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PRACTICE GUIDELINE

Gastroenterology

ESPGHAN/NASPGHAN guidelines for treatment of irritable bowel syndrome and functional abdominal pain-not otherwise specified in children aged 4–18 years

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Abstract

Objectives: Abdominal pain related disorders of gut–brain interaction (AP-DGBIs) such as irritable bowel syndrome (IBS) and functional abdominal pain-not otherwise specified (FAP) are common conditions in children, significantly impacting quality of life. This treatment guideline for IBS and FAP in children of 4–18 years is a collaborative effort of the European and North

Jip Groen, Morris Gordon, and Ashish Chogle share first authorship for this study. Vasiliki Sinopoulou, Merit Tabbers, and Miguel Saps share senior authorship for this study.

American Societies for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN and NASPGHAN). We aim to comprehensively review the current evidence on treatment options and offer evidence-based recommendations with utility across all treatment settings worldwide, as well as to provide methodological directions for future research.

Methods: The guideline development followed the "Grading of Recommendations Assessment, Development and Evaluation" (GRADE) approach, which is in accordance with the GRADE handbook and supported by the World Health Organization. The Guideline Development Group (GDG) comprised clinical experts, representing ESPGHAN, NASPGHAN, and Cochrane. Individual members have put forward a final consensus list of treatment options, which were then translated into "patient, intervention, comparison, outcome" (PICO) format options. Prospective agreement on decision thresholds for efficacy and safety outcomes was reached through a Delphi process among the GDG to support GRADEing of the literature. Consensus voting was used to finalize recommendations, and a treatment algorithm was developed.

Results: Systematic literature searches for this output identified 86 original randomized controlled trials assessing treatment of IBS and FAP. Consensus was reached for 25 GRADEd recommendations. Ten best practice statements were formulated, and guidance for future research methodology was proposed.

Conclusion: This guideline represents the first collaborative output of ESPGHAN and NASPGHAN on treatment options for AP-DGBIs. Systematic review of the evidence has exposed major evidence gaps for the treatment of these disorders and incentivizes large pediatric trials, particularly on treatment options for which, to date, no evidence exists.

KEYWORDS

disorders of gut brain interaction, functional abdominal pain, gut-brain psychotherapies, irritable bowel syndrome, pediatric

Executive summary of recommendations with at least low certainty evidence

- **Hypnotherapy** is **recommended** as a treatment option
  (Strong recommendation, Moderate certainty evidence)
- **Cognitive Behavioral therapy** (CBT) is **recommended** as a treatment option
  (Strong recommendation, Low certainty evidence)
- **Percutaneous Electrical Nerve Field Stimulation (PENFS)** is **suggested** as a treatment option
  (Conditional recommendation, Moderate certainty evidence)
- **Probiotics (Multi-strain) and Synbiotics (multi-strain probiotics and prebiotic)** may be **suggested** as a treatment option
  (Conditional recommendation, Low certainty evidence)
- **Enteric-coated peppermint capsules** may be **suggested** as a treatment option
  (Conditional recommendation, Low certainty evidence)
- **Amitriptyline** may be **suggested** as a treatment option
  (Conditional recommendation, Low certainty evidence)

What is known

- AP-DGBIs like IBS and FAP-NOS share overlapping mechanisms and are often studied together in pediatric trials.
- Clinical treatment practices vary regionally and include numerous options, many lacking strong pediatric data.

What is new

- Gut-brain psychotherapies, especially hypnotherapy, show the strongest evidence and effect size.
- Common treatments like anticholinergics, bile acid sequestrants, and loperamide lack pediatric evidence.

- **Domperidone** may be **suggested** as a treatment option
  (Conditional recommendation, Low certainty evidence)
- **Cyproheptadine** may be **suggested** as a treatment option

(Conditional recommendation, Low certainty evidence)

- **Buspirone** is **NOT suggested** as a treatment option (Conditional recommendation, Low certainty evidence)
- **Mebeverine** is **NOT suggested** as a treatment option (Conditional recommendation, Low certainty evidence)
- **Drotaverine** is **NOT suggested** as a treatment option (Conditional recommendation, Low certainty evidence)
- **Citalopram** is **NOT suggested** as a treatment option (Conditional recommendation, Low certainty evidence)
- **Yoga** is **NOT suggested** as a treatment option (Conditional recommendation, Low certainty evidence)

Irritable Bowel Syndrome (IBS) Specific recommendations

- **Soluble dietary fiber supplements** (i.e., hydrolized guar gum, glucomannan, psyllium) are **suggested** as a treatment option for IBS only (Conditional recommendation, Moderate certainty evidence)
- ***Lactobacillus rhamnosus GG*** is **suggested** as a treatment option for IBS (Conditional recommendation, Moderate certainty evidence) (Figures 1 and 2)

Executive summary of Best Practice Statements

- The Guideline Development Group (GDG) notes that a crucial emphasis should be placed on education regarding the abdominal pain-related disorders of gut–brain interaction (AP-DGBI) diagnosis during initial outpatient consultation sessions. Education should focus on the positive nature of the diagnosis, the relevance of the connection between the gut and brain, the effects of lifestyle and other triggers, and an outline of potential treatment approaches and options.
- The GDG recognizes that dietary treatment options can seem harmless and, therefore, receive consideration as an entry-level treatment option, particularly for motivated families. The GDG wishes to highlight that restrictive diets may require unrealistic or even disproportionate commitment from children and should be employed with the same consideration as all active interventions, with particular caution in children with risk factors for disordered eating.
- The GDG has made "Grading of Recommendations Assessment, Development and Evaluation" (GRADE) recommendations about specific preparations of – probiotic/synbiotic. All other preparations do not have sufficient evidence at a strain level to support such recommendations due to low study numbers and variable outcomes.
- The GDG recognizes that over-the-counter (OTC) analgesics are commonly used. Whereas they may have a role in intermittent or periodic symptom control, the GDG raises caution beyond local OTC dosing and duration guidance.
- The GDG finds that several alternative analgesic treatment classes should NOT be used without input and guidance through an appropriate specialist with expertise in treating therapy-refractory pediatric AP-DGBIs.
- The GDG acknowledges that the use of anticholinergic antispasmodics for symptom control is common in AP-DGBIs, but there is no evidence supporting or rejecting their use as a treatment.
- The GDG suggests loperamide as a treatment option for symptom control in patients with IBS-Diarrhea subtype (IBS-D).
- The GDG suggests bile acid sequestrants as a treatment option for symptom control in patients with IBS-D.
- The GDG suggests against the use of cannabidiol/cannabis.
- The GDG strongly recommends against the use of surgery for the evaluation and treatment of AP-DGBIs.

1 | INTRODUCTION

AP-DGBIs have a pooled worldwide prevalence of 13.5% in children aged 4–18 years old.[1] These disorders have a significant impact on quality of life, resulting from chronic pain and increased psychological comorbidities, such as anxiety and depression.[2–6] The Rome IV criteria propose a subcategorization of 4 subtypes of AP-DGBIs, that is, IBS, functional abdominal pain-not otherwise specified (FAP), functional dyspepsia (FD) and abdominal migraine (AM).[7] Considerable clinical overlap exists between these entities, notably between IBS and FAP. These two conditions may even share a common etiopathogenetic pathway, potentially representing different manifestations of a similar disorder, where pain presentation is comparable and differentiation is based on defecation pattern.[8] Similar management approaches have been adopted for IBS and FAP in clinical practice, and they are often studied together in research settings.[9–12] Management approaches predominantly target the reduction of chronic pain to restore function and include various pharmacological therapies, dietary modifications, gut–brain psychotherapies, probiotics, and percutaneous electrical nerve field stimulation (PENFS).[13]

Recent advancements in the understanding of the etiopathogenesis of AP-DGBIs have led to the increased endorsement of the biopsychosocial model.

This model suggests that structural and functional disruptions of the gut–brain axis may be induced by both gastrointestinal factors (e.g., intestinal infection) and psychosocial sensitizing events (e.g., traumatic experience), against a background of potential genetic predisposition.[13] Triggers for disease onset may present long before symptoms become evident, limiting preventive strategies or establishing direct causality. A wide array of treatment options has been studied or empirically utilized in the pediatric population.[9–12] These treatment options target various aspects of the biopsychosocial model.

There has been a continued momentum for collaborative guideline outputs by the European and North American societies for pediatric gastroenterology, hepatology, and nutrition (ESPGHAN and NASPGHAN) since the publication of the treatment guideline for functional constipation.[14] The current guidelines aim to provide evidence-based recommendations for the treatment of AP-DGBIs, such as IBS and FAP in children. These recommendations are based on a systematic review and comprehensive synthesis of the literature.

1.1 | Target audience

These guidelines are directed towards patients and their caregivers, primary up to quaternary health care professionals, researchers in gut motility and DGBI, and public policy makers. The treatment recommendations in this guideline are formulated to establish a framework for shared decision making between patients, caregivers, and healthcare professionals, rather than to mandate a standard of care. It is essential to exercise caution when interpreting these guideline recommendations in isolation and consider the qualifying remarks that accompany them, as they may be important in individual cases.

2 | METHODS

This document outlines the recommendations of the joint ESPGHAN/NASPGHAN GDG. The development process was guided by the GRADE framework, as outlined in the GRADE handbook, supported by the World Health Organization (WHO).[15] In line with this guidance, a complete protocol for the technical review, along with associated operating procedures, was agreed upon in advance and published previously,[16] in line with other similar guidelines.[17]

The GDG was chaired by a member of each of the societies (for ESPGHAN, M.B., for NASPGHAN, A.D.), as well as a GRADE methodologist, pediatrician, and Editor of the Cochrane Gut group (M.G.). Wider GDG members were chosen as experts in AP-DGBI management, and to ensure a wide range of clinical expertise. The 15 voting members included a general pediatrician (A.V.), pediatric gastroenterologists (M.B., R.B., O.B., A.C., A.D., J.D., J.K., C.D.L., H.P., R.S., N.T., M.T., and M.S.), a pediatric psychiatrist (H.P.), and a clinical psychologist (J.S.). A nonvoting methodological team comprised the GRADE co-chair (M.G.) and two members (J.G. and V.S.), who were primarily responsible for technical systematic review and GRADE analysis of data and data synthesis summaries. One of the methodological team members (V.S.) is also a registered dietitian. All members agreed to co-author the full guideline and maintain the confidentiality of open discussion and debate within the process. Any relevant conflicts of interest were declared at the start of the process and again before each step of the voting process.

2.1 | Scope of treatment options

The development process began by reaching an agreement on a final list of thematic questions (i.e., treatment options) that were then translated into Patient–Intervention–Comparison–Outcome (PICO format questions). The prospectively agreed-upon list of treatment options can be found in the previously published protocol.[16]

2.2 | Scope of recommendations

As per the original scope of the guideline, FD has not been considered.[16] It was planned to consider all three remaining AP-DGBIs sub-diagnostic categories (i.e., IBS, FAP and AM). The included studies' summary table (Supporting Information S1: File 1 – Table 2) demonstrates the range of potential diagnostic categories eligible in each study. AM was considered in the scope of some of these studies, but actual recruitment of patients from this category was very low, consistent with the overall prevalence of AM. Patients with AM represent less than 5% of the included population, despite being considered throughout. Moreover, there is an absence of any AM-focused studies, and especially those focusing on migraine-specific mechanisms and/or migraine-targeted therapies. As a consequence, a consensus decision was made that where recommendations are stated for AP-DGBIs, it is suggested that these be considered to only include IBS and FAP. This decision supports the distinct – best practice – management approach that patients with AM receive. There is no treatment algorithm for AM, which is pending future research focusing on AM in general and specific therapies.

