antidepressant				
Treatment success	Study population		RR 1.17 (0.87 to 1.56)	205 (2 RCTs)	⊕⊕⊝⊝ LOW[a]	-
	440 per 1000	515 per 1000 (383 to 686)				
Withdrawals due to adverse events	Study population		RR 3.17 (0.65 to 15.33)	238 (3 RCTs)	⊕⊕⊝⊝ LOW[a]	-
	17 per 1000	54 per 1000 (11 to 262)				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a]Downgraded two levels due to significant imprecision for extremely sparse data.

BACKGROUND

Description of the condition

This review is an update of a review previously published in the Cochrane Library on *Antidepressants for the treatment of abdominal pain-related functional gastrointestinal disorders in children and adolescents* (Kaminski 2012). Apley 1958 introduced the term “recurrent abdominal pain” (RAP) for clinically-apparent, non-organic, chronic or recurrent abdominal pain in children, with three or more episodes within three months that are severe enough to interfere with daily activities. Drossman 2006 replaced RAP with the term "abdominal pain related functional gastrointestinal disorders" (AP-FGIDs) in the Rome III system. Drossman described AP-FGIDs as chronic or recurrent abdominal pain without evidence of an organic cause.

In 2016, the Rome III criteria were replaced with the Rome IV criteria. This has updated the nomenclature with "functional abdominal pain disorders" (FAPDs) (Hyams 2016).

The Rome IV criteria (Hyams 2016) divide FAPDs into the following subcategories:

- Functional dyspepsia (FD)
- Irritable bowel syndrome (IBS)
- Abdominal migraine (AM)
- Functional abdominal pain - not otherwise specified (FAP-NOS)

The diagnosis of FD must include one or more of the following bothersome symptoms at least four days a month (Hyams 2016):

- Postprandial fullness
- Early satiation
- Epigastric pain or burning not associated with defecation
- After appropriate evaluation, the symptoms cannot be fully explained by another medical condition.

These criteria should be fulfilled for at least two months before diagnosis.

Within FD, two subtypes are adopted:

- Postprandial distress syndrome includes bothersome postprandial fullness or early satiation that prevents finishing a regular meal. Supportive features include upper abdominal bloating, postprandial nausea, or excessive belching
- Epigastric pain syndrome, which includes all of the following: bothersome (severe enough to interfere with normal activities) pain or burning localised to the epigastrium. The pain is not generalised or localised to other abdominal or chest regions and is not relieved by defecation or passage of flatus. Supportive criteria can include
  * burning quality of the pain but without a retrosternal component, and
  * the pain commonly induced or relieved by ingestion of a meal but may occur while fasting

The diagnosis of IBS must include all of the following (Hyams 2016):

- Abdominal pain at least four days per month associated with one or more of the following:
  * Related to defecation;
  * A change in frequency of stool; and
  * A change in form (appearance) of stool.
- In children with constipation, the pain does not resolve with resolution of the constipation (children in whom the pain resolves have functional constipation, not IBS).
- After appropriate evaluation, the symptoms cannot be fully explained by another medical condition.

These criteria should be fulfilled for the last three months with symptom onset at least six months before diagnosis of IBS.

The diagnosis of AM must include all of the following (Hyams 2016):

- Paroxysmal episodes of intense, acute periumbilical, midline or diffuse abdominal pain lasting one hour or more (should be the most severe and distressing symptom);
- Episodes are separated by periods of usual health lasting weeks to months;
- The pain is incapacitating and interferes with normal activities;
- Stereotypical pattern and symptoms in the individual patient;
- The pain is associated with two or more of the following:
  * Anorexia;
  * Nausea;
  * Vomiting;
  * Headache;
  * Photophobia;
  * Pallor.
- After appropriate evaluation, the symptoms cannot be fully explained by another medical condition.

These criteria should be fulfilled two or more times in the past 12 months.

The diagnosis of FAP-NOS must be fulfilled at least four times a month, and must include all of the following (Hyams 2016):

- Episodic or continuous abdominal pain that does not occur solely during physiologic events (e.g. eating, menses)
- Insufficient criteria for IBS, FD, or AM
- After appropriate evaluation, the abdominal pain cannot be fully explained by another medical condition

These criteria should be fulfilled for at least two months before diagnosis.

FAPDs are common in children and adolescents, with a worldwide pooled prevalence of 13.5% (Korterink 2015). Paediatric FAPDs have a major impact on daily life, resulting in a significantly lower quality of life (QOL) and higher rates of school absenteeism (Assa 2015; Varni 2015). Moreover, patients are at higher risk of developing anxiety or depressive disorders compared to healthy school-aged children (Newton 2019). The pathophysiological mechanisms underlying FAPDs are poorly understood and are thought to be multifactorial. Psychosocial, genetic and physiological factors, such as inflammation, poor gastric emptying, increased rectal sensitivity and altered gut microbiota, have been suggested to contribute to the development

of functional abdominal pain by influencing the visceral sensitivity, gastrointestinal motility and gut-brain axis (Korterink 2015). Paediatric FAPDs are now labelled 'Disorders of Gut Brain Interaction,' given that their bio-psychosocial basis encompasses complex interactions within the gut-brain axis (Drossman 2016). More recently, the latter is termed the 'microbiota-gut-brain axis' to reflect an increase in our understanding of the magnitude, complexity, role and interactions of the microbial populations hosted within the lumen of the gastrointestinal tract.

The management of paediatric FAPDs consists of non-pharmacological and pharmacological interventions. The first step of treatment includes 'standard Medical Treatment' and contains explanation, reassurance and simple dietary and behavioural advice (Schurman 2010). Non-pharmacological interventions consist of dietary interventions and psychosocial interventions such as cognitive behavioural therapy (CBT) and hypnotherapy.

Pharmacological agents used for the treatment of paediatric FAPDs include prokinetics, antispasmodics, anti-inflammatory agents, analgesics, anti-serotonergic agents and antidepressants (Santucci 2020). In North America, 62% of paediatric gastroenterologists are reported to prescribe tricyclic antidepressants (TCAs), and up to 20% chose selective serotonin reuptake inhibitors (SSRIs) for the treatment of FAPDs (Schurman 2010). In 29.1% of children, symptoms persist for more than five years after treatment (range 1 - 29 months) (Gieteling 2008; Pate 2020).

Description of the intervention

Antidepressants include first-generation drugs such as TCAs (i.e. amitriptyline and nortriptyline) as well as second-generation antidepressants such as SSRIs (i.e. escitalopram, citalopram, fluoxetine, paroxetine, and sertraline), serotonin and norepinephrine reuptake inhibitors (SNRIs), and other drugs with related mechanisms of action that selectively target neurotransmitters. Antidepressants are commonly used in depression treatment.

In adults with major depressive disorders, first- and second-generation antidepressants have equivalent efficacy (Boylan 2020; Furukawa 2019; Geoffroy 2019; Ogawa 2019). However, first-generation drugs are often accompanied by multiple adverse events that many people find intolerable. For example, TCAs tend to cause anticholinergic effects, including dry mouth and eyes, urinary hesitancy, and sometimes urinary retention and constipation. They also have a high rate of lethality when overdose occurs. Therefore, first-generation antidepressants are no longer considered first-line agents of choice for the treatment of psychiatric disorders in most circumstances.

Second-generation antidepressants can also lead to substantial adverse effects (e.g. nausea, vomiting, diarrhoea, sexual dysfunction, and others) in up to 90% of adults. In people with depressive disorders, some of these adverse effects can be life-threatening (e.g. suicidality, seizures). However, the potential for lethality when overdose occurs is low compared with TCAs (Cooper 2017; Gartlehner 2011; Rexwinkel 2019; Zar-Kessler 2017).

The literature for treatment with antidepressants for paediatric FAPDs is sparse.

How the intervention might work

The exact mechanism of action of antidepressants, particularly for the treatment of FAPDs in children and adolescents, is poorly understood. In general, these drugs work through their effect on prominent monoaminergic neurotransmitters (serotonin, noradrenalin and dopamine) in the central nervous system (Drossman 2018). Although the drugs can be grouped based on their primary mechanism of action as TCAs, SSRIs, SNRIs, and other antidepressants, drugs within these groups are not homogeneous and the specific activity may vary.

Why it is important to do this review

Current evidence on the efficacy and safety of antidepressant agents in children and adolescents with FAPDs is limited, with no antidepressants currently approved by regulatory agencies for treating FAPDs in children and adolescents. International guidelines from key professional societies are out of date, and do not give updated guidance on this treatment class.

OBJECTIVES

To evaluate the efficacy and safety of antidepressant agents for the treatment of FAPDs in children and adolescents.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) comparing antidepressants to placebo, to no treatment or to any other interventions. Cross-over trials were considered.

Types of participants

Children aged 4 to 18 years with functional abdominal pain disorders (FAPDs), as defined by Rome criteria or any other criteria, as specified in the primary study.

