EFFICACY AND SAFETY OF THERAPIES FOR FAPD (FAP-NOS, IBS) IN CHILDREN: PROTOCOL FOR A NETWORK META-ANALYSIS

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Contributorship Statement:

An original draft for this protocol manuscript was made by MG, VS and JG and then finalized by the wider team.

Co-Authors agreed on the review questions, approved the protocol and contributed to the final version of this manuscript.

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Abstract

Introduction: Functional Abdominal Pain Disorders (FAPDs or Disorders of Gut-Brain Interaction) are chronic, debilitating conditions impacting over 250 million children and their families globally. Pediatric Abdominal Pain Disorders (FAPDs) are subcategorized into Functional abdominal pain – not otherwise specified (FAP-NOS), Irritable Bowel Syndrome (IBS), Functional dyspepsia (FD) and Abdominal Migraine (AM). There are multiple therapies that have been tested in randomized trials, but direct comparisons are rare and results heterogeneous. We present the protocol for a network meta-analysis to investigate the efficacy and safety of these treatments. The scope will be all of the sub-categories, except FD, which owing to its very different presentation and sets of treatments will be unlikely to be included in any network analysis.

Methods: Cochrane and 'Grading of Recommendations Assessment, Development and Evaluation' (GRADE) methodology will be followed throughout. A structured search will be run for all randomized trials with no date limits. The results will be screened in duplicate by two authors independently and disagreements solved by a third author. This will also be done for full text selection and data extraction. Risk of bias assessments will be made for each study with authors contacted for missing information. We will express outcomes as risk ratios and mean differences with 95% confidence intervals. We will perform network meta-analyses and assess the certainty of the evidence using GRADE. The primary outcomes will be treatment success, serious adverse events, frequency of pain and severity of pain.

Key messages:

What is already known on this topic: Abundant therapeutic approaches exist for FAPD, yet none are FDA or European Medicine Agency approved in children. A key reason for lack of regulatory approved therapies is a lack of international consensus on best evidence-based practice, preventing optimal treatment of these common disorders.

What this manuscript adds: This publication represents a unique network meta-analysis (NMA) with novel methodologies to enhance the precision of intervention estimates, rank therapies with consideration of certainty (GRADE), and produce subgroup or sensitivity networks. This manuscript describes the prospectively agreed methods and operating procedures that will be followed to produce an NMA for the various studied therapies for FAP-NOS, IBS and AM.

How this manuscript might affect practice: We aim for this network meta analysis to provide more insight into the ranking of the various therapies available for children aged 4-18 with FAP-NOS, IBS, and AM, worldwide for all treatment settings. This could lead to more uniformity in treatment, as well as yield more capacity for collaboration in a scientific setting.

Main text

Introduction

Functional Abdominal Pain Disorders (FAPDs or Disorders of Gut-Brain Interaction) have a world-wide prevalence of 13.5% with up to one third of children continuing to demonstrate symptoms into adulthood. FAPDs have a small, but consistent predisposition in girls over boys (15.9% vs. 11.5%).(1) FAPDs are categorized into four subtypes, i.e. functional abdominal pain not otherwise specified (FAP-NOS), Irritable Bowel Syndrome (IBS), Functional Dyspepsia (FD) and Abdominal Migraine AM.(2) Although each subtype is recognized as a separate entity, there is some degree of overlap among them. This overlap particularly applies for FAP-NOS and IBS, both in clinical presentation, as well as in treatment options and response. Children diagnosed with FAP-NOS exhibit similar characteristics to those with pediatric IBS in terms of pain frequency and intensity, quality of life, and symptoms of anxiety and depression. Therefore, distinguishing between these two entities based on these factors alone is not possible.(3) Management of FAP-NOS and IBS in children is focused on multidisciplinary approaches, including dietary modifications, gut-brain psychotherapies, pharmacological treatments, pre- and probiotics, and percutaneous electrical nerve field stimulation.(4) Functional dyspepsia is subdivided into postprandial distress syndrome and epigastric pain syndrome, with the mainstay for treatment being prokinetic medication, proton pump inhibitors and neuromodulators, thus representing an evidently distinct category of disease, whilst still regarded as an abdominal pain condition following Rome IV criteria.(5) AM presents with paroxysmal abdominal pain episodes, lasting for at least 1 hour and for which treatment is mostly based on analgesic medication to alleviate symptoms in the short period they occur.(5) Symptomatic episodes may be separated by weeks to even months.(4) A specific and evidence based treatment for this entity is clearly lacking and currently based on expert opinion.