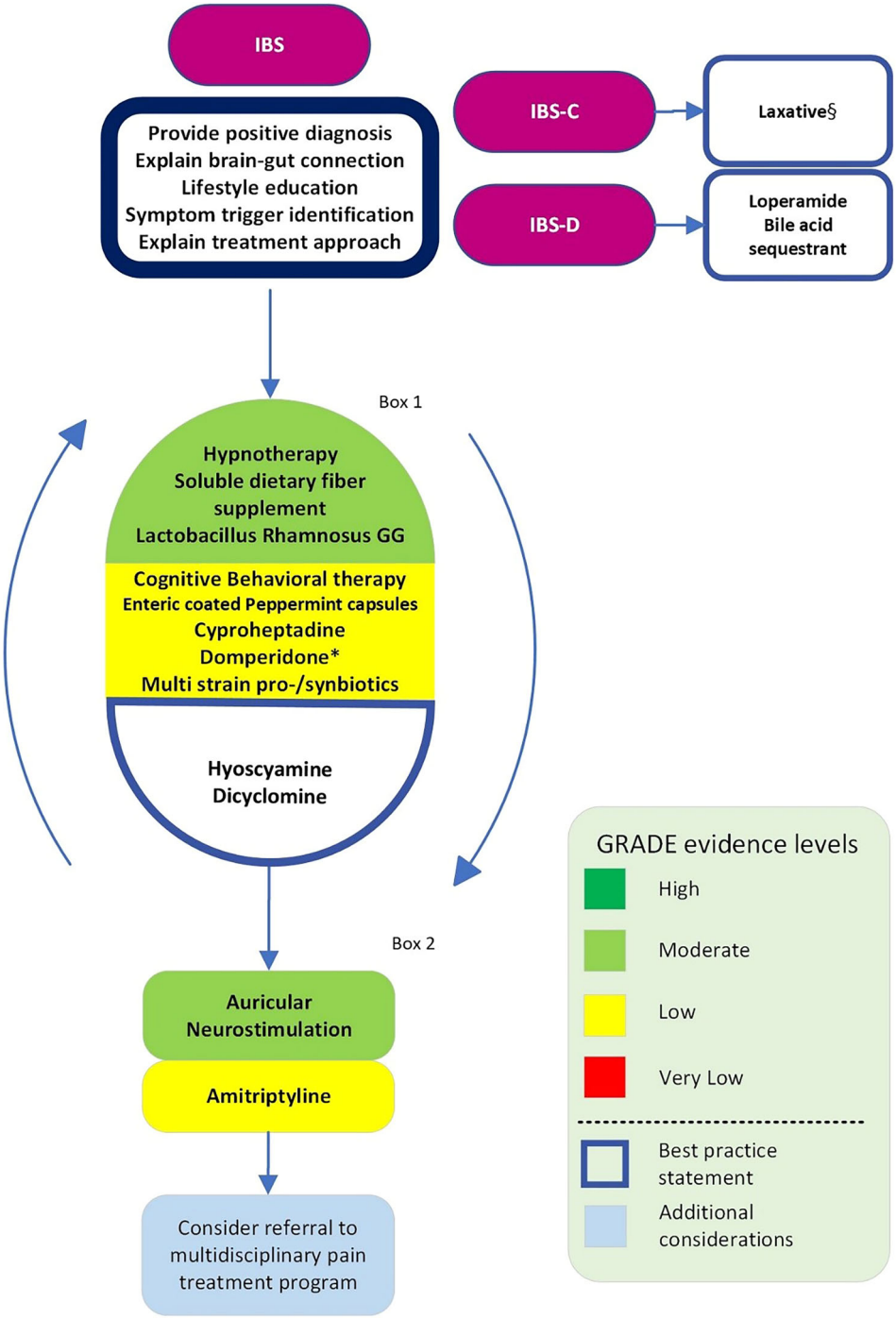

FIGURE 1 Treatment algorithm for irritable bowel syndrome (IBS); The "Grading of Recommendations Assessment, Development and Evaluation" (GRADE) data synthesis is the primary source informing the flow of treatments. However, best practice statements and additional considerations have also been included as they may be of additional value. The suggested flow provides a framework for shared decision-making. The choice of any particular treatment option should strongly reflect the balance of efficacy and safety from an individual patient perspective, local availability and feasibility, and potentially legal frameworks. The consecutive order of treatments as proposed in this algorithm, may as such be modified following local context. Time to manifestation of treatment effect may vary depending on the chosen treatment option. Evaluation should be performed accordingly. IBS-C, constipation; IBS-D, diarrhea. §For choosing a laxative, use the European and North American Societies for Gastroenterology, Hepatology and Nutrition (ESPGHAN/NASPGHAN) guidelines on functional constipation.[14] *Despite low certainty evidence supporting efficacy to treat abdominal pain disorders of gut–brain interaction symptoms, the consensus among the guideline's authors is that they lack sufficient experience in using domperidone in clinical practice.

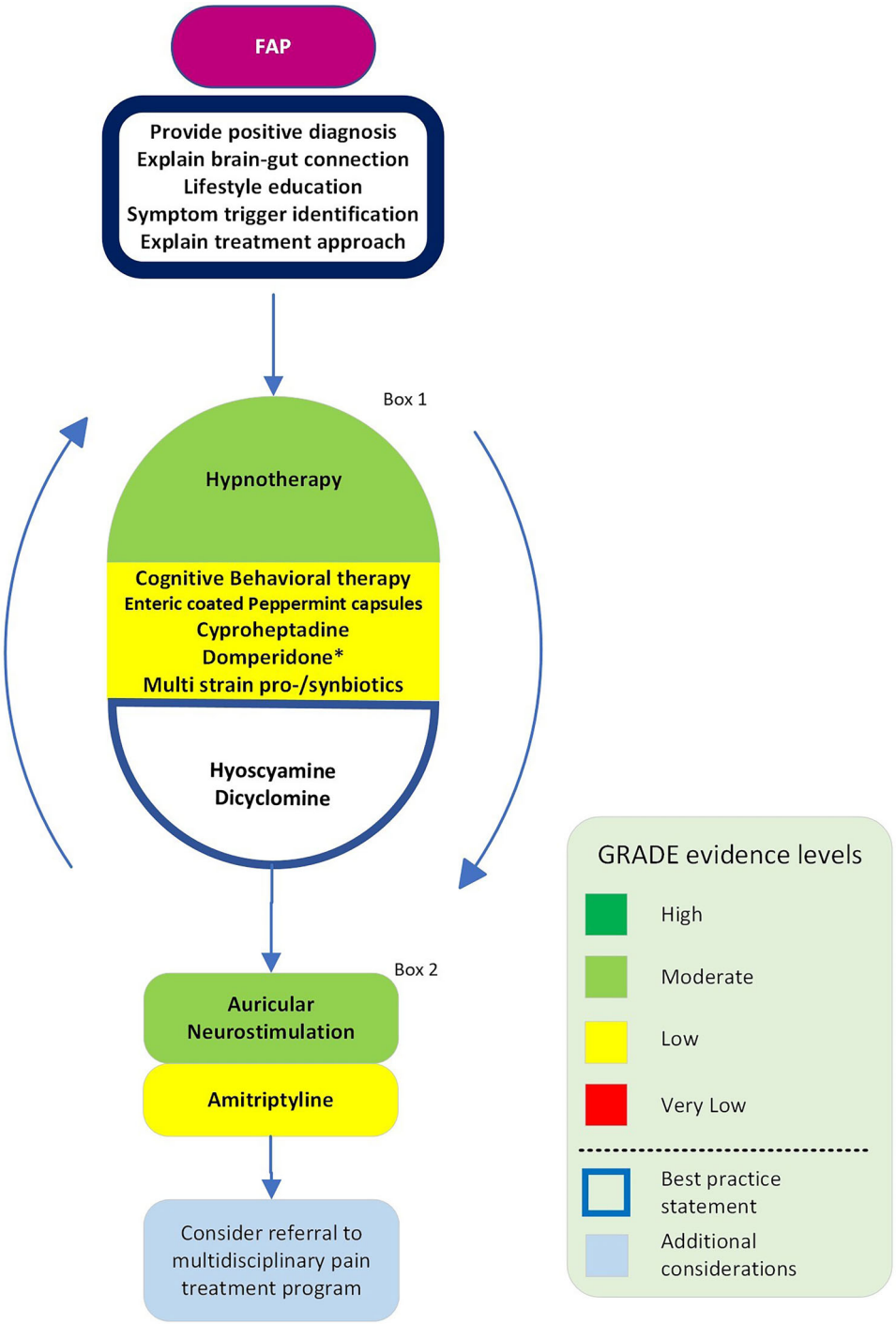

FIGURE 2 Treatment algorithm for Functional Abdominal Pain-Not Otherwise Specified (FAP); The "Grading of Recommendations Assessment, Development and Evaluation" (GRADE) data synthesis is the primary source informing the flow of treatments. However, best practice statements and additional considerations have also been included as they may be of additional value. The suggested flow provides a framework for shared decision-making. The choice of any particular treatment option should strongly reflect the balance of efficacy and safety from an individual patient perspective, local availability and feasibility, and potentially legal frameworks. The consecutive order of treatments as proposed in this algorithm may as such be modified following local context. Time to manifestation of treatment effect may vary depending on the chosen treatment option. Evaluation should be performed accordingly. *Despite low certainty evidence supporting efficacy to treat abdominal pain disorders of gut–brain interaction symptoms, the consensus among the guideline's authors is that they lack sufficient experience in using domperidone in clinical practice.

2.3 | Outcomes

The previously published core outcome set (COS) for assessing the treatment of AP-DGBIs was the primary source for the chosen outcomes of interest in this guideline.[18] The COS was developed by a group of patients, parents, and healthcare professionals. GRADE approach required that outcomes were prioritized into those that were critical (i.e., primary outcomes) and important (secondary outcomes), and limited to a total of seven outcomes (Table 1). This was agreed before technical review in May 2023. When outcomes were measured at multiple time points during the study time frame, the measurement point at the end of or closest to the end of the study treatment was used.

2.4 | Thresholds for outcomes

Also in May 2023, before technical review analysis being completed, a Delphi process was run among the GDG to identify decision thresholds for efficacy and safety outcomes.[19] This ensures that the magnitude of effect sizes can be used to inform judgment of imprecision on GRADE analysis, and ensure consistent interpretation when making recommendations.[20] This Delphi process was run in the form of an online questionnaire that requested identification of the following thresholds:

- The minimum threshold for a small difference to be defined (lower than this would be "trivial")
- The minimum threshold for a moderate difference to be defined (lower than this would be "small")
- The minimum threshold for a large difference to be defined (lower than this would be "moderate" and all above this would be "large")

These thresholds were to be identified without the context of a particular treatment option or comparator (e.g., placebo) in mind. For dichotomous outcomes (e.g., treatment success), a difference in people per 1000 reaching an outcome served as an endpoint. For continuous outcomes (e.g., pain intensity), an absolute difference on a validated scale (e.g., Visual Analog Scale [VAS]) served as an endpoint. The survey used for this exercise is presented in Supporting Information S3: File 3.

The results of this exercise were evaluated and discussed during an in-person meeting of the GDG at Digestive Diseases Week in Chicago, in May 2023. Overall, there was very good alignment for dichotomous and for most continuous efficacy outcomes, in line with other experiences using this technique in the field.[21] For safety outcomes, there was less good alignment across the GDG, especially for serious adverse events and withdrawals. Disagreements were resolved after discussion, resulting in the presented thresholds(Table 1). Initial anonymous results of the exercise are available in Supporting Information S4: File 4.

2.5 | Search strategy

An experienced Cochrane information specialist conducted a comprehensive search of the following databases (the Cochrane Central Register of Controlled Trials (CENTRAL) (via Ovid EBMR) (inception to present); MEDLINE (via Ovid) (1946 to present); PsycINFO (via Ovid) (1987 to present); AMED (via Ovid) (Allied and Complementary Medicine) (1985 to present); CINAHL (via EBSCO) (Cumulative Index to Nursing and Allied Health Literature) (1984 to present). The search was performed over several iterations and is up to date as of June 2023. No restrictions were placed on language of publication. Abstract publications were included to reduce publication bias, but given the risk of differences between this form of publication and final manuscripts, authors were contacted for more information.[22] Multiple additional search methods were deployed to identify any missing reports, such as checking relevant systematic reviews, contacting experts, and scanning the internet and abstracts submitted to major congresses. A final list of studies was presented to the GDG members to account for any missing but relevant reports. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart shows the results of this search (Supporting Information S1: File 1 – Figure 1).