Types of interventions

Interventions of interest include all commonly-prescribed antidepressant agents. We include all second-generation antidepressants such as selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs), as well as some first-generation antidepressants. We include the following treatments:

- tricyclic antidepressants: amitriptyline, amoxapine, clomipramine, desipramine, dibenzepine, dothiepin, doxepin, imipramine, lofepramine, nortriptyline, protriptyline, trimipramine;
- selective serotonin reuptake inhibitors: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline;
- selective serotonin-norepinephrine reuptake inhibitors: desvenlafaxine, duloxetine, milnacipran, venlafaxine; and
- antidepressants with other mechanisms of action: bupropion, maprotiline, mirtazapine, reboxetine, trazodone.

Types of outcome measures

The following outcome measures are of interest for this review:

Primary outcomes

The primary outcomes include:

- Treatment success, as defined by the authors
- Pain frequency or change in frequency of pain
- Pain intensity or change in pain intensity
- Withdrawal due to adverse events

Secondary outcomes

Secondary outcome measures include:

- Quality of life or change in quality of life, measured using any validated measurement tool
- Anxiety/depression
- Defaecation pattern (disease-specific (IBS-C/D))
- (Serious) adverse events
- Adequate relief
- School attendance or change in school attendance or performance

Search methods for identification of studies

Electronic searches

We searched the following online databases from inception to 03 February 2020:

- Cochrane Central Register of Controlled Trials (CENTRAL) (via Ovid EBMR) (Appendix 1);
- MEDLINE (via OvidSP) (Appendix 2);
- Embase (via OvidSP) (Appendix 3).

Detailed search strategies can be found in Appendices.

Searching other resources

- Reference searching: we inspected the references of all identified studies for more relevant papers.
- Personal contacts: we contacted leaders in the field to identify other studies.
- Drug companies: we contacted manufacturers of appropriate preparations for additional information.

Data collection and analysis

Selection of studies

Using the search strategy, two review authors independently identified studies that appear to be potentially relevant. The two review authors read the full texts to assess the eligibility of the papers identified. After reading the full texts, the two review authors independently assessed the eligibility of all studies identified based on the inclusion criteria above. Disagreement among reviewers was discussed and agreement reached by consensus. We implemented this process in order to reduce the risk of bias and decrease the chances of any inaccuracies during the interpretation of the studies.

Data extraction and management

We developed a data extraction form and extracted information on relevant features and results of the included studies. Two review authors extracted and recorded data on the predefined data extraction form, independently and in duplicate. Extracted data included the following items:

- characteristics of participants: age, sex, diagnosis;
- total number of participants originally assigned to each intervention group;
- intervention: type and dose; mode of administration;
- control: no intervention, placebo or other interventions;
- concurrent medications; and
- outcomes: time of assessment, length of follow-up, success, pain frequency, pain severity, quality of life, anxiety, defecation, adverse events, adequate relief, school attendance.

Assessment of risk of bias in included studies

Two review authors independently assessed bias using the Cochrane 'Risk of bias' tool (Higgins 2011). For the cluster-RCTs, we assessed risk of bias following guidance listed in Table 23.1.a of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020). The study features assessed included:

- random sequence generation;
- allocation concealment;
- blinding of participants and personnel;
- blinding of outcome assessment;
- completeness of outcome data;
- selective reporting; and
- other potential sources of bias.

We rate each of these factors as ‘low risk’, ‘high risk’ or ‘unclear risk’ of bias.

Measures of treatment effect

We calculated the risk ratio (RR) for dichotomous outcomes. We planned to report time-to-response data as hazard ratios (HRs). However, where studies reported mean response time, we calculated the mean difference (MD), provided that the studies indicate that all participants responded to treatment during the trial period. If the studies assess health-related quality-of-life data using different scales, we estimated the treatment effect using the standardised mean difference (SMD). We presented SMDs as standard deviation units, interpreted as follows: 0.2 represents a small effect, 0.5 a moderate effect and 0.8 a large effect (Cohen 2010). We reported these measures of treatment effects alongside associated 95% confidence intervals (CIs).

Unit of analysis issues

For cross-over trials, we extracted data from the first phase of the study for analysis (i.e. before the cross-over occurred). We planned to conduct separate analyses for comparisons between antidepressant versus placebo, and antidepressants versus active comparator (e.g. alternative antidepressant intervention), but no such studies were included. If studies randomised participants to more than one treatment arm (e.g. with different doses), we planned to combine these for the primary analysis. Where outcomes are reported at several time points, we analysed a single time point that is consistently reported by the studies and at the final point of follow-up.

Dealing with missing data

We contacted the authors of included studies to supply any missing data. If data were needed to judge the risk of bias, we made a judgement of unclear risk in the relevant category. Where 'response' outcome data were missing, we used the intention-to-treat principle (ITT) on the assumption that all participants lost to follow-up were non-responders.

Assessment of heterogeneity

We assessed heterogeneity and inconsistency to ensure the validity of the analysis. Initially, we assessed heterogeneity through visual inspection of forest plots and the calculation of the Chi^2 and I^2 statistics (Borenstein 2009). We interpreted I^2 statistic according to the guide below (Deeks 2020):

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity; and
- 75% to 100%: considerable heterogeneity.

Assessment of reporting biases

If there was an appropriate number of studies in a pooled analysis (i.e. 10 or more studies), we planned to investigate potential publication bias using funnel plots: trial effects versus trial size (Page 2020), but there were insufficient numbers of studies to do this.

Data synthesis

We analysed data using Review Manager 5. We rated the quality of the evidence based on the system developed by the GRADE Working Group (Atkins 2004).

Subgroup analysis and investigation of heterogeneity

Where appropriate, we planned subgroup analyses to explore the role of specific dosing regimens or sub-diagnosis, but insufficient study numbers were available and such analyses were not performed.

Sensitivity analysis

We had planned to conduct sensitivity analyses based on the following:

- random-effect versus fixed-effect modelling;
- excluding studies assessed at unclear or high risk of bias according to the Cochrane 'Risk of bias' tool; and
- only including participants whose outcome is known (i.e. number of participants who completed the study used as a denominator).

However, as the number of studies were very low, these analyses were not possible.

Summary of findings and assessment of the certainty of the evidence

We planned to present the main results on response and serious adverse events in 'Summary of findings' tables, reporting the results for a representative set of contrasts, with one row for each intervention versus the reference comparator. This presents key information about the certainty of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data (Schünemann 2020). 'Summary of findings' tables also include an overall grading of the evidence using the GRADE approach, and follow the examples in Yepes-Nuñez 2019. We were able to report for the primary outcome (treatment success) and safety data.

RESULTS

Description of studies

See Characteristics of included studies and Characteristics of excluded studies.