All FAPDs can have severe implications on quality of life, reflected by higher incidences of anxiety and depression and increased utilization of health care.(6-9) The burden of FAPDs is reflected by the fact that quality of life is rated similarly low as in inflammatory bowel disease.(10, 11) The current understanding of the etiopathogenesis describes a biopsychosocial model, in which disease arises from a genetic predisposition where both gastrointestinal factors (e.g. intestinal dysbiosis, gut inflammation and motility disorders) as well as psychosocial sensitizing events (e.g. trauma, depression, passive coping mechanisms) lead to structural and functional disruption of the gut-brain-axis.(4) These disruptions translate to the core mechanisms for disease, i.e. visceral hypersensitivity and central hypervigilance.(4) A delay may exist between disruption of the gut-brain axis and the translation to these core mechanisms and thereby the onset of symptoms, hampering direct causal correlation and better preventive strategies. It is known that a large proportion of children with an FAPD continues to have symptoms into adolescence and adulthood(12), emphasizing the need for targeted treatment approaches and education at the earliest stage possible, as well as preventive strategies.

Members of ESPGHAN and NASPGHAN are currently completing a joint guideline outlining the therapeutic approach for FAPDs, focusing on FAP-NOS, IBS and AM in children.(2) The decision to exclude FD from the scope of this guideline was made based on its distinct classification as a separate disease category and its notably different treatment approaches. However, pilot searches and previous reviews have identified the significant heterogeneity in not just active interventional groups, but in the control or comparator groups as well. Whilst further diverse head-to-head trials will resolve this issue, given the range of studied intervention and control groups this will take significant time and resource. This currently limits the scope for meta-analysis and is a barrier to interpretation of the many trials published. This team proposes a network meta-analysis to support guideline development through informing and engaging clinicians and researchers in the wider field.

A network meta-analysis (NMA) is where multiple treatments are compared using both direct comparisons of interventions within randomized controlled trials (RCTs) and indirect comparisons across trials based on a common comparator (i.e., placebo). In other words, if compound A is compared with compound B in one trial, and the same compound B is compared with compound C in another trial, indirect information can be obtained from compound A versus compound C under the assumption of transitivity.

NMA is often understood to allow ranking of therapies, but there are significant limitations in this approach and goal. The main opportunities for NMA analysis in this context are much broader than simply ranking a top therapy and include:

- To allow interventions studied in multiple standalone comparisons to be combined in a single node and therefore enhance the precision of estimates for such interventions.
- To allow borderline therapies to be considered with greater precision.
- To rank therapies with consideration of certainty, ensuring the interpretation of both elements of the data together
- To produce subgroup or sensitivity networks to clarify the effect of clinical and method factors on findings.

This protocol describes the steps that will be followed to produce this NMA.

Methods

Evidence selection

Types of studies

All published, unpublished, and ongoing randomized controlled trials (RCTs) that compared interventions for the management of FAPD with other active interventions or standard therapy, placebo, or no therapy will be considered for inclusion. We will exclude studies that do not report on any of the outcome measures specified below.

We plan to include cross-over studies for quantitative analysis only if data were separately reported before and after cross-over and use only pre-cross-over data. We do not anticipate finding any cluster-RCTs; we would only use study data from such trials if the authors employed appropriate statistical methods in taking the clustering effect into account. We would also exclude cluster-RCTs in a sensitivity analysis to assess their impact on the results.