2.6 | Ethics statement

Ethical clearance to publish the results of this exercise was granted by the University of Central Lancashire.[17]

2.7 | Study selection, data collection, and analysis

Only randomized controlled trials (RCTs) conducted in children in the age range of 4–18 years, comparing interventions of interest for AP-DGBIs with other active interventions or standard therapy, placebo, or no therapy, were considered. We excluded RCTs solely focusing on patients with FD. If studies did not define subgroups within AP-DGBIs, they were included, and authors were contacted for discriminatory data, with analysis performed as much as possible. If the study included mixed data from adults and children, it was only included if the authors provided children's data separately. Crossover studies were only included in

TABLE 1 Decision thresholds outlining the magnitude of effect sizes for crucial and important outcomes.

	Decision thresholds for effect sizes (small – moderate – large)
Crucial outcomes	
Primary dichotomous efficacy outcome (as defined by the author)	11% – 25% – 40% absolute risk difference
Abdominal pain frequency or change in frequency of pain using any validated scale	4 – 8 – 12 episodes per week
Abdominal pain intensity or change in pain intensity using any validated scale	0.7 – 1.5 – 2.6 points on a 0–10 VAS
Serious adverse events	1% – 3% – 5% absolute risk difference
Important outcomes	
Quality of life or change in quality life measured using any validated measurement tool.	11 – 25 – 40 points on a 0–100 PEDS QL
Stool consistency or change in stool consistency using the Bristol Stool Scale	0.8 – 1.6 – 2.5 points on a 1–7 Bristol Stool Scale
Total adverse events	5% – 9% – 17% absolute risk difference
Withdrawal due to adverse events	1% – 3% – 5% absolute risk difference

Abbreviations: PEDS QL, Pediatric Quality of Life Inventory; VAS, Visual Analog Scale.

data synthesis when authors were able to provide pre-crossover outcome data.

Title and abstract screening, as well as data extraction, were performed in duplicate, and any disagreements were resolved through discussion and/or consultation with a third author. If there was any incomplete or unclear information regarding methodology, results, or potential bias risk, the study authors were contacted to request clarification, as this is a common occurrence.[23]

Meta-analyses were performed using Review Manager (Version 5.4, the Cochrane Collaboration).

2.8 | Certainty of the evidence

Risk of bias was assessed using the Cochrane risk-of-bias tool for RCTs and certainty of the evidence was assessed using the GRADE approach.[24] Since we only used the adapted COS (Table 1), indirectness of reported outcomes was not considered an issue and rated as "not serious" by default. Publication bias had been addressed through our search strategy, with insufficient study numbers to allow funnel plot use and therefore was also judged as "not serious" by default.

2.9 | Voting

Before voting, all GDG members completed educational modules on the GRADE approach to enhance their understanding of the evidence summaries. All voting GDG members received a full technical summary of the data synthesis before attending a 2-day guideline summit in Reykjavik, Iceland on October 16th and 17th, 2023, during which all GDG members were physically present. The evidence synthesis summary for all treatment options, as outlined prospectively, was discussed in depth. This allowed GDG members to (re)evaluate (the certainty of) the evidence, the balance of benefit and harm, patient values and preferences, and (when applicable) feasibility, acceptability, equity, and resource use. Evidence-based recommendations were presented by the methodologists (M.G., J.G., and V.S.) and were discussed in detail, including the various factors in evidence-based decision frameworks influencing the strength of final recommendations.[25] When the explicit strength and phrasing of the recommendation had been discussed, the GDG proceeded to vote. A minimum of 75% of the voting members had to agree with the explicit formulation. This percentage remained equal in the case of the exclusion of voting members due to a conflict of interest, and thus, the number of threshold and maximum votes decreased proportionally.

A digital binary (i.e., "agree" or "disagree") and an anonymous voting system were used (www.polleverywhere.com). After the recommendation was final, justifications and other considerations were finalized through discussion. The GDG reached consensus for all recommendations without the need for further voting rounds. As per the GRADE methodology, recommendations are either positive (in favor) or negative (against). Additionally, recommendations are labeled strong or conditional. The phraseology and terminology used to clarify these distinctions are outlined in Table 2. The strength and direction of these recommendations strongly reflect the GRADEd conclusions of synthesized evidence (Table 3),

supplemented with any other considerations as put forward by the GDG members. For some treatment options, best practice statements (BPS) were generated on an eminence basis. These were not directly informed by the evidence base gathered for these guidelines. For BPS, there was no voting, and consensus was achieved through open discussion.

Because of repetitively following the same approach in formulating recommendations for every treatment option, the GDG followed a structured learning curve that enhanced the decision-making process during the 2-day guideline summit. To prevent this learning curve from influencing voting with alternative arguments having more or less weight later in the process, summaries were frequently presented during the summit to retrospectively evaluate previous recommendations and to maintain consistency throughout. Any amendments or deviations from the published protocol are described in Supporting Information S1: File 1 – Text 1.

2.10 | Presentation of results

The presentation of data summaries in these guidelines follows a clear and consistent structure that ensures maximum transparency. Only data on crucial efficacy outcomes are displayed in the evidence summary tables. An example of data summary presentation, along with explanatory statements, is displayed in Figure 1. A full technical summary of evidence summaries, meta-analyses, and grading can be found in Supporting Information S2: File 2 (Tables 1–3 and Figure 3).

Should hypnotherapy be used as a treatment option for AP-DGBIs?

Hypnotherapy is recommended **as a treatment option**

Strong recommendation, Overall **Moderate** certainty evidence, Effect size **Moderate** (Table 4)

Hypnotherapy induces a relaxed and focused state in patients, making them more receptive to therapeutic suggestions. This receptive state aims to achieve sensory and emotional changes for AP-DGBI patients, reducing symptoms and providing adequate relief. Hypnotherapy can be administered by a therapist or through a remote program such as an audio track.

Summary of evidence: Eight studies were included assessing hypnotherapy in various forms, including guided imagery modules ($n = 496$; age range 5–18 years).[26–33] Of these studies, five compared a form of hypnotherapy to a control group without an interventional character or otherwise elements of hypnotherapy.[26,27,31–33] The other three studies compared different forms of hypnotherapy against each other, including home-based versus provider-delivered therapy, as well as gut-directed programs versus unspecified programs.[28–30] Four of eight studies exclusively assessed IBS and FAP patients,[26–29] whereas others assessed all subtypes of AP-DGBIs.[30–33]

TABLE 2 Terminology used in the formulation of recommendations.

Recommendation terminology	Direction	Explanation	Terminology
Strong recommendation	In favor	Benefits clearly outweigh the harms	Recommend
Conditional recommendation	In favor	Benefits probably outweigh the harms/particular considerations limit generalization	Suggest
Conditional recommendation	Against	Harms may outweigh the benefits	Not suggest
Strong recommendation	Against	Harms definitely outweigh the benefits	Not recommend

TABLE 3 Terminology linked to "Grading of Recommendations Assessment, Development and Evaluation" (GRADE) certainty levels of the evidence.

GRADE certainty	Definition	Terminology
High ⨁⨁⨁⨁	The estimate of the effect matches the actual effect	Definitely
Moderate ⨁⨁⨁	The estimate of the effect probably matches the actual effect	Probably
Low ⨁⨁	The estimate of the effect may match the actual effect	Maybe
Very Low ⨁	No conclusion can be drawn	Unclear

Efficacy: Treatment success was reported in four studies comparing hypnotherapy to a non-interventional comparator without hypnotherapy elements.[26,27,31,33] The control groups included waitlist,[27] standard care,[33] standard care + ample attention,[26] and progressive muscle relaxation.[31] Meta-analysis of pooled data showed greater treatment success for hypnotherapy than for control groups (54.2% vs. 11.6%; risk ratio [RR] 3.76 [1.98; 7.15]).

Safety: No GRADEd conclusions were drawn for safety outcomes.

Certainty: The overall certainty of the efficacy outcomes was moderate. Risk of bias issues were common and primarily present for blinding. Ranges of estimates on treatment effect for crucial efficacy outcomes included a trivial effect size only for pain frequency, whereas treatment success and pain intensity were at least of "small" effect size or larger (Table 4). Of note, in spite of the absence of any statistical heterogeneity ($I^2 = 0\%$) for treatment success, control group treatment varied greatly between these four studies, as did the hypnotherapy protocols. Overall, control group success rates were poor (11.6%). This may be attributed to the generally non-interventional character of patient treatment in control groups.

Rationale: The GDG made a strong recommendation for hypnotherapy after evaluating the benefits and harms of the treatment. Data synthesis of hypnotherapy trial results had the highest GRADE certainty level of evidence among all treatment options reviewed for these guidelines. Despite considerable clinical heterogeneity in both treatment as well as control group designs, favorable effects of hypnotherapy in different forms over control groups were consistent and remained robust in subgroup and sensitivity analyses. The GDG notes that hypnotherapy is considered safe, even outside the scope of research settings, despite data synthesis providing no relevant safety contributions.

Data synthesis showed that the superiority of care provider-delivered (or physical) programs for hypnotherapy over self-directed (or remote) programs was not substantiated with evidence. Similarly, the superiority of gut-directed versus unspecified treatment modules was also not substantiated. The GDG suggests that when considering hypnotherapy treatment options, no particular delivery route or treatment module is preferential. The choice between in-person, telehealth, or self-directed programs should be based on the availability of resources and patient preference.

Should CBT be used as a treatment option for AP-DGBIs?

Cognitive Behavioral therapy **is recommended** as a treatment option

Strong recommendation, Overall **Low** certainty evidence, Effect size **small** (Table 5)

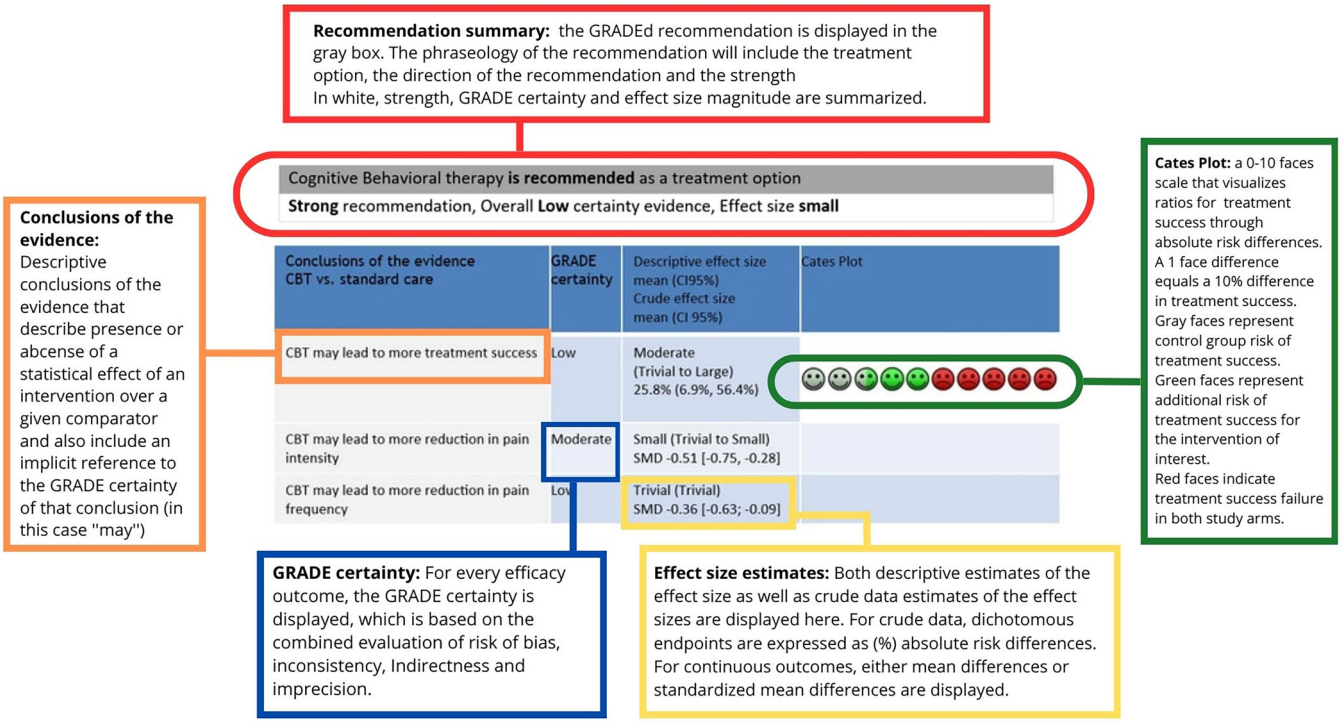

FIGURE 3 Infographic describing the contents of the evidence boxes presented for each treatment option discussed in this guideline.CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; SMD, standardized mean difference.