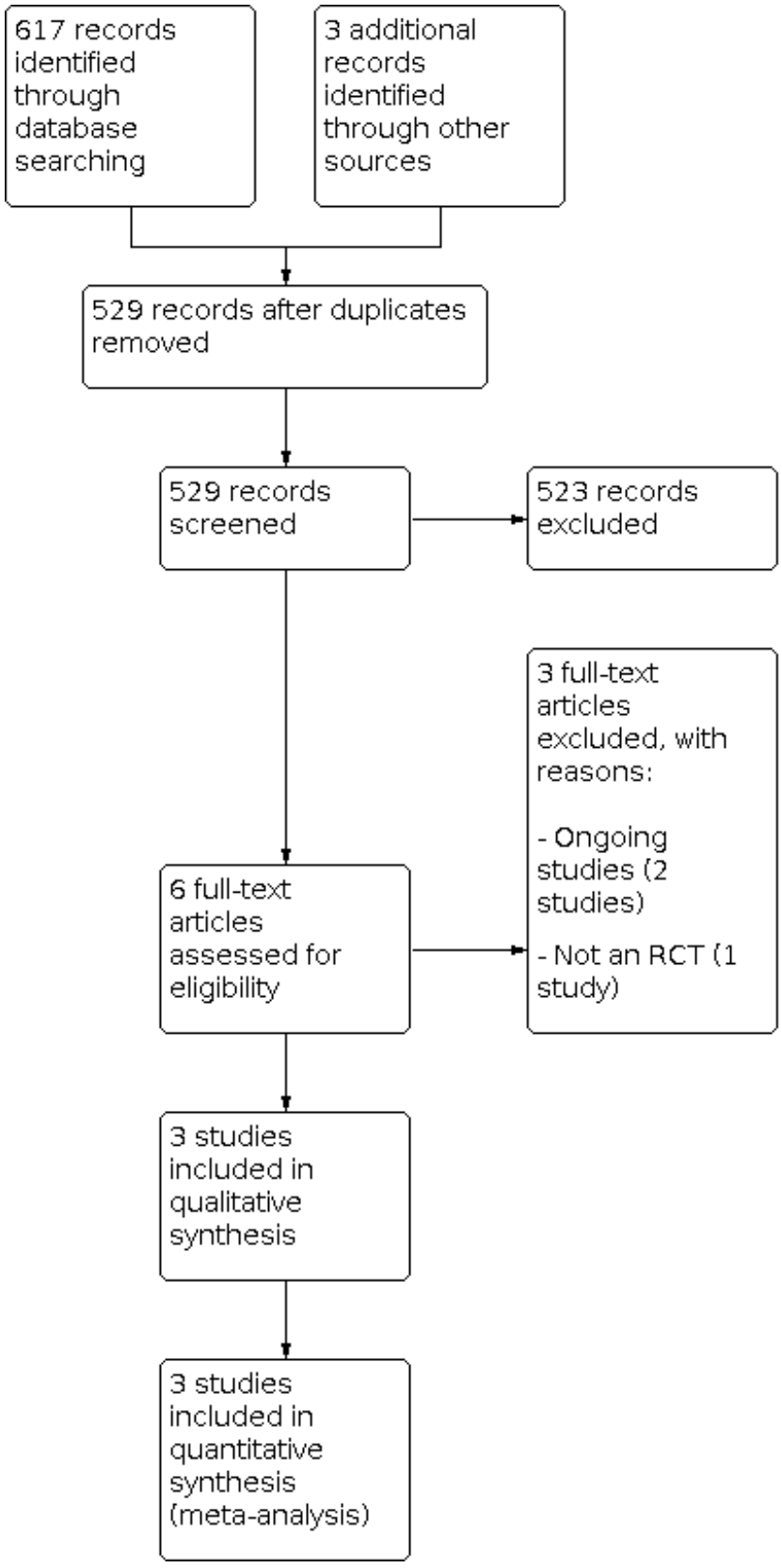
Results of the search

The updated search identified 617 citations. We removed 91 duplicates, and identified three further studies through previous reviews, and added them to the search. We then screened 529 citations by title and abstract. We excluded one study as it was not an RCT and lacked comparison with a control group (Campo 2004). We contacted the authors of all three included studies (Bahar 2008; Roohafza 2014; Saps 2009); one author responded (Saps 2009).

In the updated search we identified two ongoing randomised trials (CTRI/2018/08/015365; ACTRN12613000158763). Details of these ongoing RCTs are available in the Characteristics of ongoing studies.

We present the search results in a PRISMA diagram (Figure 1). Details of included and excluded studies are presented in the Characteristics of included studies and the Characteristics of excluded studies.

Figure 1. Study flow diagram.



Included studies

Study design and setting

We included three studies (Bahar 2008; Roohafza 2014; Saps 2009). Two studies were single-centre (Bahar 2008; Roohafza 2014); one study enrolled participants from a suburban, private-practice paediatric gastroenterology clinic in California (Bahar 2008) and the other study was performed at a tertiary clinic of paediatric gastroenterology in Isfahan, Iran (Roohafza 2014). One multicentre study was included; this study recruited participants from paediatric gastroenterology clinics of six tertiary care centres in the USA (Saps 2009).

Participants

The age of participants ranged between 6 years and 18 years (Bahar 2008; Roohafza 2014; Saps 2009). The studies randomised 33 participants in Bahar 2008, 115 in Roohafza 2014, and 90 in Saps 2009. In all studies, most of the participants were girls. All studies described the extent of the disease, which included participants with a diagnosis of FAP, FD, or IBS according to the Rome II (Bahar 2008; Saps 2009), or children with FAP according to the more up-to-date Rome III criteria (Roohafza 2014). Two studies reported that participants with underlying organic gastrointestinal disorders were excluded (Roohafza 2014; Saps 2009). Two studies reported that concurrent treatment was restricted: participants may not have been receiving any concurrent pharmacotherapy for depression, anxiety, or chronic pain syndromes in Bahar 2008, and in Roohafza 2014 participants may not have been receiving psychotropic drugs, antibiotics, or probiotics in the preceding two months. One study did not mention if participants had received concurrent treatment (Saps 2009).

Interventions

All included studies had two trial arms. Two studies investigated the comparison of amitriptyline versus placebo (Bahar 2008; Saps 2009), and one study randomised participants to receive either citalopram or placebo (Roohafza 2014). In the studies assessing amitriptyline dosage was administered according to bodyweight, ranging from 10 mg/day (Bahar 2008; Saps 2009) to 30 mg/day (Bahar 2008). The dose of citalopram ranged from 10 mg/day in the first week of intervention, increasing to 20 mg/day for the remaining three weeks of intervention for all participants in Roohafza 2014. Interventions were administered daily for a period of four weeks in Roohafza 2014 and Saps 2009, and for eight weeks in Bahar 2008.

Outcomes

- Treatment success, as defined by the authors, was reported in all three included studies (Bahar 2008; Roohafza 2014; Saps 2009). Saps 2009 defined treatment success as the child's assessment of satisfactory relief and satisfaction with treatment with "good" or "excellent", assessed by two questions: "Overall how do you feel your problem is?" and ''How did the medication relieve your pain?''. Bahar 2008 defined treatment success as an improvement in overall QOL score, assessed with the IBS Quality of Life questionnaire. Roohafza 2014 defined treatment response as at least a two-point reduction on a visual analogue pain scale with scores of 0 to 5.
- Pain frequency or change in frequency of pain scores were reported in one study (Bahar 2008), using a visual analogue scale (VAS).
- Pain intensity or change in pain intensity was reported by two studies (Bahar 2008; Saps 2009), using a VAS.
- Withdrawal due to adverse events was reported in all included studies (Bahar 2008; Roohafza 2014; Saps 2009).
- Quality of life was reported in one study (Bahar 2008).
- Anxiety and depression were reported in two studies (Roohafza 2014; Saps 2009). In both studies, depression was assessed using the Children's Depression Inventory (CDI). Roohafza 2014 assessed anxiety using the Revised Children's Manifest Anxiety Scale (RCMAS), where Saps 2009 used the State-Trait Anxiety Inventory for Children (STAIC).
- (Serious) adverse events were reported in two studies (Roohafza 2014; Saps 2009).
- One study reported adequate relief as part of the primary outcome (Saps 2009), assessed by the question: ''How did the medication relieve your pain?''.
- Defaecation pattern and school attendance or change in school attendance or performance were not reported in any of the studies.

Funding and declaration of interest

Funding was declared in all studies (Bahar 2008; Roohafza 2014; Saps 2009). Roohafza 2014 reported that they were supported by a University grant. Saps 2009 stated clearly that they did not receive financial support from the pharmacological industry, but they did receive partial support by two different grants. Bahar 2008 reported that the study was partly funded by a University grant, and they also received financial support from the pharmaceutical industry.

Roohafza 2014 declared no conflict of interest. Two studies did not report on conflicts of interest (Bahar 2008; Saps 2009).

Excluded studies

Three studies did not meet the inclusion criteria due to the following reasons:

- Design of the study was not an RCT and lacked comparison with a control group (Campo 2004).
- Two were ongoing randomised trials (CTRI/2018/08/015365; ACTRN12613000158763).

Risk of bias in included studies

The risk of bias in the three included studies (Bahar 2008; Roohafza 2014; Saps 2009) varied (Figure 2 and Figure 3).

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

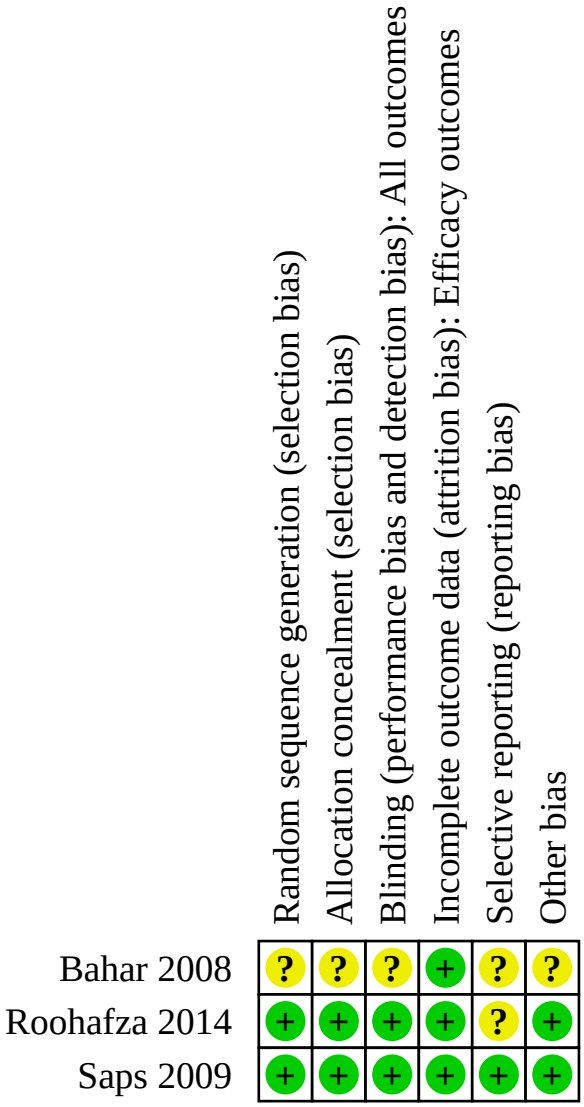
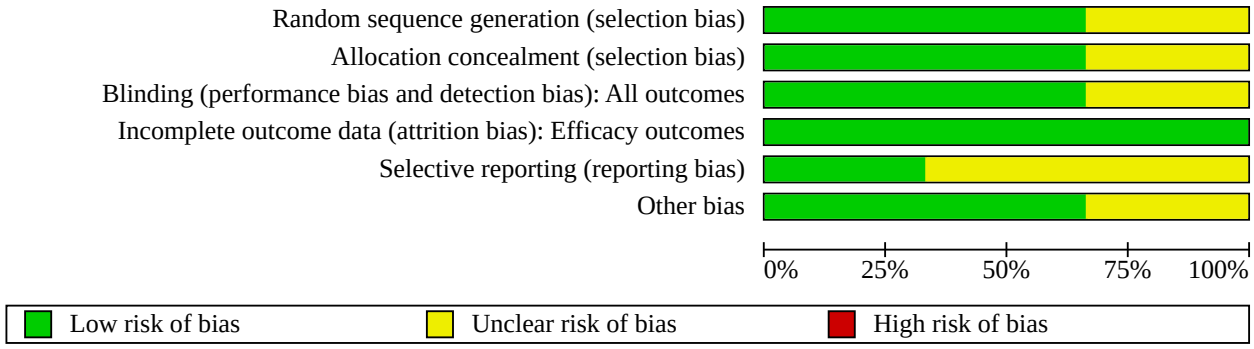