Types of participants

Trials enrolling children from the age of 4 to 18 years, with a clinical FAP-NOS, IBS or AM diagnosis as defined by any version of the issued Rome criteria or otherwise previously utilized diagnostic classification system (e.g. Apley), with the most recent Rome IV criteria as a reference (ref. table 1), will be considered for inclusion.(2) If studies do not define subgroups within FAPD, authors will be contacted for discriminatory data, but studies will still be included if they do not provide this. If studies include a mix of adults and children and the data is not separated, authors will be contacted, and the study will only be included if separate data on children can be provided upon request. Studies that focus solely on FD will

be excluded, but studies were FD patients are included alongside the other FAPD diagnoses, and their outcome data cannot be separated will be included.

Table 1: Diagnostic criteria for FAP-NOS, IBS and AM according to the Rome IV criteria (5)

Diagnosis	**Criteria**
Functional Abdominal Pain – Not Otherwise Specified	*Must include all of the following criteria, being fulfilled at least 4 times per month and for at least 2 months prior to diagnosis* 1. Episodic or continuous abdominal pain that does not occur solely during physiologic events (e.g., eating, menses) 2. Insufficient criteria for irritable bowel syndrome, functional dyspepsia or abdominal migraine 3. After appropriate evaluation, the abdominal pain cannot be fully explained by another medical condition
Irritable Bowel Syndrome	*Must include all of the following criteria, being fulfilled for at least 2 months prior to diagnosis* 1. Abdominal pain at least 4 days per month over at least 2 months associated with *one or more* of the following 2. Related to defecation 3. A change in frequency of stool 4. A change in form (appearance) of stool 5. In children with abdominal pain and constipation, the pain does not resolve with resolution of the constipation (children in whom the pain resolves have functional constipation, not IBS) 6. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition
Abdominal Migraine	*Must include all of the following occurring at least twice:* **Criteria fulfilled for at least 6 months prior to diagnosis* 1. Paroxysmal episodes of intense, acute periumbilical, midline or diffuse abdominal pain lasting 1 hour or more

(should be the most severe and distressing symptom)
2. Episodes are separated by weeks to months
3. The pain is incapacitating and interferes with normal activities
4. Stereotypical pattern and symptoms in the individual patient
5. The pain is associated with two or more of the following:
    1. Anorexia
    2. Nausea
    3. Vomiting
    4. Headache
    5. Photophobia
    6. Pallor
6. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition

Types of interventions

Trials studying the interventions outlined in tables 2 and 3 can be included.

Table 2: Types of pharmacological interventions for FAPDs:

Type	Group
Antispasmodics	Peppermint oil
	Drotaverine
	Mebeverine
	Trimbebutine
	Hyoscine butylbromide
	Dicyclomine
	Hyoscyamine
Neuromodulators	Amitriptyline
	Citalopram
	Mirtazapine
	Gabapentin
	Pregabalin
Laxatives	Osmotic (polyethylene glycol, lactulose, lactitol)
	Stimulant (bisacodyl, senna, sodium picosulphate)
	Lubricants (mineral oil, paraffin)

	Secretagogues and prokinetic laxatives (linaclotide, lubiprostone, prucalopride, plecanatide)
	Tegaserod, alosetron
	Enemas
Anti-diarrheal medication	Loperamide
Antibiotics	
Analgesics	Paracetamol/acetaminophen, non steroidal anti-inflammatory drugs (NSAID), tramadol
Anti-reflux medication	(PPI, H2-receptor antagonist, prokinetics, domperidone)
Anti-emetics	
Antimigraine medication	Sumatriptan, propranolol
Antihistamines	Cyproheptadine, ebastine
Serotonin agonist	Buspirone
Melatonin	
Opioid agonist	Eluxadoline
Serum bovine derived immunoglobuline	
Bile acid sequestrants	