Cognitive behavior therapy aims to assist patients in understanding the connection between thoughts, feelings, and behaviors. Components of CBT include learning both cognitive (e.g., identifying and altering unhelpful thoughts related to pain symptoms) and behavioral strategies (e.g., relaxation techniques, improving healthy habits).

Summary of evidence: In total, 19 studies ($n = 1877$; age range 5–18 years) were included comparing CBT to various control group designs.[34–52] Of these, six studies compared CBT to an educational support program [34,37,41,47,49,52] and 12 studies compared CBT to standard care.[35,36,38,40,42–46,48,50,51] Eleven out of the 19 studies assessed healthcare provider-delivered CBT programs exclusively,[34,37,38,41,43–46,49,50] whereas the others studied effects of remotely delivered programs[35,40,42,47,51] or mixed programs that included both physical and remote elements or trial arms.[36,52] Most studies assessed all subtypes of AP-DGBIs.

Efficacy: Six studies assessing CBT versus standard care reported treatment success and showed greater success for CBT (50.6% vs. 23%; RR 2.12 [1.30; 3.45]).[38,40,44–46,51] Of the six studies, four were physically delivered,[38,44–46] and two were internet-delivered programs.[40,51] One study compared physically delivered CBT to standard care in combination with ample attention to adjust for increased patient and care provider time.[46] Subgroup analyses for physically delivered programs and internet programs did not impact these findings.

Safety: Only one GRADEd conclusion of at least low certainty could be made for CBT versus standard care for safety outcomes. This was based on one study that showed total adverse events to be comparable between CBT and standard care (17.4% and 20%, respectively).[40] The occurrence of serious adverse events and withdrawals due to adverse events was reported inconsistently, and data could not be GRADEd due to an overall lack of events.

Certainty: The overall certainty of the efficacy outcomes was low. Risk of bias issues were common, outside of blinding patients and effect assessors. All estimates of crucial efficacy outcomes crossed multiple predefined effect sizes, including trivial (Table 5), which led to downgrading for imprecision on all efficacy outcomes. Control group designs were comparable overall, aside from the comparison to educational programs. Hence, measured inconsistency ($I^2 = 46\%$) for treatment success may result from CBT type, study population, and treatment duration.

Rationale: The GDG made a strong recommendation for CBT after evaluating the benefits and harms of the treatment. Despite the low certainty overall for evidence for efficacy outcomes, suggesting it may be efficacious, CBT has been studied most extensively of all treatment options in these guidelines. These studies broadly show favorable effects over standard care, with downgrading occurring mainly because of issues with magnitude imprecision. This means that although there

TABLE 4 Data summary for hypnotherapy versus comparator, refer to Figure 3 for table content explanation.

Conclusions of the evidence hypnotherapy versus comparator	GRADE certainty	Descriptive effect size mean (95% CI)Crude effect size mean (95% CI)	Cates plot
Hypnotherapy probably leads to more treatment success	Moderate	Moderate (small to large) 32% (11.3%; 71.3%)	
Hypnotherapy probably leads to more reduction in pain intensity	Moderate	Moderate (moderate to large) SMD −0.99 [−1.63, −0.35]	
Hypnotherapy may lead to more reduction in pain frequency	Low	Trivial (trivial) SMD −0.77 [−1.52, −0.02]	

Abbreviations: 95% CI, 95% confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; SMD, standardized mean difference.

TABLE 5 Data summary for cognitive behavioral therapy versus standard care, refer to Figure 3 for table content explanation.

Conclusions of the evidenceCBT versus standard care	GRADE certainty	Descriptive effect size mean (95% CI) Crude effect sizemean (95% CI)	Cates plot
CBT may lead to more treatment success	Low	Moderate (trivial to large) 25.8% (6.9%, 56.4%)	
CBT may lead to more reduction in pain intensity	Moderate	Small (trivial to small) SMD −0.51 [−0.75, −0.28]	
CBT may lead to more reduction in pain frequency	Low	Trivial (trivial) SMD −0.36 [−0.63; −0.09]	

Abbreviations: 95% CI, 95% confidence interval; CBT, cognitive behavioral therapy; GRADE, Grading of Recommendations Assessment, Development and Evaluation; SMD, standardized mean difference.

most likely is an effect, its size is difficult to define. The GDG notes that CBT is considered safe, even outside the scope of research settings, despite data synthesis providing no relevant safety information.

Data synthesis of the efficacy outcomes in this guideline demonstrates no clear evidence of inferiority of remote programs when compared to physical programs. The GDG suggests that remote programs can be considered as a treatment option, especially when local accessibility and feasibility are taken into consideration.

Should percutaneous electrical nerve field stimulation be used as a treatment option for AP-DGBIs?

Auricular percutaneous electrical nerve field stimulation is **suggested** as a treatment option

Conditional recommendation, Overall **Moderate** certainty evidence, Effect size **Moderate** (Table 6)

PENFS involves (externally) influencing pain modulation by accessing neural pathways that communicate with nuclei in the brainstem or cerebral cortex.[53,54] These nuclei act as relay stations that allow signaling of brain structures involved in autonomic control and pain, including the rostral ventral medulla, hypothalamus, amygdala, and spinal cord.[55–57]

Summary of evidence: One study ($n = 115$; age range 11–18 years) assessed PENFS through an auricular device, compared to sham therapy using the same, yet inactive device.[58] This included patients with all subtypes of AP-DGBIs. A post hoc analysis was performed on only the IBS patients in this cohort and was published separately.[59]

Efficacy: Treatment success was achieved in significantly more patients following PENFS than sham stimulation (48.3% vs. 18.2%; RR 2.66 [1.43; 4.94]). A post hoc analysis of the IBS patients in this trial showed similar results.

Safety: GRADEd conclusions of low certainty were drawn, indicating that no difference may exist for the occurrence of total adverse events between true and sham therapy (10% vs. 18.2%; RR 0.55 [0.21; 1.41]). These adverse events included ear discomfort, adhesive allergy, and syncope due to needle phobia. Also, the rate of withdrawals due to adverse events was found to be similar between the two groups (5% vs. 14.5%; RR 0.34 [0.10; 1.23]).

Certainty: The overall certainty of the efficacy outcomes was moderate. The risk of bias overall was low. The GRADE certainty for primary efficacy outcomes was downgraded for imprecision, as estimates of effect ranged from trivial to large sizes.

Rationale: The GDG made a conditional recommendation for auricular PENFS after evaluating the benefits and harms of the treatment. Despite moderate certainty of evidence, the pain intensity reduction was among the highest across all studied treatment options. This is a very new field in the treatment of AP-DGBIs and has only been studied in a small population. The study included in these guidelines comes from a single institution. This study shows that a favorable effect likely exists, but that its size has yet to be determined, which, in the context of limited availability and experience, does not create sufficient grounds for a strong recommendation for all children AP-DGBIs.

The GDG notes that this treatment comes at a relatively high initial cost and requires weekly new device placement for the duration of the treatment course. Moreover, PENFS has only recently been implemented as a treatment option for AP-DGBIs and will likely undergo further development in the coming years. The GDG suggests that this treatment option may be utilized for patients who have shown considerable difficulty in achieving pain relief.

Should pro- and synbiotics be used as a treatment option for AP-DGBIs?

Probiotics (multistrain probiotics) and synbiotics (multistrain probiotics combined with prebiotics) **may be suggested** as a treatment option

Conditional recommendation, Overall **Low** certainty evidence, Effect size **Small**

Lactobacillus rhamnosus GG **is suggested** as a treatment option for IBS

Conditional recommendation, Overall **Moderate** certainty evidence, Effect size **Small** (Table 7)

TABLE 6 Data summary for neurostimulation versus sham stimulation, refer to Figure 3 for table content explanation.

Conclusions of the evidenceneurostimulation versus sham stimulation	GRADE certainty	Descriptive effect size mean (95% CI)Crude effect sizemean (95% CI)	Plot
Neurostimulation probably leads to more treatment success	Moderate	Moderate (trivial to large) 30.2% (7.8; 71.7%)	
Neurostimulation probably leads to more reduction in pain intensity	Moderate	Moderate (small to large) *MD −2.00 [−3.02, −0.98]	

Abbreviations: 95% CI, 95% confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; MD, mean difference.
*MD score for pain intensity was measured on a 0–10 scale.

TABLE 7 Data summary for pro-/synbiotics versus placebo, refer to Figure 3 for table content explanation.

Conclusions of the evidencebiotics versus placebo	GRADE certainty	Descriptive effect size mean (95% CI) Crude effect size mean (95% CI)
Pro- and synbiotics (pooled)		
No conclusion can be drawn about treatment success	Very low	Small (trivial to moderate) 16% (4.3%; 31.1%)
No conclusion can be drawn for pain intensity	Very low	SMD −0.59 [−1.05, −0.13]
No conclusion can be drawn for pain frequency	Very low	*MD −0.64 [−1.06, −0.21] Trivial (Trivial)
Probiotics		
No conclusion can be drawn treatment success	Very low	Small (trivial against to large in favor) 13.6% (−0.5%; 51.6%)
Probiotics may lead to more reduction in pain intensity	Low	Small (trivial to large) SMD −0.42 [−0.80, −0.05]
No conclusion can be drawn for pain frequency	Very low	*MD −0.43 [−0.92, 0.07]
Synbiotics		
No conclusion can be drawn for treatment success	Very low	Small (trivial to large) 17.5% (1.8%; 40.8%)
No conclusion can be drawn for pain intensity	Very low	SMD −0.38 [−1.05, 0.29]
No conclusion can be drawn for pain frequency	Very low	Trivial (trivial) *MD −1.00 [−1.38, −0.63]
Multistrain symbiotic		
Multistrain synbiotics may lead to more treatment success	Low	Moderate (trivial to large) 37.1% (6.7%; 88.6%)
Multistrain synbiotics may lead to more reduction in pain intensity	Low	Large (moderate to large) MD −3.11 [−4.12; −2.10]
Multistrain synbiotics probably lead to more reduction in pain frequency	Moderate	Trivial (trivial) *MD −0.86 [−1.16; −0.56]
Lactobacillus rhamnosus		
L. rhamnosus may not lead to differences in treatment success for IBS	Low	Large (trivial against to large in favor) 42.3% (−7.3%; 68.4%)
L. rhamnosus probably leads to more reduction in pain intensity for IBS	Moderate	Small (trivial to moderate) SMD −0.60 [−0.97; −0.23]
L. rhamnosus probably leads to more reduction in pain frequency for IBS	High	Trivial (trivial to trivial) *MD −1.50 [−2.03; −0.97]

Abbreviations: 95% CI, 95% confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; IBS, irritable bowel syndrome; SMD, standardized mean difference.

*All presented MD scores were measured as pain episodes per week

Interventions that aim to enrich or alter intestinal microbiota composition have been proposed as potentially leading to symptom relief in AP-DGBIs. This follows the hypothesis that modifications of gut microbiota may precede and contribute to AP-DGBI onset. Two studies showed an association between early life antibiotic exposure and increased rates of recurrent abdominal pain (RAP) and/or FAP.[60,61]

Summary of evidence: Fifteen placebo-controlled studies were included, assessing different probiotic strains ($n = 1396$; age range 4–18 years).[62–76] Specific strains studied, included *Bacillus clausii*,[75] *Bifidobacterium lactis*,[62] *Lactobacillus reuteri*,[63,68,69,71–73,76] *Lactobacillus rhamnosus*,[64,65,74] and a multistrain compound.[66,67,70] Included age groups were comparable, limiting any age-based subgroup analysis. The majority solely assessed treatment effect in populations with either IBS[62,67,75] or FAP[63,69–71,73,76] or in both.[64,66,68] Of the latter, subgroup analyses were performed per category of disorder in 3 studies.[64,65,72] Two of these assessed *L. rhamnosus*.[64,65]

Seven studies compared synbiotics to a placebo ($n = 511$; age range 4–18 years).[62,77–82] Specific strains that were assessed included *Bacillus coagulans*,[77,82] *B. lactis*,[62] *L. rhamnosus*,[78,80] and a multistrain compound (fructo-oligosaccharides [FOS] and seven types of bacteria including *Lactobacillus casei, Streptococcus thermophilus, Lactobacillus acidophilus, Lactobacillus bulgaricus, L. rhamnosus, Bifidobacterium breve*, and *Bifidobacterium infantis*).[79] One study did not specify the included strain(s).[81] Prebiotic compounds included FOS[77,79,82] and inulin.[62,78,80] One study compared a synbiotic and a probiotic without prebiotics.[62] Synbiotics were predominantly studied in either IBS or FAP populations. No age-based subgroup analysis was possible.