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Bahar 2008 did not report methods of randomisation, nor indicate any attempts at allocation concealment. The risk of selection bias is therefore rated as unclear. We received no response from the authors.

Roohafza 2014 states that randomisation was performed using random numbers generated by random allocation computer software in four blocks. They reported allocation was concealed during selection.

Saps 2009 did not report the exact method of randomisation and allocation concealment. We contacted the author and team. They responded and confirmed computer randomisation in a 1:1 fashion and that allocation concealment was achieved through a central pharmacy allocation.

Blinding

Bahar 2008 did not describe whether adequate blinding of investigators and participants was achieved, and we rated it as unclear, with no response from the authors.

Roohafza 2014 described that treatment (citalopram or placebo) contained opaque drug bottles coded by a pharmacist. The physician, participants and outcome assessor were unaware of the drug codes and so was rated low risk.

In the Saps 2009 study both participants and outcome assessors were masked. Treatment (amitriptyline or placebo) was provided in identical capsules and data were analysed independently at a central co-ordinating site which did not have access to the randomisation code until analysis was completed. We rated it at low risk.

Incomplete outcome data

Two dropouts were reported in Bahar 2008 prior to medication in the treatment group. Seven female participants (8%) did not complete the Saps 2009 study, with reasons given and balance between groups, so we rated this as low risk. Roohafza 2014 reported a high dropout rate: 32 participants (25%) did not complete the trial, but this was balanced between groups and all participants were accounted for, so we judged it to be at low risk.

Selective reporting

Bahar 2008 suggested that there may have been extra outcomes that were determined post hoc. No protocol was available and the authors did not respond to requests for clarification and so judged it to be at unclear risk. The protocol for Roohafza 2014 did not match with the study design, although all reported outcomes are well described. We asked the author for clarification, but received no response, and so rated it as unclear. Saps 2009 reported on all prespecified outcome measures assessing efficacy and these were as expected, and so was judged to be at low risk.

Other potential sources of bias

Bahar 2008 had significant baseline demographic imbalance and we therefore rated it at unclear risk. We found no other potential sources of bias, so rated the other two trials at low risk..

Effects of interventions

See: **Summary of findings 1** Antidepressant compared to placebo for the treatment of functional abdominal pain disorders in children and adolescents

Antidepressant vs placebo

All three studies compared an antidepressant with a placebo.

Primary outcomes

Treatment success

For the primary outcome of treatment success, two studies used reports of success on a Likert scale. Bahar 2008 defined success as a 15% improvement in quality-of-life ratings scales. Roohafza 2014 used a visual analogue pain scale with scores of 0 to 5, with a two-point reduction defined as success. Saps 2009 used a five-point scale at study end, with 'good' or 'excellent' defined as success.

Given the heterogeneity of this outcome, we included only two studies in meta-analysis (Roohafza 2014; Saps 2009). There is low-certainty evidence that there may be no difference when antidepressants are compared with placebo (RR 1.17, 95% CI 0.87 to 1.56; 2 studies, 205 participants; I^2 = 0%; random-effects model; Analysis 1.1). We downgraded the evidence for significant imprecision due to extremely sparse data (Summary of findings 1).

Bahar 2008 reported that participants receiving antidepressant were significantly more likely than those receiving placebo to experience at least a 15% improvement in overall QOL score at 10 and 13 weeks (P = 0.007 and P = 0.002, respectively (absolute figures were not given)).

Pain frequency or change in frequency of pain

Pain frequency scores were reported in one study (Bahar 2008), using a VAS. No significant differences were apparent for frequency of pain.

Pain intensity or change in pain intensity

Pain intensity scores were reported in two studies (Bahar 2008; Saps 2009), both studies using a VAS. No statistically significant difference was found between the two groups. Data were not sufficiently reported in either study to allow further analysis.

Withdrawal due to adverse events

Analysis of all three studies found low-certainty evidence that there may be no difference in the occurrence of withdrawals due to adverse events when comparing antidepressants with placebo (RR 3.17, 95% CI 0.65 to 15.33; 3 studies, 238 participants; I^2 = 0%; random-effects model; Analysis 1.2). We downgraded the evidence for significant imprecision due to extremely sparse data (Summary of findings 1).

Secondary outcomes

Quality of life

Quality of life (QOL) scores were reported in Bahar 2008. At weeks 6, 10, and 13 (after 4 and 8 weeks of treatment and 3 weeks post-treatment), participants on amitriptyline experienced significantly greater improvements in overall IBS-QOL scores than participants treated with placebo (P = 0.019, P = 0.004, and P = 0.013, respectively).

Anxiety/depression

Two trials (Roohafza 2014; Saps 2009) reported anxiety and depression. Both studies reported no significant difference between the two groups in depression scores. In Saps 2009, anxiety scores improved significantly in the amitriptyline group (P < 0.001) compared with the placebo group (P = 0.40). There was no difference between the citalopram group and the placebo group for change in anxiety scores (Roohafza 2014). We did not conduct a pooled analysis across both trials, as the outcomes were measured with different time periods and were reported inconsistently with mean or change in scores.

Defaecation pattern (disease-specific (IBS-C/D))

This outcome was not reported.

(Serious) adverse events

Two trials (Roohafza 2014; Saps 2009) reported adverse events. Saps 2009 reported three cases of adverse events (one child with fatigue, one with a rash and headaches (amitriptyline) and one with dizziness (placebo)), but none of them was considered to be serious. In Roohafza 2014, all reported adverse events (insomnia, nausea, drowsiness, dry mouth, diarrhoea, vomiting, fatigue, headache, dizziness, allergic reaction, loss of appetite) were similar for both groups, except for drowsiness and dry mouth experienced more in the citalopram group (37.2% versus 16.2%, P = 0.025 and 44.1% versus 23.2%, P = 0.034, respectively).

Adequate relief

This outcome was not reported.

School attendance or change in school attendance or performance

This outcome was not reported.

Other Outcomes

Symptom checklist

Symptom checklist scores were reported in one study (Bahar 2008). In the amitriptyline group a reduction in IBS-associated diarrhoea at weeks 6 and 10 (P = 0.029 both intervals), a reduction in periumbilical abdominal pain at 10 weeks (P = 0.018) and in right lower quadrant abdominal pain at 6, 10 and 13 weeks (P = 0.014, P = 0.039, P = 0.004) were found. For most of the symptoms associated with FAPDs (e.g. constipation, tenesmus, abdominal distension, diffuse abdominal pain, and others), no statistically significant differences in participants treated with amitriptyline or placebo could be detected at any time point.

Somatisation:

Two studies (Roohafza 2014; Saps 2009) reported somatization scores, using the Children's Somatization Inventory Questionnaire (CSI). Neither study showed a significant difference between the intervention and placebo groups. Data were not sufficiently reported in either study to allow further analysis.

Coping:

Saps 2009 measured coping using the Pain Response Inventory. There was a significant overall improvement from baseline to follow-up in coping (P = 0.02) in both groups (amitriptyline and placebo). However, there was no significant difference between the two treatment groups.

Disability:

Saps 2009 measured disability (using the Pediatric Functional Disability Inventory (PFDI)). There was a significant overall improvement from baseline to follow-up in disability (P = 0.0015) in both groups (amitriptyline and placebo). However, there was no significant difference between the two treatment groups.