Table 3: Types of non-pharmacological interventions for FAPDs:

Type	Group
Lifestyle-advices including physical activity	
Dietary interventions	Extra fluid intake
	Fiber
	Low - fermentable oligosaccharides, disaccharides, monosaccharides, and polyols FODMAP diet
	Fructans
	Fructose restricted diet
	Prebiotics (inulin)
	Lactose free diet
	Dairy free diet
	Gluten free diet
	Histamine low or free diet
	Multiple exclusion diet
	Decrease in gas producing foods
	Vitamin D
Pro- and synbiotics	
Herbs, iberogast	
Behavioral therapies	Hypnotherapy/guided imagery
	Cognitive behavioral therapy (incl. exposure therapy)
	Mindfulness

Complementary and alternative therapy	Acupuncture
	Homeopathy
	Body-oriented therapy
	Musculoskeletal therapy (osteopathy/chiropractic)
	Yoga
	Auriculotherapy
	Acupressure
	Acutherapy
Biofeedback	
Neurostimulation	

Types of outcome measures

Both dichotomous and continuous outcomes will be valid for inclusion. Ranking of the outcome measures was based on the core outcome set(13), with the core research team (MG, VS, JG, MT, MB) proposing a final ranking that received the consent of all GDG members.

Primary (critical) outcomes (assessed before and after start of treatment)

Treatment success as defined by the authors.

Abdominal pain frequency or change in frequency of pain using any validated scale.

Abdominal pain intensity or change in pain intensity using any validated scale.

Serious adverse events (participants with at least one serious event).

Thresholds for outcomes

For each of the included outcomes, the threshold will be pre-defined as per the ESPGHAN / NASPGHAN guideline. These will ensure interpretation is against this a priori defined framework.

- 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')

Search methods for identification of studies

We will use a search strategy designed and checked by an information specialist with Cochrane expertise.

We will search EMBASE, Ovid MEDLINE, and CENTRAL from inception. We will place no restrictions on language of publication. As complementary search methods, we will carefully check Cochrane systematic reviews on immunomodulators for eligible studies.

Data collection and analysis

We will carry out data collection and analysis according to the methods recommended in the Cochrane Handbook for Systematic Reviews of Interventions.(14)

Selection of studies

A PhD student (JG) working in the Emma Children's Hospital, AUMC, Amsterdam, the Netherlands in collaboration with the Cochrane team (MG, VS) and supporting fellows or health care students will independently screen the titles and abstracts identified by the literature search, excluding studies that based on title and abstract did not meet our inclusion criteria. All will be screened in duplicate independently and disagreements solved by a third author. They will obtain the full reports of studies deemed potentially eligible. These reviewers will independently assess the full texts for inclusion in the review. Any disagreements will again be resolved by discussion or by consulting another review author (MT/MB) if necessary. We will record the studies excluded at this or subsequent stages, and the main reason for their exclusion, in the 'Characteristics of excluded studies' tables.

Where there are multiple publications for a given study, we will collate the reports of the same study so that each study, rather than each report, will be the unit of interest in the review; such studies have a single identifier with multiple references.

Data extraction and management

JG, EM, MG and VS will independently perform data extraction using piloted data extraction forms. We will extract the following data from the included studies:

Trial setting: country and number of trial centers

Methods: study design, total study duration and date

Participant characteristics: age, gender, socio-demographics, ethnicity, diagnoses and diagnostic criteria, pain location, number of participants allocated to each group, funding source, and conflicts of interest

Eligibility criteria: inclusion and exclusion criteria

Intervention and comparator

Outcomes: outcome definition, unit of measurement, time of collection, and outcome data

This information will be presented in supplementary tables.

Assessment of risk of bias in included studies.