One study comparing *B. coagulans* to a placebo was initially included.[83] However, the technical review exposed outlying data and conflicts from the study team. Authors were contacted numerously for clarifications regarding these issues, but no response was received. As has been described in previous work,[12] advice was sought from the Cochrane research integrity unit, and pending any response from the authoring team or journal, data have not been included in the current synthesis.

Efficacy: When probiotic studies were sub grouped by bacterial strain, two studies on *L. rhamnosus* showed a significant effect for pain frequency (in episodes per week) over placebo, for a study population which included patients with IBS, FAP, and FD.[64,65] This was the case for pain frequency (in episodes per week). However, the effect was only trivial (MD −0.43 [95% confidence interval (95% CI) −0.92; 0.07]). When all probiotic strains were pooled in meta-analyses, a significant favorable effect over placebo for pain intensity reduction (SMD −0.42 [95% CI −0.80; −0.05]) was observed. Scale stratification of the different pain intensity scales (e.g., FACES scale or numeric rating scale) was not of additional value due to considerable heterogeneity in outcome reporting.

Subgroup analyses were performed for specific AP-DGBIs in the two *L. rhamnosus* studies,[64,65] showing that patients with IBS achieved statistically more reduction in both pain intensity and frequency (Table 7) when given the probiotic strain versus placebo, which was not the case for FAP.

When assessed per probiotic strain, regardless of prebiotic counterpart, only a multi-strain synbiotic showed a significant favorable effect over placebo for treatment success (48.6% vs. 11.4%; RR 4.25 [1.59; 11.36]).[79] This was seen in pain frequency and pain intensity, with low and moderate certainty findings of moderate and trivial magnitude improvements in both these outcomes seen, respectively. When synbiotics were assessed as a singular treatment class, they achieved significantly more treatment success than placebo, but this was of very low certainty.

Safety: Reporting of safety data was adequate overall, but due to an overall lack of events, no GRADEd conclusions could be drawn for serious adverse event (SAEs) and withdrawal due to adverse event (WAEs). For total adverse events (TAEs), event rates were similar, but all events were reported in one study.[75]

Certainty: For probiotics, the overall certainty of the evidence on efficacy outcomes was low. Strain-specific evidence for *L. rhamnosus* in patients with IBS was of moderate certainty, and the overall risk of bias was low. Certainty was often downgraded due to magnitude imprecision and considerable heterogeneity between studies, the latter likely a result of the use of different strains and dosages, variant treatment durations, and definition of outcomes.

For synbiotics, the overall certainty of the evidence was very low. All efficacy outcomes were downgraded for risk of bias, as most favorable effects of synbiotics came from studies with high risk of bias on allocation and blinding domains[77] and on selective reporting and attrition.[79] Strain-specific evidence for the multistrain synbiotic was of low certainty due to very serious imprecision and serious risk of bias. Sensitivity analyses, excluding biased studies, removed any pre-existing statistical significance from meta-analyses. Inconsistency was present for all efficacy outcomes and was severe for pain intensity ($I^2 = 90\%$), potentially due to methodological differences between studies, such as the use of different strains and treatment duration. Magnitude imprecision was also considerable, except for pain frequency, where this did not cross thresholds of a trivial effect.

Rationale: The GDG made a conditional recommendation for multistrain pro- and synbiotics after evaluating the benefits and harms of the treatment. Despite heterogeneity playing a very considerable role in the GRADEing of individual outcomes, the GDG suggests that there may be individual strains with favorable effects for children with AP-DGBIs, a statement informed by a GRADEd conclusion for pain intensity and a favorable trend for treatment success. However, there is limited evidence favoring particular strains when considering all strains combined, which restricts further strain-directed recommendations. Probiotic strains, especially those available OTC, are generally considered safe in otherwise healthy children and are often tried by patients on an empirical basis within and outside the context of AP-DGBIs.[84]

Data synthesis did indicate a role for *L. rhamnosus* as a treatment option, which was further explored in subgroup analyses showing differences for IBS and FAP. However, the recommendation is conditional with moderate certainty, targeting mainly IBS patients. Attempts were made to explore any subgroups and strain combinations, but did not result in additional recommendations.

The GDG notes that particular caution should be exercised in the choice of OTC probiotic compound, given that considerable amounts of products are in the market without any live colony-forming units and that patients should be directed to seek advice from a healthcare provider before initiating any probiotic supplement.

Should peppermint oil be used as a treatment option for AP-DGBIs?

Enteric-coated peppermint capsules **may be suggested** as a treatment option

Conditional recommendation, Overall **Low** certainty evidence, Effect size **Small** (Table 8)

Peppermint oil possesses several properties, including antimicrobial, antioxidant, anti-inflammatory, anti-spasmodic, immunomodulating, and anesthetic. These properties may contribute to its effectiveness in treating patients with AP-DGBIs. However, it is still unclear which of these properties are essential to its functionality in AP-DGBIs.

Summary of evidence: Two placebo-controlled studies assessed the treatment effect of peppermint oil ($n = 122$; age range 4–17 years old).[77,85] One study exclusively studied patients with IBS, and the other included patients across all AP-DGBIs, without providing subgroup analyses. One of the studies was designed with three study arms, allowing a pairwise comparison between peppermint oil and a synbiotic, containing *B. coagulans*.[77]

Efficacy: No meta-analyses were possible due to heterogeneity in the reporting of outcomes. Treatment success was only reported by one study, not showing a significant effect of peppermint over placebo (60% vs. 36%; RR 1.67 [95% CI 0.90; 3.08]).[85] Without presenting any data, one study reported that peppermint oil led to a significantly greater reduction in pain intensity than for placebo.[85] No significant differences existed for pain intensity and frequency between peppermint oil and synbiotics.[77]

Safety: Both studies reported that no adverse events occurred. Some subject withdrawals were reported in one study, but the reasons were not given. No GRADEd conclusions could be drawn.

Certainty: The overall certainty of the evidence was low, and the risk of bias was unclear in many domains due to inadequate reporting. Certainty for treatment success was downgraded due to magnitude imprecision. Inconsistency could not be assessed due to a lack of data to allow meta-analysis.

Rationale: The GDG made a conditional recommendation for enteric-coated peppermint capsules after evaluating the benefits and harms of the treatment. Despite an overall lack of high-quality studies, limiting any pooled analyses, the GDG notes that enteric-coated peppermint oil is generally considered safe and that some evidence exists of a favorable effect. This effect has been indicated consistently in adult studies on the use of peppermint oil and may be generalized to older children and adolescents with AP-DGBIs.[86]

Peppermint is often evaluated within the scope of anti-spasmodics. However, given the considerable variety of potential functions attributed to peppermint oil, a consensus decision was made by the GDG to assess it separately in the context of these guidelines.

Should tricyclic antidepressants be used as a treatment option for AP-DGBIs?

Amitriptyline **may be suggested** as a treatment option

Conditional recommendation, Overall **Low** certainty evidence, effect size **Small** (Table–9)

Antidepressants may stimulate an enhanced inhibitory signal from pain-related brain circuits.[87] This is achieved through targeting emotional and cognitive

TABLE 8 Data summary for peppermint oil versus placebo, refer to Figure 3 for table content explanation.

Conclusions of the evidencepeppermint oil versus placebo	GRADE certainty	Descriptive effect size mean (95% CI)Crude effect size mean (95% CI)
No conclusions could be drawn for treatment success	Very Low	Small (trivial against to large in favor) 24.1% (−3.6%; 64%)
Peppermint oil may lead to more reduction in pain intensity	Low	Small (trivial to moderate) *MD −1.13 [−1.82, −0.44]
Peppermint oil may lead to more reduction in pain frequency	Low	Trivial (trival) **MD −1.40 [−2.04, −0.76]

Abbreviations: 95% CI, 95% confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; SMD, standardized mean difference.

*MD score for pain intensity was measured on a numeric rating scale (0–10).

**MD score for pain frequency was measured as pain episodes per week.

circuits, which are highly connected to pain-processing regions in the brain.[88,89] Moreover, antidepressants may exert some function at the spinal level by interfering with pain signaling transmission in the dorsal horn of the spinal cord following peripheral stimuli.[90]

Summary of evidence: Three studies compared treatment with a tricyclic antidepressant versus placebo ($n = 291$; age range 6–18 years).[91–93] All subtypes of AP-DGBIs were included. One study solely assessed the effect of antidepressants in IBS patients.[91]

Efficacy: No GRADEd conclusion could be drawn for treatment success, due to very low certainty. Pain frequency and intensity reduction outcomes were synthesized based on one study (Table 9) that also performed subgroup analyses for different types of AP-DGBIs.[93] Due to considerable unresolved doubts regarding the correctness of these data, these results were not utilized any further, preventing separate statements for AP-DGBIs.

Safety: No GRADEd conclusions were made for SAEs and WAEs as a result of an overall lack of adverse events. TAEs were reported in one study only, not showing significant differences between amitriptyline and placebo (23.1% vs. 11.6%; RR 1.99 [95% CI 0.99; 4.03]).[93]

Certainty: Overall certainty of the evidence on efficacy outcomes was low. Certainty for treatment success was downgraded due to considerable inconsistency ($I^2 = 93\%$), which may have been the result of variation in the definition of success, or the longer duration of treatment in studies showing favorable effects over placebo (13 and 12 weeks),[91,93] compared to the one study not showing such effect (4 weeks).[92] GRADEd conclusions for pain frequency and intensity were drawn on the basis of the one open-label study.[93] The study showing no favorable effects for amitriptyline over placebo had a surprisingly high placebo success rate (52.3%).[92] It is conceivable that this rate was a result of the local setting of care, including extensive caregiver attention. Another source may be the definition for treatment success, which was defined as "better" on a scale of better-same-worse. This included arguably less discriminatory thresholds than in a wider scale symptom score, such as a VAS pain score, and may therefore more easily overestimate true control group improvement.

Rationale: The GDG made a conditional recommendation for amitriptyline after evaluating the benefits and harms of the treatment, acknowledging that serious issues exist with the studies informing this recommendation. Notably, issues with blinding of patients and assessors in one study were most worrisome, given that this study informed GRADEd conclusions on both the efficacy outcomes independently. Moreover, safety issues with antidepressants are prevalent and have not been addressed properly in the included body of evidence, limited by study design.

The GDG is aware that good-quality adult data exists, showing superiority of amitriptyline over placebo for IBS, which could allow limited generalization to older children and adolescents.[94] However, psychopharmacological therapies should be used with caution in any childhood developmental stage, in which neuroplasticity may catalyze behavioral changes or contribute to mental health issues in prone individuals as a result of these treatments. Furthermore, ECG screening can be considered due to QTc prolongation. Given these considerations, the GDG believes that prescription thresholds for amitriptyline should be carefully considered. The treatment should only be prescribed by experienced caregivers in the field.

Should domperidone be used as a treatment option for AP-DGBIs?

Domperidone **may be suggested** as a treatment option

Conditional recommendation, Overall **Low** certainty evidence, effect size **Small** (Table–10)

Domperidone has antidopaminergic properties and is best known for its effect in accelerating gastric emptying by enhancing antroduodenal contractions.[95] Delayed gastric emptying is often diagnosed in patients with FD, who could then benefit from domperidone in

TABLE 9 Data summary for amitriptyline versus placebo, refer to Figure 3 for table content explanation.