Physician-rated global severity and improvement

Roohafza 2014 reported the outcome of physician-rated global severity and improvement measured with the Clinical Global Impression Severity and Improvement scales (CGI-S and CGI-I). On per-protocol analysis, change in CGI-S score did not differ at four weeks (P = 0.125), but showed significant more reduction in the citalopram group at 12 weeks (P = 0.034). CGI-I score was significantly lower (indicating more improvement) in the citalopram group compared with the placebo group at week 4 and week 12 (1.95 ± 1.24 versus 2.58 ± 1.49, P = 0.027 and 1.68 ± 1.15

versus 2.45 ± 1.46, P = 0.008). On ITT analysis GCI-I and GCI-S scores did not differ between the two groups.

DISCUSSION

Summary of main results

This systematic review reveals that the evidence for efficacy and safety of antidepressant medications in children and adolescents with FAPDs is sparse. We found only three double-blind RCTs of mixed methodological quality, two studies comparing amitriptyline to placebo for treatment of FAPD (Bahar 2008; Saps 2009) and one study comparing the second-generation antidepressant citalopram to placebo for treatment of FAPDs (Roohafza 2014).

We analysed and summarised data from 223 participants.

- There may be no difference between antidepressants and placebo for treatment success (low-certainty evidence).
- There were insufficient data on other outcome measures; they were very heterogeneous, and no further analysis was possible.
- Antidepressants may make little or no difference to the number of people withdrawing from treatment due to adverse events compared to placebo (low-certainty evidence).
- No serious adverse events were reported when using antidepressants.

A search of the International Clinical Trials Registry Platform of the World Health Organization (WHO) detected one ongoing additional RCT on the efficacy and safety of citalopram (Campo NCT00962039) in paediatric patients with FAPDs (n = 100). To date, however, no results are available for this study.

Overall completeness and applicability of evidence

Participants in the included studies were recruited from six tertiary-care centres in the USA (Saps 2009), from one suburban, private-practice paediatric gastroenterology clinic in California (Bahar 2008) and from a single outpatient tertiary clinic of paediatric gastroenterology in Iran (Roohafza 2014). In Saps 2009, only participants with reported weekly pain of more than 25 mm on a 100-mm visual analogue/Likert pain scale were randomised. Consequently, the applicability of the study results for children with lower pain levels is uncertain. Bahar 2008 only included participants with newly-diagnosed IBS, and in Roohafza 2014, none of the participants included fulfilled IBS, FD or AM criteria, finally including only participants with FAP-NOS. As a result, it is questionable if the findings for Bahar 2008 and Roohafza 2014 are also applicable for children with other subtypes of FAPDs. The results of this review should not be extrapolated to antidepressant medications other than amitriptyline or citalopram.

Length of follow-up in the studies was relatively low, given the chronic nature of the condition, further limiting the applicability of the evidence.

Quality of the evidence

The risk of bias was low in two studies. Bahar 2008, the oldest study, was rated as unclear in a number of domains. There were no ratings of high risk of bias. We used the GRADE criteria to assess the certainty of evidence. The certainty of evidence for both treatment success and safety outcomes was low. The key factor that downgraded the evidence was imprecision, due to the low sample size and event numbers.

Potential biases in the review process

Despite extensive literature searches, we could not find studies for most antidepressant medications. It remains unclear whether this reflects a lack of research or whether such studies have not been published.

Agreements and disagreements with other studies or reviews

A recent Cochrane Review on pharmacological interventions for recurrent abdominal pain in childhood found only weak evidence supporting the use of antidepressants (first- and second-generation), 5-HT4 receptor agonists, antispasmodics, antihistamines, H2 receptor antagonists and a dopamine receptor antagonist (Martin 2017). This review did not include meta-analysis for treatment with antidepressants.

Various studies exist on the efficacy and safety of antidepressant drugs in adults with FAPDs. Data obtained from studies conducted in adults are often used to tailor treatment for children with functional gastrointestinal disorders (Saps 2016; Saps 2018). Results from a Cochrane Review on bulking agents, antispasmodic, and antidepressant medication (amitriptyline, doxepine, desipramine and trimipramine) for the treatment of people with irritable bowel syndrome (Ruepert 2011) did find evidence for the benefit of antidepressants. Results from another recent systematic review using network meta-analysis showed the efficacy of tricyclic antidepressants (TCAs) for the treatment of irritable bowel syndrome in adults (RR 0.66, 95% CI 0.53 to 0.83 for failure to improve global symptom score at study end), with it ranked second for efficacy (Black 2020). An evidence-based position statement on irritable bowel syndrome by the American College of Gastroenterologists from 2018 suggests that based on good-quality trials with a limited number of participants, tricyclic antidepressants and selective serotonin reuptake inhibitors are effective for people with all subtypes of irritable bowel syndrome (Ford 2018).

AUTHORS' CONCLUSIONS

Implications for practice

The included studies revealed there may be no differences between antidepressants and placebo for treatment success. There was heterogeneity in reporting of all other primary and secondary outcomes, and further analysis was not possible. Some study results slightly favour treatment with citalopram in children with FAPDs, while treatment with amitriptyline does not appear to provide any benefit. There may also be no difference in withdrawals due to adverse events between placebo and antidepressants. Both analyses had certainty downgraded due to serious imprecision.

Implications for research

Currently, only placebo-controlled trials on antidepressant medications in children and adolescents are available. Future research is clearly indicated to enhance the certainty of findings in this area. However, as placebo is rarely an option used in practice and there is a portfolio of other therapies, studies that consider head-to-head comparisons of non-pharmacological treatments

with antidepressants may provide valuable information about the direct advantages and disadvantages of either treatment, as well as combination versus monotherapy. Additionally, given the chronic nature of FAPDs and indeed the need for such chronicity to make a diagnosis, long-term follow-up studies may be of greater clinical relevance to professionals and patients, given the longest follow-up was less than four months. Future studies must seek to report outcome measures in a homogeneous way, consistent with recommendations of The Rome Foundation subcommittee for Pharmacological Clinical Trials in Children with IBS (Saps 2016), as well as ensuring adequate statistical power and reporting in line with key trial reporting guidance.

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The updated search strategies in December 2019 were developed and run by Yuhong Yuan (Information Specialist, Cochrane Gut Group).

We are grateful to the authors who kindly responded to our request for clarification of the protocol and additional data on the trials in which they were involved.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bahar 2008

Study characteristics	
Methods	**Study design**: double-blinded, placebo-controlled, randomised trial **Setting**: private paediatric gastroenterology outpatient clinic in Encino, California, USA **Dates:** 2002-5
Participants	**Inclusion criteria**: Patients with IBS, based on Rome II criteria **Exclusion criteria**: Concurrent pharmacotherapy for depression, anxiety, or chronic pain syndromes **Sample size:** 33 children (intervention: 16; control: 16) **Age (mean)**: Intervention 14.2 years; Control: 15.3 years

Bahar 2008 *(Continued)*

	Sex (M/F): M: 9; F: 24 **Number randomised:** Intervention: 18; Control: 17 **Number analysed:** Intervention: 16; Control: 17 **Post-randomisation exclusion:** Intervention: 2 Control: 0
Interventions	**Intervention:** AMI: 7-week course of oral AMI (10 mg if 30 to 50 kg, 20 mg if 50 to 80 kg, 30 mg if > 80 kg), taken at night **Control:** placebo
Outcomes	**Duration of study:** 13 weeks 1. Quality of life 2. Pain intensity and frequency 3. IBS symptom checklist - validated in adults (Patrick 1997) 4. Pain rating scale (Smith 1997, paediatrics) Timing of outcome assessment: measured at 6, 10 and 13 weeks
Notes	**Funding source:** This study was funded by a grant from James and Diane Brooks Medical Research Foundation and AstraZeneca **Conflict of interest**: not mentioned **Power calculation**: NS **Quality of life data:** AMI data - baseline: 109.4; 10 weeks: 128; 13 weeks: 126,2 Placebo data - baseline: 127.5; 10 weeks: 129.4; 13 weeks: 128.8

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised double-blinded fashion, no more details given. No response from author.
Allocation concealment (selection bias)	Unclear risk	Method not reported, no response from author
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blinded, no further details. No clarification
Incomplete outcome data (attrition bias) Efficacy outcomes	Low risk	No flow diagram, 2 participants dropped out after randomisation in the anti-depressant group prior to medication

Bahar 2008 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No protocol presented, lack of clarity as to predefined outcomes. Suggestion of some additional outcomes reported after data collection
Other bias	Unclear risk	Imbalance in baseline characteristics (e.g. gender, 24 female vs 9 male total, difference in baseline between QOL scores (statistically significant P = 0.05)