Three reviewers authors (JG, MG, VS) will independently assess risk of bias in the included studies with the Cohrane RoB 1 tool, based on the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions.(14)

We will assess the following 'Risk of bias' domains:

Sequence generation (selection bias)

Allocation concealment (selection bias)

Blinding of participants and personnel (performance bias)

Blinding of outcome assessment (detection bias)

Incomplete outcome data (attrition bias)

Selective reporting (reporting bias)

Other bias such as imbalance in participants' baseline characteristics.

The studies will be judged to be at low, high, or unclear risk of bias for each domain assessed, based on the guidance in the Cochrane Handbook for Systematic Reviews of Interventions.(14)

Disagreements will be resolved by consensus or by a senior reviewer.

Measures of treatment effect

We will express treatment effect as risk ratios (RR) with corresponding 95% confidence intervals (CI) for dichotomous outcomes, and mean difference (MD) with 95% CI for continuous outcomes. For continuous outcome assessed on more than one scale, we estimated internal reference SDs and change from baseline mean(SD) values using a correlation coefficient of 0·5, and standardised outcome results as change from baseline on the most commonly used outcome scale.(15) The modified intention-to-treat method was used for analysis. The random effect model was used to pool data.

Unit of analysis issues

The unit of analysis is the participant.

Dealing with missing data

We will perform analyses on a modified intention-to-treat basis. We will contact study authors in the case of missing data or studies that did not report data in sufficient detail. We will attempt to estimate missing SDs using relevant statistical tools.

Assessment of heterogeneity

Clinical and methodological heterogeneity

To evaluate the presence of clinical heterogeneity, we will examine trial and trial population characteristics across all eligible trials that compared each pair of interventions. We will assess the presence of clinical heterogeneity within each pairwise comparison by comparing these characteristics.

Assessment of transitivity across treatment comparisons

We will assess the assumption of transitivity by comparing the distribution of potential clinical, interventional, and methodological effect modifiers across the different pairwise comparisons.

We will evaluate the assumption of transitivity epidemiologically by comparing the extracted characteristics of the connected network studies.

Assessment of statistical heterogeneity and inconsistency

In standard pairwise meta-analyses we will estimate different heterogeneity variances for each pairwise comparison. In the network meta-analysis, we will assume a common estimate for the heterogeneity variance across the different comparisons.

We will assess statistically the presence of heterogeneity within each pairwise comparison using the I^2 statistic and its 95% CI.(16) We will base the assessment of statistical heterogeneity in the entire network on the magnitude of the heterogeneity variance parameter (Tau^2) estimated from the network meta-analysis models. We will compare the magnitude of the heterogeneity variance with the empirical distribution as derived by Turner 2012.(17) We will also estimate a total I^2 statistic value for heterogeneity in the network as described in Higgins 2022. We will consider downgrading the certainty of the evidence for inconsistency where I^2 is greater than 60%.

Assessment of statistical inconsistency

We will use global and local approaches to evaluate the statistical agreement between the various sources of evidence in a network of interventions (consistency) to complement the evaluation of transitivity. To evaluate the presence of inconsistency locally we will use the loop-specific approach. This method evaluates the consistency assumption in each closed loop of the network separately as the difference between direct and indirect estimates for a specific comparison in the loop (inconsistency factor). Then, the magnitude of the inconsistency factors and their 95% CIs can be used to infer the presence of inconsistency in each loop. We will assume a common heterogeneity estimate within each loop. To check the assumption of consistency in the entire network we will use the 'design-by-treatment' model as described by Higgins 2012.(18) This method accounts for different sources of inconsistency that can occur when studies with different designs (two-arm trials versus three-arm trials) give different results as well as disagreement between direct and indirect evidence. Using this approach, we will infer the presence of inconsistency from any source in the entire network based on a Chi2 test.