Conclusions of the evidenceamitriptyline versus placebo	GRADE certainty	Descriptive effect size mean (95% CI)Crude effect size mean (95% CI)
No conclusion can be drawn for treatment success	Very low	Large (trivial against to large in favor) 54% (–6.9%; 76.9%)
Amitriptyline may lead to more reduction in pain intensity	Low	Moderate (small to large) *MD –2.40 (–3.08; –1.72)
Amitriptyline may lead to more reduction in pain frequency	Low	**MD –2.80 [–3.57; –2.03]

Abbreviations: 95% CI, 95% confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; SMD, standardized mean difference.

*MD score for pain intensity was measured on a Visual Analog Scale (0–10).

**MD score for pain frequency was measured by an unvalidated author definition.[93]

the context of AP-DGBIs. However delayed gastric emptying has also been found in some patients with IBS and FAP, suggesting that domperidone could be efficacious in a broader range of AP-DGBIs.[96]

Summary of evidence: Two studies compared treatment with domperidone to placebo ($n = 201$; age range 5–14 years).[97,98] One study exclusively assessed the efficacy of domperidone in patients with FAP,[98] and one included patients with all subtypes of AP-DGBIs and provided subgroup analyses.[97]

Efficacy: Only one study defined treatment success and reported outcomes for the entire study population and for AP-DGBIs. Patients with FAP in this study were more likely to achieve treatment success with domperidone than with placebo, which was not the case for IBS.[97]

Safety: No adverse events were reported in the included studies, restricting safety assessments or GRADEd conclusions.

Certainty: The overall certainty of the evidence is low, and the certainty for treatment success was downgraded for imprecision, given that the estimate was rough and was informed by only one study. Certainty for pain intensity was downgraded due to severe inconsistency ($I^2 = 91\%$). The most obvious sources of heterogeneity were inclusion of solely FAP patients versus all AP-DGBIs and slight differences in dosages and overall duration of the intervention. Pain frequency was downgraded for both risk of bias as well as imprecision. In the study, performing subgroup analyses for AP-DGBIs subtype, the total group size of the IBS population was very small and may have been underpowered for this analysis. Moreover, placebo success rates in the IBS group were unusually high (73.3%).

Rationale: The GDG made a conditional recommendation for domperidone after evaluating the benefits and harms of the treatment. Although its mechanistic properties may provide a better fit in the management of FD, data synthesis shows limited evidence that efficacy might also extend to IBS and FAP. To allow generalization of results to adolescents in the age group 14–18 years, for whom no data on the use of domperidone is available for AP-DGBIs, adult data may be of supplemental value.[99] The two pediatric RCTs reported that no safety events occurred. This may be the result of limited monitoring time and sample size in the included studies. In addition to more common side effects, domperidone may induce QTc prolongation,[100] so ECG screening could be considered before its initiation, particularly when other QTc prolonging drugs are also used.

Should cyproheptadine be used as a treatment option for AP-DGBIs?

Cyproheptadine **may be suggested** as a treatment option

Conditional recommendation, Overall **Low** certainty evidence, effect size **Small** (Table–11)

Cyproheptadine has several assumed mechanisms of action, including antihistaminic, anti-serotonergic, and anti-muscarinic. In the context of AP-DGBIs, it may improve gastric accommodation pertaining to anti-serotonergic functionality. Additionally, it can also reduce gastric acid secretion because of its anti-histaminic function. Therefore, patients with FD or patients with nausea are likely to benefit from it.[101] However, serotonergic pathways have been implicated as drivers of secretion and motility in the lower gastrointestinal tract, and the same may be true for histaminic pathways, but further research is required to confirm this. For patients with AM, antihistaminic function may also alleviate abdominal pain.

Summary of evidence: One study compared 2 weeks of cyproheptadine treatment to placebo in patients with FAP ($n = 36$; age range 4–12 years).[102]

Efficacy: Treatment success, defined as a complete resolution of pain, was achieved by significantly more patients treated with cyproheptadine than with placebo (86.7% vs. 35.7%; RR 2.43 [95% CI 1.17; 5.04]).

TABLE 10 Data summary for domperidone versus placebo, refer to Figure 3 for table content explanation.

Conclusions of the evidencedomperidone versus placebo	GRADE certainty	Descriptive effect size mean (95% CI)Crude effect sizemean (95% CI)	Cates plot
Domperidone may lead to more treatment success	Low	Small (trivial to large) 24% (3.5%; 50%)	
No conclusion can be drawn for pain intensity	Very low	Moderate (trivial against to large in favor) *MD −1.68 [−3.98, 0.63]	
Domperidone may lead to more reduction in pain frequency	Low	Small (trivial to moderate) **MD −7.08 (−10.58; −3.58)	

Abbreviations: 95% CI, 95% confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; SMD, standardized mean difference.

*MD score for pain intensity was measured on a faces scale (0–10).

**MD score for pain frequency was measured as pain episodes per week.

Safety: Only SAEs were reported, but due to a lack of events, no GRADEd conclusions could be drawn.

Certainty: Overall certainty of the evidence on efficacy outcome was low. The risk of bias was unclear for randomization and allocation of concealment due to inadequate reporting. Magnitude imprecision was considerable, with an effect estimate ranging from trivial to large. The total sample size was very small.

Rationale: The GDG made a conditional recommendation for cyproheptadine after evaluating the benefits and harms of the treatment. The GDG acknowledges the limitations of the data synthesis summary but notes that clinical experience with cyproheptadine efficacy affirms that an effect may exist. The magnitude of this effect remains uncertain. Safety concerns are expressed by GDG members for mood swings, weight gain, and sedating effects, prevalent in first-generation antihistaminic medications. These have not been reported in the included study, which may result from the small sample size and very limited follow-up duration.

Should supplemental fiber be used as a treatment option for AP-DGBIs?

Soluble dietary fiber supplements (i.e., hydrolized guar gum, glucomannan, psyllium) are **suggested** as a treatment option for IBS only

Conditional recommendation, Overall **Moderate** certainty evidence, effect size **Moderate** (Table–12)

Dietary fiber exerts its function through the enhancement of colonic metabolism in patients with AP-DGBIs. Insoluble fibers are generally poorly fermented and have limited prebiotic action. They work by increasing fecal bulk and stimulating bowel transit by irritating colonic mucosa and drawing in fluid.[103] On the other hand, soluble fibers are fermentable to various degrees and have a considerable prebiotic effect.[104] They produce short-chain fatty acids through fermentation processes, which may have beneficial effects on the stimulation of gut motility and enhance gut microbiota diversity.[104,105] Insoluble fibers attract fluid to the intestinal lumen without absorbing it. Therefore, patients with constipation may experience softening of stools. Soluble fibers absorb fluid and create a gel-like substance, which regulates bowel movements and can have beneficial effects in both diarrhea as well as in constipation.

Summary of evidence: Five studies compared a soluble fiber compound to a placebo ($n = 385$; age range 5–18 years).[106–110] One study assessed the use of a corn fiber cookie versus a placebo cookie.[106] One other study used fruit juice, fortified with hydrolyzed guar gum,[109] and yet another study assessed glucomannan versus maltodextrin sachets.[107] Two studies compared psyllium to maltodextrin sachets.[108,110] Although chosen as a placebo, maltodextrin acts as a soluble fiber itself. Three out of the five studies only included IBS patients,[108–110] whereas the other two included all AP-DGBIs.[106,107] IBS subtypes were not categorized. Treatment duration ranged from 4 to 6 weeks.

Efficacy: Treatment success was achieved more frequently for fiber than for placebo (47.9% vs. 23.4%; RR 2.52 [1.10; 5.76]). When subgrouped for subtype of AP-DGBI, which allowed separate evaluation of IBS in 2 studies[108,109] and combined AP-DGBIs in two others,[106,107] this effect was robust only for IBS and not for overall AP-DGBI populations.

Safety: Due to an overall lack of events, no GRADEd conclusions could be drawn for safety.

Certainty: Overall certainty of the evidence on efficacy outcomes for fiber in IBS patients was moderate. Certainty for treatment success was only downgraded due to magnitude imprecision, resulting from a confidence interval ranging from a small to a large effect size. When considering all subgroups of AP-DGBIs, inconsistency was a considerable issue ($I^2 = 75\%$), potentially resulting from decreased efficacy in children with AP-DGBIs, but not IBS. The interpretation of meta-analysis for pain intensity presented unresolved issues due to uncertainties in the unit of variance in the data of one study.[109] Overall risk of bias was low.

Rationale: The GDG made a conditional recommendation for soluble dietary fiber supplements for IBS only, after evaluating the benefits and harms of the treatment. Some clinical heterogeneity existed in terms of the chosen type of fiber, but the overall evidence favoring fiber for IBS was of good quality. The GDG notes that, despite a lack of GRADEd evidence for safety, fiber is generally considered safe and is available OTC. Although fibers seem broadly beneficial, independently assessing studies to support recommendations for specific types of fiber – that is, in more detail than soluble dietary supplements – would not

TABLE 11 Data summary for cyproheptadine versus placebo, refer to Figure 3 for table content explanation.

Conclusions of the evidence cyproheptadine versus placebo	GRADE certainty	Descriptive effect size mean (95% CI)Crude effect sizemean (95% CI)	Cates Plot
Cyproheptadine may lead to more treatment success	Low	Large (trivial to large) 51% (6%; 64.3%)	

Abbreviations: 95% CI, 95% confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation.

TABLE 12 Data summary for domperidone versus placebo, refer to Figure 3 for table content explanation.

Conclusions of the evidenceSoluble dietary fiber supplements versus placebo	GRADE certainty	Descriptive effect size mean (95% CI)Crude effect sizemean (95% CI)	Cates Plot
Fiber may lead to more treatment success	Low	Moderate (trivial to large) 35.6% (2.3%; 76.6%)	
No conclusion could be drawn for pain intensity	Very low	SMD −0.86 [−1.63, −0.10]	
For IBS, fiber probably leads to more treatment success	Moderate	Moderate (small to large) 35.2% (10.1%; 92.6%)	
For IBS, fiber may lead to more reduction in pain frequency	Moderate	Not applicable *MD −4 (−4.81; −3.19)	

Abbreviations: 95% CI, 95% confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; MD, mean difference.
*MD score for pain frequency was measured by an unvalidated author definition.[108]

TABLE 13 Data summary for buspirone versus placebo, refer to Figure 3 for table content explanation.

Conclusions of the evidencebuspirone versus placebo	GRADE certainty	Descriptive effect sizemean (95% CI)Crude effect size mean (95% CI)
There may be no difference for treatment success	Low	Trivial against (small against to small in favor) −0.9% (−15.9%; 20.8%)
There is probably no difference for pain intensity	Moderate	Trivial against (trivial against to trivial in favor) *MD −0.10 [−0.60; 0.40]

Abbreviations: 95% CI, 95% confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; MD, mean difference.
*MD score for pain intensity was measured on a Faces scale (0–10).

support a better GRADE conclusion. Moreover, the GDG has discussed extensively and found it valid to present a blanket recommendation with the current categorization. Insoluble fibers have not been studied in RCTs in this field, and therefore, no recommendations can be made regarding their use, either positive or negative. While general dietary advice should be given to any patient with an AP-DGBI, including recommendations for sufficient dietary intake of fibers, the GDG suggests that soluble fiber supplements may have a role as a first- or second-line treatment option for IBS. This decision is further informed by considerations of accessibility and a favorable safety profile.

Should buspirone be used as a treatment option for AP-DGBIs?

Buspirone is not **suggested** as a treatment option

Conditional recommendation, Overall Low certainty evidence, effect size **Trivial against** (Table–13)

Buspirone predominantly acts as a serotonergic agonist and enhances fundic accommodation, which in turn may influence oral intake due to decreased satiety.[111] Weak anti-dopaminergic properties have previously linked buspirone to stimulation of gastric peristalsis, but this has not been substantiated with evidence.[112]

Summary of evidence: One study compared a 4-week treatment with buspirone to a placebo in patients with FAP ($n = 117$; age range 6–18 years).[113]

Efficacy: Treatment success was not statistically different between the two study arms (47.5% vs. 48.3%; RR 0.98 [0.67; 1.43]).

Safety: Safety reporting was adequate, although no statistical differences existed for WAE, and a lack of events restricted a GRADEd conclusion. A trend towards the occurrence of more TAEs existed for buspirone (47.5% vs. 32.8%; RR 1.45 [0.92; 2.29]).