Roohafza 2014

Study characteristics	
Methods	**Study design**: double-blinded, placebo-controlled, randomised trial **Setting**: outpatient tertiary clinic of paediatric gastroenterology in Isfahan, Iran **Dates:** February - December 2013
Participants	**Inclusion criteria**: Patients with FAP based on Rome III criteria **Exclusion criteria**: Other concomitant gastrointestinal disorders and those with a history of receiving psychotropic drugs, antibiotics, or probiotics in the preceding 2 months **Sample size:** 115 children (intervention: 59; control: 56) **Age (mean)**: Intervention: 10.4 ± 1.9 years; control: 8.5 ± 2.2 years **Sex (M/F):** Intervention: 11/32 Control: 19/24 **Number randomised:** Intervention: 59; Control: 56 **Number analysed:** Intervention: 59; Control: 56 **Post-randomisation exclusion:** Intervention: 16 Control: 13
Interventions	**Intervention:** Citalopram for 4 weeks (10 mg/day for the first week; 20 mg/day for the remaining 3 weeks) **Control:** placebo (in same order as citalopram group)
Outcomes	**Duration of study:** 12 weeks

Roohafza 2014 *(Continued)*

	1: Change in participant's pain score in 12 weeks measured with the Wong-Baker Pain Rating Scale (6 faces that show pain effect from 0- no hurt to 5- hurts worse) 2: Change in Clinical Global Impression Scale Improvement (CGI-I) in 4 and 12 weeks measured by physician-rated global improvement that is scored 1 (very much improved) to 7 (very much worse. 3. Changes in the severity of depression assessed by Children Depression Inventory 4. Changes in the severity of anxiety assessed by Revised Children's Manifest Anxiety Scales 5. Changes in somatization by using the Children's Somatisation Inventory-Revised Form
Notes	**Funding source:** this study was funded by a grant from the Isfahan University of Medical Sciences **Conflict of interest**: no competing interests declared **Power calculation**: power calculation performed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation by allocation software
Allocation concealment (selection bias)	Low risk	Allocation was concealed and completed by a pharmacist not involved in the rest of the trial
Blinding (performance bias and detection bias) All outcomes	Low risk	Opaque bottles with placebo or citalopram
Incomplete outcome data (attrition bias) Efficacy outcomes	Low risk	Flow is well described for all participants with reasons given (high general dropout rate of 25%, balanced)
Selective reporting (reporting bias)	Unclear risk	Reporting of all reported outcomes. Protocol is given; there are some methodological discrepancies that are not explained
Other bias	Low risk	No other biases reported

Saps 2009

Study characteristics

Methods	**Study design**: multicentre, double-blinded, placebo-controlled, parallel-group, randomised trial **Setting**: 6 paediatric gastroenterology clinics of 6 tertiary care centres geographically dispersed in the USA **Dates:** January 2003 - August 2006
Participants	**Inclusion criteria**: Patients with IBS, FAP or FD based on Rome II criteria **Exclusion criteria**:

Saps 2009 *(Continued)*

	Diagnosis with an organic disease, plotted below the 5th percentile for weight or height, abnormal testing (EKG, complete blood count, erythrocyte sedimentation rate, albumin, pancreatic and liver enzymes, urine analysis, stool examination for occult blood and ova and parasites, tissue transglutaminase), positive lactose breath test or history of symptoms resolving after 2 weeks of a lactose-free diet **Sample size:** 90 children (intervention: 46; control: 44) **Age (mean / SD)**: Intervention: 12.5 ± 2.9 years; control: 13.0 ± 2.7 years **Sex (M/F):** Intervention: 35/11 Control: 31/13 **Disease type:** Intervention: FD = 13%, FAP = 53%, IBS = 40% Control: FD = 8%; FAP = 31%; IBS = 62% **Number randomised:** Intervention: 46; Control: 44 **Number analysed:** Intervention: 43; Control: 40 **Post-randomisation exclusion:** Intervention: 3 Control: 4
Interventions	**Intervention:** amitriptyline for 4 weeks (10 mg/day < 35 kg; 20 mg/day > 35 kg) **Control:** placebo
Outcomes	**Duration of study:** 5 weeks 1. 1. Participant's satisfactory relief and satisfaction with treatment assessed by the questions: a. "Overall how do you feel your problem is?" (Better/Same/Worse) b. "How did the medication relieve your pain?" (Excellent/Good/Fair/Poor/Failed) 2. Effect on psychosocial traits and ability to perform daily activities, measured by the a. Pain Response Inventory 3. Children's Depression Inventory (CDI) 4. State-Trait Anxiety Inventory for Children (STAIC) 5. Children Somatisation Inventory Questionnaire 6. Paediatric Functional Disability Inventory (PFDI) 7. Visual analogue scale for pain intensity
Notes	**Funding source:** this study was supported in part by the 2003 Clinical Research Award of the American College of Gastroenterology, the CHP 19596 RA501 grant and the grants M01 RR-00048, M01 RR00084 and M01 RR-02172 from the National Center for Research Resources, National Institute of Health **Conflict of interest**: no competing interests declared **Power calculation**: power calculation performed

Saps 2009 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Method not reported in the study Author response: it was computer-randomised 1:1 (drug vs placebo)
Allocation concealment (selection bias)	Low risk	Method not reported in the study Author response: double-blinded, randomisation and dispensation of drug/ placebo was done by central pharmacy after the participant left the clinic
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical capsules as medical intervention, data were analysed independently of the investigators at a central co-ordinating site, which did not have access to the code until analysis was completed
Incomplete outcome data (attrition bias) Efficacy outcomes	Low risk	7 dropouts with detailed explanation. For those lost to follow-up the specific group was not defined, but these were not study-relevant dropouts
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes are reported. No protocol is given but outcomes were as expected
Other bias	Low risk	The study appears to be free of other sources of bias

EKG: electrocardiogram; FAP: functional abdominal pain; FD: functional disorder; IBS: irritable bowel syndrome

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Campo 2004	Not RCT, no control group

Characteristics of ongoing studies *[ordered by study ID]*

ACTRN12613000158763

Study name	Evaluating treatment efficacy of citalopram, symbiotic, and mebeverine for children with functional abdominal pain
Methods	Randomised, double-blind, placebo-controlled trial
Participants	Children and adolescents aged 6 to 18 years with functional abdominal pain (FAP)
Interventions	Citalopram (10 mg/ day for 1 week and 20 mg/day for 3 weeks) or Mebeverine (135 mg twice daily) or Lactol tablet (150 million spores + 100 mg FOS twice daily) or placebo (twice daily) for 4 weeks
Outcomes	Primary outcomes: Clinical Global Impression-Global Improvement (CGI-I), Clinical Global Impression-severity (CGI-S) and Wong-Baker Faces Pain Rating Score at 4 weeks. Secondary outcomes: CGI-I, CGI-S and Wong-Baker Faces Pain Rating Score at 12 weeks after end of treatment
Starting date	November 2012 to December 2013
Contact information	Principal Investigator: Zahra Pourmoghaddas, Emam Hosein Children Hospital, Iran

ACTRN12613000158763 *(Continued)*

Notes	anzctr.org.au Identifier: ACTRN12613000158763 Principal investigator was contacted, no response received.

CTRI/2018/08/015365

Study name	Study of efficacy of drug amitriptyline in reducing pain symptoms in children with functional abdominal pain: comparison with placebo
Methods	Randomised, parallel-group, placebo-controlled trial
Participants	Children and adolescents aged 7 to 8 years with a functional abdominal pain disorder (FAPD) according to the ROME IV criteria
Interventions	Amitriptyline (10 to 25 mg/day) or placebo for 12 weeks
Outcomes	Primary outcome: effect of amitriptyline on intensity, duration, frequency of pain and daily activity based on the PAIN SCORE TABLE 12 weeks after starting medication. Secondary outcome: effect of amitriptyline on intensity, duration, frequency of pain and daily activity at 1 month after starting medication
Starting date	May 2018 to December 2019
Contact information	Principal Investigator: Ujjal Poddar, Department of Paediatric Gastroenterology, Sanjay Gandhi Postgraduate Institute of Medical Sciences
Notes	ctri.nic.in Identifier: CTRI/2018/08/015365 Principal investigator was contacted, but no response received

CGI: clinical global impression; FOS: Fructo-oligosacharides

DATA AND ANALYSES

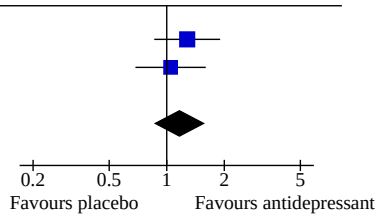
Comparison 1. antidepressant versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Global improvement	2	205	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.87, 1.56]
1.2 Withdrawals due to adverse events	3	238	Risk Ratio (M-H, Random, 95% CI)	3.17 [0.65, 15.33]

Analysis 1.1. Comparison 1: antidepressant versus placebo, Outcome 1: Global improvement