All analyses will be run with R statistical package (R Development Core Team) and the netmeta library.(19)

Assessment of reporting biases

Most reporting biases are minimized by using an inclusive search strategy. We plan to investigate publication bias using a funnel plot if there were 10 or more studies. The magnitude of publication bias will be determined by visual inspection of the asymmetry of the funnel plot. In addition, we will test funnel plot asymmetry by performing a linear regression of intervention effect estimate against its standard error, weighted by the inverse of the variance of the intervention effect estimate.(20)

Data synthesis

Direct comparisons of treatment effects

We will combine data from individual trials for meta-analysis when the interventions, patient groups and outcomes are sufficiently similar (as determined by consensus). A random-effect model was used to pool data.(21)

Indirect and network comparisons

We will initially generate and assess the network diagrams to determine if a network meta-analysis is feasible. Then we will perform the network meta-analysis on all outcomes within a frequentist framework using multivariate meta-analysis..(19)

Relative treatment ranking

We will estimate the cumulative probabilities for each treatment being at each possible rank and obtained a statistical treatment hierarchy using the surface under the cumulative ranking curve (SUCRA); the larger the SUCRA the higher its statistical rank among all available agents.(19)

To avoid basing our rankings only on a statistical measure, we will integrate GRADE certainty with SUCRA. Therefore, statistically effective treatments will first be ranked from high to low GRADE certainty. They will then be ranked via SUCRA hierarchy within their respective GRADE certainty groupings. Very low GRADE certainty treatments will not be ranked.

Subgroup and sensitivity analyses

Our pre-planned subgroup analyses are

- Control analysis where the control treatments placebo, waitlist and standard care, or no intervention, are considered as separate treatments.
- Sub-diagnosis analysis (IBS, FAP)
- Per age group (4-12, 13-18 years)

Our pre-planned sensitivity analysis are

- Random vs common (fixed) effects statistical model
- Component NMA (cNMA) analysis(22)
- Per diagnostic criteria (e.g. Rome criteria iterations, Apley's criteria)
- Per outcome definition (only applicable to treatment success)
- Removal of studies with high risk of bias judgements

Summary of findings and assessment of the certainty of the evidence

The summary of findings tables present evidence comparing all methods with a reference comparator. Each table describes key features of the evidence relating to a single outcome. There is a table for each primary outcome in accordance with the GRADE approach.

We will assess the certainty of the evidence using the GRADE approach as outlined in the GRADE handbook in order to assess the certainty of the body of evidence relating to each outcome for all comparisons.(23)

We will use the GRADE working group's approach for rating the certainty of the network meta-analysis effect estimates for all the comparisons and all outcomes.(23) We will appraise the certainty of the direct, indirect, and network evidence sequentially.

First, we will assess the certainty of the direct evidence (where available) for a given outcome, and rate the evidence using the standard GRADE approach based on consideration of: trial design limitations (risk of bias); inconsistency; imprecision; indirectness and publication bias.(24) In this approach, the direct estimates are rated for risk of bias, inconsistency, indirectness and publication bias; followed by the indirect estimates are rated based on the lowest ratings of the direct comparisons forming the most dominant loop and intransitivity; and finally, the network estimates are will be rated based on imprecision, incoherence, and the rating of the direct or indirect estimate that contributes the most.

Then we will rate the certainty of the indirect evidence for the same given outcomes, based on the lower of the certainty ratings of the two direct arms forming the dominant 'first-order' loop in the network diagram for this outcome.

Finally, we will determine the certainty of network evidence based on:

- The higher certainty rating of the direct and indirect evidence;
- Whether the relevant network exhibited 'transitivity', that is, whether all the comparisons contributing data to the estimate were directly consistent with the PICO question;
- Consideration of coherence between direct and indirect effect estimates;
- And precision of the network effect estimate.

At each of these stages, review authors (MG, VS, JG) will independently appraise the certainty ratings for the direct, indirect and network evidence. We will resolve disagreements between authors through discussion and consultation. We will rate the certainty of network evidence for each outcome as 'high', 'moderate', 'low' or 'very low' in accordance with the GRADE approach.

- High certainty: we are very confident that the true effect lies close to that of the effect.
- Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
- Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

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