Certainty: Overall certainty for the efficacy outcomes was low to moderate, which was solely due to the magnitude imprecision. The overall risk of bias was low.

Rationale: The GDG made a conditional recommendation against buspirone, given a lack of evidence favoring the efficacy of buspirone over placebo, and the potential safety issues. The GDG made a conditional recommendation, since the data summary was only based on one study, and no particular safety issues were raised by individual GDG members to support a strong recommendation against the option.

Should antispasmodics (other than peppermint oil) be used as a treatment option for AP-DGBIs?

Mebeverine is not **suggested** as a treatment option

Conditional recommendation, Overall **Low** certainty evidence, effect size **Small**

Drotaverine is not **suggested** as a treatment option

Conditional recommendation, Overall **Low** certainty evidence, effect size Trivial (Table–14)

Anti-spasmodic agents aim to relax intestinal smooth muscle through various pathways. The exact mechanism of action for mebeverine is unknown, but effects may result from inhibition of intracellular calcium accumulation.[114,115] Drotaverine has two-fold spasmolytic activity. One is through inhibition of voltage-dependent calcium channels, limiting influx and activating spasms. The other is through inhibition of phosphodiesterase-4, an enzyme responsible for the degradation of cyclic adenosine monophosphate (cAMP), which results in elevated cAMP levels that allow smooth muscle tissue to relax.[116]

Summary of evidence: One study compared treatment with mebeverine to placebo in FAP patients ($n = 115$; age range 6–18 years).[117] One study compared treatment with drotaverine to placebo in RAP (Apley's criteria) ($n = 132$; age range 4–12 years).[118]

Efficacy: The study on mebeverine showed no statistical differences for treatment success (54.2% vs. 41.1%; RR 1.32 [0.89; 1.95]). The study on drotaverine did not predefine a dichotomous treatment success endpoint. Separate from reporting on the number of pain episodes during the study period, the study on drotaverine also reported the number of pain-free days during the same period (4 weeks). No significant differences were found for pain-free days when comparing drotaverine to placebo (mean 17.4 days, standard deviation [SD] 8.2 vs. mean 15.6 days, SD 8.7).

Safety: No GRADEd conclusions were drawn for SAEs and WAEs due to an overall lack of events. The study on drotaverine showed similar rates for TAEs, leading to a low certainty GRADEd conclusion that there may be no difference in the occurrence of TAEs.

Certainty: Overall certainty of efficacy outcomes was low, which was solely based on magnitude imprecision. The lack of the ability to conduct a meta-analysis limited the assessment of consistency. Overall risk of bias was low.

Rationale: The GDG made a conditional recommendation against mebeverine and drotaverine, after evaluating the benefits and harms of the treatment. Mebeverine did not show additional efficacy over placebo, therefore, the GDG decided to suggest against its use. Adult studies show conflicting results in patients with IBS, with no clear efficacy over placebo.[119] For drotaverine, one positive GRADEd conclusion was drawn for efficacy on pain frequency reduction, however effect size magnitude was trivial to small. Furthermore, another of the reported outcomes in the study on drotaverine, that is, a number of pain-free days, was highly contradictory to these results, which questioned the robustness of the GRADEd conclusion.

Should selective serotonin reuptake inhibitors (SSRIs) be used as a treatment option for AP-DGBIs?

Citalopram is not **suggested** as a treatment option

Conditional recommendation, Overall **Low** certainty evidence, effect size **Small** (Table–15)

Serotonin enhances gut motility and plays a complex role in gut inflammation, with the potential to both promote and protect against it. The reduction of serotonin reuptake can enhance gastric accommodation and increase chloride and fluid secretion in the intestinal lumen.[120]

Summary of evidence: One study compared citalopram to placebo in children with FAP ($n = 115$; age range 6–18 years).[121] Treatment duration was 4 weeks.

Efficacy: Treatment success was not significantly different between groups. The treatment success definition

TABLE 14 Data summary for antispasmodics versus placebo, refer to Figure 3 for table content explanation.

Conclusions of the evidenceantispasmodics versus placebo	GRADE certainty	Descriptive effect size mean (95% CI)Crude effect size mean (95% CI)
Mebeverine – There may be no difference for treatment success	Low	Small (trivial against to moderate in favor) 13.1% (–4.6%; 39%)
Mebeverine – There may be no difference for pain intensity	Low	Trivial (small against to small in favor) MD –0.20 [–0.77; 0.37]*
Drotaverine may lead to more reduction in pain frequency	Low	Trivial (trivial to small) MD –11.30 [–20.19; –2.41]**

Abbreviations: 95% CI, 95% confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; MD, mean difference.

*MD score for pain intensity was measured on a faces scale (0–5) (ref).

**MD score for pain frequency was measured as pain episodes during the study period (4 weeks).

was set at a 2-point reduction on a 0–5 faces scale (ref). When assessed as a continuous endpoint, pain intensity reduction was significantly greater for citalopram than for placebo. However, this was of small magnitude.

Safety: Due to a lack of events, no GRADEd conclusion was drawn for WAEs. TAEs were prevalent, but data could not be GRADEd due to reporting methods. Drowsiness and dry mouth were significantly more prevalent during citalopram treatment than during placebo treatment.

Certainty: Overall certainty of the efficacy outcomes was low. Certainty was downgraded due to the risk of bias for selective reporting resulting from discrepancies between the protocol and manuscript. Second, magnitude imprecision was also a reason for the downgrading of certainty.

Rationale: The GDG made a conditional recommendation against citalopram after evaluating the benefits and harms of the treatment. Even though limited low-certainty evidence for the efficacy of citalopram over placebo was available, small effect size and relevant safety issues led the GDG to suggest against its use. Adult studies show inconsistent results but indicate there may be efficacy of SSRIs over placebo for IBS, although its effect size remains unclear.[122]

Should yoga be used as a treatment option for AP-DGBIs?

Yoga is not **suggested** as a treatment option

Conditional recommendation, Overall **Low** certainty evidence, effect size **Small** (Table–16)

Yoga has been proposed to foster relaxation and alleviate stress and anxiety. Similar to hypnotherapy, yoga induces a state of calmness, enhancing self-awareness and receptiveness to relaxing cues provided by the instructor. This tranquil state is achieved through controlled breathing, gentle movements, and meditation.

Summary of evidence: Four studies assessed groups that followed yoga modules to groups that received standard medical care ($n = 248$; age range 5–18 years).[123–126] Included AP-DGBIs subtypes were IBS and FAP. One study also included FD patients.[125] One study used a yoga program with 1 physical session, followed by video sessions at home.[126] One study utilized a fully instructor-delivered program, involving Iyengar yoga.[123] One study used a physical module involving Hatha yoga.[125] The most recently published study combined yoga with a dance program over a particularly long duration of 8 months.[124]

Efficacy: Treatment success was not significantly different between groups. Of note, 1 of 3 studies showed a clearly favorable effect of yoga over standard care for treatment success. This particular study involved a combination of yoga and dance and had a longer treatment duration of 8 months.[124] Pain intensity reduction was statistically greater for the treatment group than for standard care.

Safety: Due to an overall lack of events, no GRADEd conclusions were drawn.

Certainty: Overall certainty of the crucial efficacy outcomes was low. Aside from evident issues with blinding, risks of bias were present in several other domains. Certainty for both treatment success as pain intensity was downgraded due to magnitude imprecision.

Rationale: The GDG made a conditional recommendation against yoga after evaluating the benefits and harms of the treatment. The GDG recognizes that yoga is generally safe and that physical exercise can be of benefit to the general population. However, the data summary has not evidently shown yoga to be superior to standard care. In the context of limited availability and cost implications of programs that include repeated sessions of yoga provided by an instructor, there is insufficient evidence to support a positive recommendation for yoga as a treatment option at this time.

3 | TREATMENT OPTIONS WITH VERY LOW CERTAINTY DATA AND/OR LACKING DATA

The following treatments were prospectively registered for PICO formatted questions, yielded at least one RCT, and underwent the same systematic approach, but received a negative conditional recommendation (i.e., suggested against the use of) due to lack of any GRADEd crucial efficacy conclusions of at least low certainty and/or lack of data. Results of the

TABLE 15 Data summary for selective serotonin reuptake inhibitors versus placebo, refer to Figure 3 for table content explanation.

Conclusions of the evidencecitalopram versus placebo	GRADE certainty	Descriptive effect size mean (95% CI)Crude effect size mean (95% CI)
There may be no difference for treatment success	Low	Small (trivial against to moderate in favor) 11.4% (–5.8%; 36.9%)
Citalopram may lead to more reduction in pain intensity	Low	Small (trivial to moderate) MD –0.67 [–1.25; –0.09]]

Abbreviations: 95% CI, 95% confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; MD, mean difference.
*MD score for pain intensity was measured on a faces scale (0–5).

TABLE 16 Data summary for yoga versus Standard care, refer to Figure 3 for table content explanation.

Conclusions of the evidenceyoga versus standard care	GRADE certainty	Descriptive effect size mean (95% CI)Crude effect size mean (95% CI)
No conclusion can be drawn for treatment success	Very low	Small (trivial against to large in favor) 12% (−3.5%; 41.8%)
Yoga may lead to more reduction in pain intensity	Low	Small (trivial to moderate) *MD −0.87 (−0.20; −1.55)

Abbreviations: 95% CI, 95% confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; MD, mean difference.
*MD score for pain intensity was measured on a 0–10 scale.

available data synthesis can be found in Supporting Information S2: File 2.

All of the following therapies were therefore *not suggested* as treatment options.

- Acupuncture[127]
- Osteopathy[128]
- Biofeedback[39]
- Strict Low FODMAP diet[129,130]
- Fructan limited diet[131]
- Fructose-restricted diet[132]
- Serum bovine-derived immunoglobulin[133]
- Antibiotics[134,135]
- Trimebutine[136]
- Melatonin[137]

The following treatments were assessed in an RCT, however, the GDG decided not to cast votes as these treatment options were considered outside of scope.

- Vitamin D[138]
- Gluten-free diet[139]

Any other treatment options that were prospectively registered and transformed into PICO format questions did not yield any RCTs in the systematic search and therefore did not receive a GRADEd recommendation. The list of treatment options is available in the study protocol.[16]

4 | BEST PRACTICE STATEMENTS

The GDG notes that a crucial emphasis should be placed on education regarding the AP-DGBI diagnosis during initial outpatient consultation sessions. Education should focus on the nature of the diagnosis, the relevance of the connection between the gut and brain, the effects of lifestyle and other triggers, and an outline of potential treatment approaches and options.

Rationale: Symptoms of AP-DGBIs partially originate through or are reinforced by amplified feedback loops from the gut that stimulate increased central sensitivity to painful stimuli. Therefore, it is of crucial importance to provide a structured and optimistic appraisal of the nature of the disorder to patients and caregivers of patients. Not only does this instill hope, but it also supports successful shared decision making, realistic goals of care, and empowers patients and their families in managing the illness. This approach, in which symptoms should be validated and the benign character of the disorder highlighted, can prevent families from feeling stigmatized and disregarded, as medical testing is typically normal, and there is no biologic marker for visceral pain. To this end, expectations set by patients and caregivers for both diagnostic testing as well as choice for and effect of treatment should be clearly addressed during consultation, and feedback provided. The GDG notes that sufficient time should be spent to deploy this educational approach, before initiating any specific treatment option to facilitate a successful program.

The GDG recognizes that dietary treatment options can seem harmless and therefore, receive consideration as an entry-level treatment option, particularly for motivated families. The GDG wishes to highlight that restrictive diets may require unrealistic or even disproportionate commitment from children and should be employed with the same consideration as all active interventions, with particular caution in children with risk factors for disordered eating.

Rationale: The evidence base considered and presented in this guideline is broadly very sparse and of very low certainty for most dietary interventions. The lack of evidence is not always an indicator of lack of efficacy, and so the GDG recognizes that many of these therapies will continue to have a role for certain patients, particularly when motivation is high. The GDG believes that such dietary options should always be considered for efficacy and, when not achieving shared care goals, should be curtailed. The GDG also wishes to highlight that stringent limitations raise concerns about the negative impact on the physical and psychological well-being of children. Nutritional deficiencies may emerge in growing children, particularly when following unproven fad diets. Strict regimens can reinforce unhealthy relationships with food or precipitate disordered eating. Imposing stringent restrictions on young patients can be impractical. There should be an individualized, patient-centered approach while integrating guidance from a registered dietitian when available.