Study or Subgroup	Antidepressant Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Roohafza 2014	31	59	23	56	53.3%	1.28 [0.86 , 1.90]
Saps 2009	23	46	21	44	46.7%	1.05 [0.69 , 1.60]
Total (95% CI)		**105**		**100**	**100.0%**	**1.17 [0.87 , 1.56]**
Total events:	54		44			

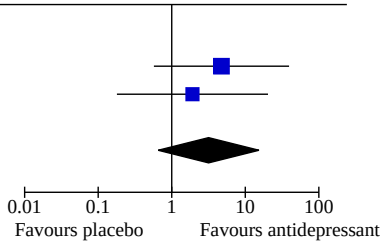
Heterogeneity: Tau² = 0.00; Chi² = 0.46, df = 1 (P = 0.50); I² = 0%
Test for overall effect: Z = 1.04 (P = 0.30)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: antidepressant versus placebo, Outcome 2: Withdrawals due to adverse events

Study or Subgroup	Antidepressant Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bahar 2008	0	16	0	17		Not estimable
Roohafza 2014	5	59	1	56	55.5%	4.75 [0.57 , 39.37]
Saps 2009	2	46	1	44	44.5%	1.91 [0.18 , 20.35]
Total (95% CI)		**121**		**117**	**100.0%**	**3.17 [0.65 , 15.33]**
Total events:	7		2			

Heterogeneity: Tau² = 0.00; Chi² = 0.32, df = 1 (P = 0.57); I² = 0%
Test for overall effect: Z = 1.43 (P = 0.15)
Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. Search Strategy - Cochrane CENTRAL (via Ovid RMBR)

1. (functional gastrointestinal disorder* or FGIDs).tw,kw.
2. exp Irritable Bowel Syndrome/
3. (irritable bowel syndrome or irritable colon* or IBS).tw,kw.
4. exp Dyspepsia/
5. (dyspepsia or dyspeptic or indigestive or indigestion or NUD or FD).tw,kw.
6. ((recurre* or replap* or refractor* or chronic) adj5 ((abdominal or abdomen) adj3 (pain* or migraine* or colic* or discomfort* or ache* or aching))).tw,kw.
7. (functional adj5 ((abdominal or abdomen) adj3 (pain* or migraine* or colic* or discomfort* or ache* or aching))).tw,kw.
8. exp Recurrence/ and exp Abdominal Pain/
9. ((abdominal or abdomen) adj migraine*).tw,kw.
10. or/1-9
11. exp Antidepressive Agents/
12. (antidepress* or anti-depress*).tw,kw.
13. exp Monoamine Oxidase Inhibitors/
14. (MAOI* or RIMA* or ((monoamine oxidase or MAO) adj3 (inhibit* or antagonist* or block*))).tw,kw.
15. dopamine uptake inhibitors/
16. "serotonin and noradrenaline reuptake inhibitors"/ or serotonin uptake inhibitors/
17. ((((serotonin or norepinephrine or noradrenaline or neurotransmitter* or dopamin*) adj2 (uptake or reuptake or re-uptake)) or 5HT* or 5-HT*) adj3 (inhibit* or antagonist* or block*)).tw,kw.
18. (SSRI* or SNRI* or NARI* or SARI* or NDRI* or TCA* or tricyclic* or tetracyclic*).tw,kw.
19. (Agomelatine or Alaproclate or Amoxapine or Amineptine or Amfebutamone or Amitriptylin* or Amitriptylinoxide or Atomoxetin* or Befloxatone or Benactyzine or Binospirone or Brofaromine or Bupropion or Butriptyline).tw,kw.

20. (Caroxazone or Cianopramine or Cilobamine or Cimoxatone or Citalopram or Chlorimipramin* or Clomipramin* or Chlomipramin* or Clomipramine or Clorgyline or Clovoxamine or CX157 or Tyrima or Demexiptiline or Deprenyl or Desipramine* or Pertofrane or Desvenlafaxine or Dibenzepin or Diclofensine or Dimetacrin* or Dosulepin or Dothiepin or Doxepin or Duloxetine or Desvenlafaxine or DVS-233).tw,kw.
21. (Escitalopram or Etoperidone or Edivoxetine or Femoxetine or Fluotracen or Fluoxetine or Fluvoxamine or Hyperforin or Hypericum or Imipramin* or Iprindole or Iproniazid* or Ipsapirone or Isocarboxazid* or Levomilnacipran or Lofepramine* or "Lu AA21004" or Vortioxetine or "Lu AA24530" or LY2216684).tw,kw.
22. (Maprotiline or Melitracen or Metapramine or Mianserin or Milnacipran or Minaprine or Mirtazapine or Moclobemide or Nefazodone or Nialamide or Nitroxazepine or Nomifensine or Norfenfluramine or Nortriptylin* or Noxiptilin*).tw,kw.
23. (Opipramol or Oxaflozane or Paroxetine or Phenelzine or Pheniprazine or Pipofezine or Pirlindole or Pivagabine or Pizotyline or Propizepine or Protriptylin* or Quinupramine or Reboxetine or Rolipram or Scopolamine or Selegiline or Sertraline or Setiptiline or Teciptiline or Thozalinone or thymoanaleptic* or Tianeptin* or Toloxatone or Tranylcypromin* or Trazodone or Trimipramine or Venlafaxine or Viloxazine or Vilazodone or Viqualine or Zalospirone).tw,kw.
24. or/11-23
25. exp Adolescent/
26. exp Child/
27. exp Infant/
28. exp Minors/
29. exp Pediatrics/
30. exp Puberty/
31. exp Schools/
32. (baby or babies or child or children or neonatal or pediatric* or paediatric* or peadiatric* or infan* or neonat* or newborn* or new born* or kid or kids or adolescen* or preschool or pre-school or toddler*).tw,kw.
33. (elementary school* or high school* or highschool* or kinder* or Jugend* or nursery school* or primary school* or secondary school* or youth* or young or student* or juvenil* or school age* or schoolchild* or underage* or (under* adj age*) or under 16 or under 18).tw,kw.
34. (postmatur* or prematur* or preterm* or perinat* or boy* or girl* or teen* or minors or prepubescen* or prepuberty* or pubescen* or puber*).tw,kw.
35. or/25-34
36. 10 and 24 and 35
37. limit 36 to yr="2011 -Current"

Appendix 2. Search Strategy - Medline (via OvidP)

1. (functional gastrointestinal disorder* or FGIDs).tw,kw.
2. exp Irritable Bowel Syndrome/
3. (irritable bowel syndrome or irritable colon* or IBS).tw,kw.
4. exp Dyspepsia/
5. (dyspepsia or dyspeptic or indigestive or indigestion or NUD or FD).tw,kw.
6. ((recurre* or replap* or refractor* or chronic) adj5 ((abdominal or abdomen) adj3 (pain* or migraine* or colic* or discomfort* or ache* or aching))).tw,kw.
7. (functional adj5 ((abdominal or abdomen) adj3 (pain* or migraine* or colic* or discomfort* or ache* or aching))).tw,kw.
8. exp Recurrence/ and exp Abdominal Pain/
9. ((abdominal or abdomen) adj migraine*).tw,kw.
10. or/1-9
11. exp Antidepressive Agents/
12. (antidepress* or anti-depress*).tw,kw.
13. exp Monoamine Oxidase Inhibitors/
14. (MAOI* or RIMA* or ((monoamine oxidase or MAO) adj3 (inhibit* or antagonist* or block*))).tw,kw.
15. dopamine uptake inhibitors/
16. "serotonin and noradrenaline reuptake inhibitors"/ or serotonin uptake inhibitors/
17. ((((serotonin or norepinephrine or noradrenaline or neurotransmitter* or dopamin*) adj2 (uptake or reuptake or re-uptake)) or 5HT* or 5-HT*) adj3 (inhibit* or antagonist* or block*)).tw,kw.
18. (SSRI* or SNRI* or NARI* or SARI* or NDRI* or TCA* or tricyclic* or tetracyclic*).tw,kw.
19. (Agomelatine or Alaproclate or Amoxapine or Amineptine or Amfebutamone or Amitriptylin* or Amitriptylinoxide or Atomoxetin* or Befloxatone or Benactyzine or Binospirone or Brofaromine or Bupropion or Butriptyline).tw,kw.