The GDG has made GRADE recommendations about some specific probiotic/synbiotic preparations, but other preparations do not have sufficient evidence at a strain level to support such recommendations due to low study numbers and variable outcomes.

Rationale: The GDG recognizes that many probiotic and synbiotic preparations are readily available without prescription and are often used by members of the public for abdominal complaints. However, outside of two specific strains that had low and moderate certainty evidence for all of their core efficacy outcomes, evidence was not consistent, and this limited an overall class recommendation. While individual outcomes of individual strains did show effect, which may be the reason for interest in these agents, further research must address the pervasive issues with sample size, methods, and choice of outcome measures. It is suggested that if families and their professionals are motivated to consider the use of such agents that they should be monitored for efficacy and safety in line with other active therapies

The GDG recognizes that over-the-counter analgesics are commonly used. Whereas they may have a role in intermittent or periodic symptom control, the GDG raises caution beyond local OTC dosing and duration guidance

Rationale: The use of OTC analgesics in the management of pediatric AP-DGBIs warrants careful consideration. While readily accessible and frequently utilized for short-term relief of episodic symptoms, NSAIDs and acetaminophen have risks of adverse events, including gastrointestinal bleeding, hepatotoxicity, renal impairment, and medication overuse headaches when consumed beyond the limits outlined in pediatric dosing guidelines. Evidence-based dosing parameters should be followed to reduce the potential for harm while acknowledging the intermittent role OTC analgesics may play in a multimodal approach to AP-DGBI management.

The GDG finds that several alternative analgesic treatment classes should NOT be used without input and guidance through an appropriate specialist with expertise in treating therapy-refractory pediatric AP-DGBIs.

Rationale: The specialized nature of second-line analgesics warrants expert guidance when considering their application to pediatric AP-DGBIs. Agents like gabapentin or pregabalin have roles in wider pain management, but come with well-recognized significant side effect profiles and the complete absence of pediatric-specific evidence for the treatment of AP-DGBIs. Specialist involvement ensures that such treatments are only considered with extreme caution and within a comprehensive, multidisciplinary approach tailored to the individual patient. This should not be considered unless patients have symptoms refractory to a large number of other therapy options that were delivered with good compliance. If used, limiting use when efficacy is not demonstrated is mandatory.

The GDG acknowledges that the use of anticholinergic antispasmodics for symptom control is common in AP-DGBIs, but there is no evidence supporting or rejecting their use as a treatment.

Rationale: Anticholinergic antispasmodics such as hyoscyamine, dicyclomine, and scopolamine butylbromide are commonly used to alleviate intermittent pain in the management of AP-DGBIs. The use of antispasmodics is based on usual practice, anecdotal experience, data from animal studies, and recommendations from adult and pediatric guidelines. These medications work by blocking the action of acetylcholine on muscarinic receptors, reducing gastrointestinal smooth muscle spasms, which can provide symptomatic relief. However, their potential adverse effects, including dry mouth, dizziness, blurred vision, and constipation, require careful consideration. Therefore, clinical expertise is necessary to ensure a balanced approach to patient care. Clinical trials are recommended due to the low level of evidence regarding their effectiveness.

On the other hand, this guideline suggests against the use of antispasmodic medications like drotaverine and mebeverine for the treatment of IBS or FAP. Drotaverine is a phosphodiesterase-4 inhibitor that promotes muscle relaxation by reducing muscle cell phosphorylation. Mebeverine, on the other hand, acts as a direct musculotropic spasmolytic, inhibiting the accumulation of intracellular calcium and stabilizing muscle cell membranes. The efficacy of drotaverine and mebeverine is not supported by evidence, possibly due to their distinct mechanisms of action.

The GDG suggests Loperamide as a treatment option for symptom control in patients with IBS-D

Rationale: Despite a lack of any evidence of the efficacy of loperamide in children, the GDG is in consensus that they frequently use it for patients with IBS-D specifically and have good experience with its effect on improving stool consistency. It acts as an opioid receptor agonist and impedes colonic transit time through a direct effect on intestinal muscles, and it also inhibits luminal electrolyte loss, causing hardening of stools. Availability, ease of use, and low cost support its use for symptom control. Limited evidence of very low certainty exists for efficacy on stool consistency in adults.[140,141] Caution

should be exercised beyond dosing for infrequent symptom control, as loperamide may induce QTc prolongation, as well as cause central side effects due to crossing of the blood–brain barrier at higher dosages. It is also contraindicated in specific clinical situations, including bacterial enterocolitis due to the risk of toxic megacolon.

The GDG suggests Bile acid sequestrants as a treatment option for symptom control in patients with IBS-D

Rationale: In spite of a lack of any evidence of the efficacy of bile acid sequestrants, such as cholestyramine, in children, the GDG is in consensus that they are used for patients with IBS-D and have good experience with their effect in improving stool consistency. It is hypothesized that some IBS-D patients suffer from diarrhea resulting from increased bile acid synthesis or reduced reabsorption of bile, leading to imbalanced fecal lipid profiles and increased fluid secretion in the intestinal lumen.[142] Bile acid sequestrants aim to restore that balance and subsequently decrease diarrhea. Availability of bile acid sequestrants, ease of use, and a favorable safety profile support its use for symptom control. Limited evidence of very low certainty exists for efficacy on stool consistency in adults.[143]

The GDG suggests against the use of cannabinol/cannabis for the treatment of AP-DGBIs

Rationale: Despite growing interest and use, high-quality evidence supporting safety and efficacy in pediatric populations remains lacking. The developing central nervous system in children may incur harm from early cannabinoid exposure. Inconsistencies in product quality and composition complicate dosing guidance. Furthermore, legal and regulatory frameworks differ across various countries, and even within different states/provinces of a single country. For these reasons, the GDG suggests against the use of cannabinol/cannabis until methodologically rigorous investigations provide compelling pediatric-specific data.

The GDG strongly recommends against the use of surgery for the evaluation and treatment of AP-DGBIs

Rationale: While some children prove refractory to maximal medical therapy, the lack of evidence at present argues against extrapolating surgical solutions from other contexts. Surgery carries serious risks of complications and may not address the underlying pathophysiology of AP-DGBIs, potentially leading to unnecessary harm without benefit. Our statement shields children from unsubstantiated procedures.

5 | PLACEBO AND CONTROL RESPONSE

Previous studies have assessed the placebo treatment success rates in the context of AP-DGBIs, as both significant in magnitude (Mean improvement 41%) and range 2.8%–62.5%.[144] Within the studies included in the current technical review, this effect was even more pronounced with pooled control therapies demonstrating a mean rate of treatment success of 28% but range of 0%–78.4%, although this also included studies using standard care or waitlist control group designs, with lower expected success rates than placebo. Such large ranges of effect size are difficult to account for using reported sources of clinical and methodological heterogeneity within the published studies, suggesting other non-explicit factors must be at play.

Further extraction was undertaken, and a number of control group design categories were delineated. Those included no intervention/waitlist (mean success rate 10.5%), ample attention instead of waitlist (18%), placebo alone (17%), standard care alone (21%), and the largest category, placebo together with standard care (31%). These control group subgroup treatment success rates do appear clinically appropriate and reinforce the placebo effect in this context, but what was also apparent was the wide range of effects within each category. The largest control group category for treatment success, with 25 RCTs, was placebo in combination with standard care. Success rates in this group ranged from 0% up to 78.4% with an SD of 20% (95% CI 10.4%–51.6%).

Detailed consideration was undertaken to better understand variations in the placebo and control response. This was not possible due to limited reporting and a lack of response from study authors. A shortcoming included a paucity of reporting in key aspects such as the concept of standard care, education, advice, consultations with health care providers, frequency of consultations, discussion of prognosis, and baseline testing. These were not described universally or in sufficient detail to support dissemination and replication.

6 | FUTURE BROAD RESEARCH GPS

The GDG supports detailed reporting of placebo/control group interventions. This should include detailed information on the methods, such as the nature of the intervention and every aspect related to the procedures of both the active and control groups, to allow dissemination and replication. Categories such as the nature and frequency of clinic assessments, education content and modes of

delivery, dietary guidance offered, and prognostic information should all be considered. This will be aided by work to reach an international consensus on a framework to guide consistent reporting of these vital details for this and other functional bowel disorders, which are similarly reported.

The GDG has noted several consistent methodological limitations within the randomized trials that considerably hamper the capacity to synthesize data from multiple studies, as well as to formulate GRADEd recommendations. These pitfalls were frequently present across all therapeutic domains of AP-DGBIs. Without aiming to develop a research agenda for AP-DGBIs, the GDG proposes methodological guidance on the following subjects:

- Reporting of trials in full alignment with international trial reporting guidelines and with particular attention to the core items assessed within risk of bias reporting, such as the presentation of full details of randomization and allocation concealment methods (which is separate to blinding) and inclusion of a trial registry/protocol.
- Primary researchers to consider the previously published COS[18] and the critical (primary) outcomes identified by consensus within this guideline to ensure the most appropriate outcomes are reported, not just for the individual trial, but to support wider synthesis of the whole evidence base
- Sample size calculations should take into account the significant placebo effect and thresholds for outcomes, with the support of the thresholds in this publication, to ensure more appropriate and likely larger sample sizes to enhance the precision of outcomes.

6.1 | Future guideline updates

The methodological approach used in this guideline has been innovated in many core areas. The GDG would suggest that, as a minimum, an update is commissioned within 3 years to allow completion and publication of a new guideline within 5 years. However, the significant achievement to identify, extract, appraise, and synthesize the evidence base offers an opportunity to also innovate in future guideline efforts.

The GDG suggests that the option of a living review of the evidence and therefore a living guideline is considered.[145] Given the relatively small number of new trials per year, such an approach would offer the chance for any significant changes in the overall certainty of evidence and, in turn, potential recommendations to be identified and actioned in a more timely fashion.

As such, an approach would have implications for resources, requiring the sponsoring societies to consider methods to commission this, as well as agreeing on specific operating procedures for such an innovation for both societies, due consideration and joint agreement prospectively would be required. In spite of such barriers, such an approach would be the most appropriate to truly achieve ongoing evidence-based guidance within clinical practice.

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CONFLICTS OF INTEREST STATEMENT

Regulations for conflict of interest followed the Cochrane handbook as well as the GRADE body. These implied that not only the receipt of financial contributions of institutions with links to assessed treatment options implied a conflict, but academic involvement in research on a specific treatment option without commercial funding as well. Marc Alexander Benninga indicated conflicts of interest for Cognitive Behavioral Therapy (CBT), Yoga, Hypnotherapy, and laxatives, due to involvement in studies assessing these therapies. Marc Alexander Benninga also indicated consulting services for Norgine, Coloplast, Wellspect, Allergan, Mallinckrodt, United Pharmaceuticals, Danone, FrieslandCampina, and HIPP. Marc Alexander Benninga also served as speaker for Abbott and Menarini. Ashish Chogle indicated a conflict of interest for neurostimulation, due to involvement in studies assessing these therapies. Julie Khlevner indicated a conflict of interest for laxatives, due to involvement in studies assessing these therapies. Julie Khlevner also indicated consulting services for Abbvie Inc. Carlo Di Lorenzo indicated conflicts of interest for neurostimulation, amitriptyline, linaclotide, and prucalopride, due to involvement in studies assessing these therapies. Miguel Saps indicated conflicts of interest for amitriptyline and linaclotide, due to involvement in studies assessing these therapies. Miguel Saps also indicated consulting services for Abbvie Inc., IQVIA, and Focus Medical Communications. Nikhil Thapar indicated conflicts of interest for probiotics, due to receiving honoraria from both Biogaia and Nutricia for roles in the advisory board and in moderating a key opinion leaders meeting on the addition of pre-/probiotics in infant formula, respectively. Arine Vlieger indicated a conflict of interest for Hypnotherapy, due to involvement in studies assessing these therapies. Arine Vlieger also indicated an unpaid position as Chair of the Dutch Society for Hypnosis in Children. The remaining authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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