20. (Caroxazone or Cianopramine or Cilobamine or Cimoxatone or Citalopram or Chlorimipramin* or Clomipramin* or Chlomipramin* or Clomipramine or Clorgyline or Clovoxamine or CX157 or Tyrima or Demexiptiline or Deprenyl or Desipramine* or Pertofrane or Desvenlafaxine or Dibenzepin or Diclofensine or Dimetacrin* or Dosulepin or Dothiepin or Doxepin or Duloxetine or Desvenlafaxine or DVS-233).tw,kw.
21. (Escitalopram or Etoperidone or Edivoxetine or Femoxetine or Fluotracen or Fluoxetine or Fluvoxamine or Hyperforin or Hypericum or Imipramin* or Iprindole or Iproniazid* or Ipsapirone or Isocarboxazid* or Levomilnacipran or Lofepramine* or "Lu AA21004" or Vortioxetine or "Lu AA24530" or LY2216684).tw,kw.
22. (Maprotiline or Melitracen or Metapramine or Mianserin or Milnacipran or Minaprine or Mirtazapine or Moclobemide or Nefazodone or Nialamide or Nitroxazepine or Nomifensine or Norfenfluramine or Nortriptylin* or Noxiptilin*).tw,kw.
23. (Opipramol or Oxaflozane or Paroxetine or Phenelzine or Pheniprazine or Pipofezine or Pirlindole or Pivagabine or Pizotyline or Propizepine or Protriptylin* or Quinupramine or Reboxetine or Rolipram or Scopolamine or Selegiline or Sertraline or Setiptiline or Teciptiline or Thozalinone or thymoanaleptic* or Tianeptin* or Toloxatone or Tranylcypromin* or Trazodone or Trimipramine or Venlafaxine or Viloxazine or Vilazodone or Viqualine or Zalospirone).tw,kw.
24. or/11-23
25. exp Adolescent/
26. exp Child/
27. exp Infant/
28. exp Minors/
29. exp Pediatrics/
30. exp Puberty/
31. exp Schools/
32. (baby or babies or child or children or neonatal or pediatric* or paediatric* or peadiatric* or infan* or neonat* or newborn* or new born* or kid or kids or adolescen* or preschool or pre-school or toddler*).tw,kw.
33. (elementary school* or high school* or highschool* or kinder* or Jugend* or nursery school* or primary school* or secondary school* or youth* or young or student* or juvenil* or school age* or schoolchild* or underage* or (under* adj age*) or under 16 or under 18).tw,kw.
34. (postmatur* or prematur* or preterm* or perinat* or boy* or girl* or teen* or minors or prepubescen* or prepuberty* or pubescen* or puber*).tw,kw.
35. or/25-34
36. 10 and 24 and 35
37. limit 36 to yr="2011 -Current"

Appendix 3. Search Strategy - Embase (via OvidSP)

1. (functional gastrointestinal disorder* or FGIDs).tw,kw.
2. exp irritable colon/
3. (irritable bowel syndrome or irritable colon* or IBS).tw,kw.
4. exp dyspepsia/
5. (dyspepsia or dyspeptic or indigestive or indigestion or NUD or FD).tw,kw.
6. ((recurre* or replap* or refractor* or chronic) adj5 ((abdominal or abdomen) adj3 (pain* or migraine* or colic* or discomfort* or ache* or aching))).tw,kw.
7. (functional adj5 ((abdominal or abdomen) adj3 (pain* or migraine* or colic* or discomfort* or ache* or aching))).tw,kw.
8. exp recurrent disease/ and exp abdominal pain/
9. ((abdominal or abdomen) adj migraine*).tw,kw.
10. or/1-9
11. exp antidepressant agent/
12. (antidepress* or anti-depress*).tw,kw.
13. (MAOI* or RIMA* or ((monoamine oxidase or MAO) adj3 (inhibit* or antagonist* or block*))).tw,kw.
14. exp dopamine uptake inhibitor/
15. ((((serotonin or norepinephrine or noradrenaline or neurotransmitter* or dopamin*) adj2 (uptake or reuptake or re-uptake)) or 5HT* or 5-HT*) adj3 (inhibit* or antagonist* or block*)).tw,kw.
16. (SSRI* or SNRI* or NARI* or SARI* or NDRI* or TCA* or tricyclic* or tetracyclic*).tw,kw.
17. (Agomelatine or Alaproclate or Amoxapine or Amineptine or Amfebutamone or Amitriptylin* or Amitriptylinoxide or Atomoxetin* or Befloxatone or Benactyzine or Binospirone or Brofaromine or Bupropion or Butriptyline).tw,kw.
18. (Caroxazone or Cianopramine or Cilobamine or Cimoxatone or Citalopram or Chlorimipramin* or Clomipramin* or Chlomipramin* or Clomipramine or Clorgyline or Clovoxamine or CX157 or Tyrima or Demexiptiline or Deprenyl or Desipramine* or Pertofrane or

Desvenlafaxine or Dibenzepin or Diclofensine or Dimetacrin* or Dosulepin or Dothiepin or Doxepin or Duloxetine or Desvenlafaxine or DVS-233).tw,kw.

19. (Escitalopram or Etoperidone or Edivoxetine or Femoxetine or Fluotracen or Fluoxetine or Fluvoxamine or Hyperforin or Hypericum or Imipramin* or Iprindole or Iproniazid* or Ipsapirone or Isocarboxazid* or Levomilnacipran or Lofepramine* or "Lu AA21004" or Vortioxetine or "Lu AA24530" or LY2216684).tw,kw.
20. (Maprotiline or Melitracen or Metapramine or Mianserin or Milnacipran or Minaprine or Mirtazapine or Moclobemide or Nefazodone or Nialamide or Nitroxazepine or Nomifensine or Norfenfluramine or Nortriptylin* or Noxiptilin*).tw,kw.
21. (Opipramol or Oxaflozane or Paroxetine or Phenelzine or Pheniprazine or Pipofezine or Pirlindole or Pivagabine or Pizotyline or Propizepine or Protriptylin* or Quinupramine or Reboxetine or Rolipram or Scopolamine or Selegiline or Sertraline or Setiptiline or Teciptiline or Thozalinone or thymoanaleptic* or Tianeptin* or Toloxatone or Tranylcypromin* or Trazodone or Trimipramine or Venlafaxine or Viloxazine or Vilazodone or Viqualine or Zalospirone).tw,kw.
22. or/11-21
23. exp adolescence/
24. exp child/
25. exp high school/
26. exp kindergarten/
27. exp middle school/
28. exp newborn/
29. exp nursery school/
30. exp pediatrics/
31. exp primary school/
32. exp puberty/
33. exp school/
34. (baby or babies or child or children or neonatal or pediatric* or paediatric* or peadiatric* or infan* or neonat* or newborn* or new born* or kid or kids or adolescen* or preschool or pre-school or toddler*).tw,kw.
35. (elementary school* or high school* or highschool* or kinder* or Jugend* or nursery school* or primary school* or secondary school* or youth* or young or student* or juvenil* or school age* or schoolchild* or underage* or (under* adj age*) or under 16 or under 18).tw,kw.
36. (postmatur* or prematur* or preterm* or perinat* or boy* or girl* or teen* or minors or prepubescen* or prepuberty* or pubescen* or puber*).tw,kw.
37. or/23-36
38. 10 and 22 and 37
39. limit 38 to yr="2011 -Current"

WHAT'S NEW

Date	Event	Description
2 February 2021	New search has been performed	[Need to complete]
8 January 2021	New citation required and conclusions have changed	Update review completed

HISTORY

Protocol first published: Issue 4, 2009
Review first published: Issue 7, 2011

CONTRIBUTIONS OF AUTHORS

Review design: MG
Review co-ordination: MT, MG, RR, CB
Data collection:
Search results screening: MG, RR, CB
Retrieval of papers: MG, RR, CB
Paper screening and appraisal, and extraction of data: MG, RR, CB

Writing to authors for additional information: MG, RR, CB
Entering the data into Review Manager 5: MG, RR, CB
Analysis of the data: MG, RR, CB
Interpretation of the data: MG, RR, CB
- Methodological perspective: MG, RR, CB
- Clinical perspective: MB, MT, RR, CB

DECLARATIONS OF INTEREST

MB: Consultant for Shire, Norgine, Coloplast, Danone, Takeda, Allergan, Shire, FrieslandCampina, United Pharamceuticals.

MT: None known

MG: Since August 2016, I have received travel fees to attend international scientific and training meetings from Pharma companies. These grants included no honoraria, inducement, advisory role or any other relationship and were restricted to the travel and meeting related costs of attending such meetings. These include: DDW May 2017, World Congress of Gastroenterology October 2017, DDW May 2018, Advances in IBD December 2018, DDW May 2019. None of these companies have had any involvement in any works completed by me and I have never had any payments for any other activities for them, as confirmed below. From this date onwards, I have made a personal undertaking to take no further funds from any pharmaceutical or formula company in any form for travel or other related activities. This is to lift the limitations such funding has on my ability to act as a first and corresponding author on reviews, in line with the Cochrane policies on such matters and is reported in line with these policies. These current declarations will expire over the next three years and this statement updated regularly to reflect this.
RR: None known.

CB: None known.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There were no differences between the protocol and the review.

INDEX TERMS

Medical Subject Headings (MeSH)

Abdominal Pain [*drug therapy] [psychology]; Amitriptyline [adverse effects] [*therapeutic use]; Antidepressive Agents, Tricyclic [adverse effects] [therapeutic use]; Gastrointestinal Diseases [*drug therapy] [psychology]; Irritable Bowel Syndrome [drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Adolescent; Child; Humans