IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 19, Issue 8 Ser.6 (August. 2020), PP 49-57
www.iosrjournals.org

Consolidated Summary of Current Treatment Modalities of Childhood Functional Abdominal Pain

Raju C Shah[1], Lalit Verma[2], Vaibhav Shah[3], Ashley George Suares*[4],Krishna Chaitanya Veligandla[4]

1)Pediatrician, Ankur Institute of Child Health, Ahmedabad, India
2)Consultant Pediatric gastroenterologist and Hepatologist, Wockhardt Hospital, Mumbai, India
3)Consultant Pediatric gastroenterologist and Hepatologist, Gujarat Super Speciality Clinic, Ahmedabad, India
4)Medical Affairs, Dr Reddy's Laboratories, Hyderabad, India
Corresponding Author:*Ashley George Suares, PharmD,Medical Affairs, Dr Reddy's Laboratories, Hyderabad*

Abstract
Functional gastrointestinal disorders (FGIDs) consists of range of disorders which cannot be explained by structural or biochemical abnormalities. Managing functional abdominal pain by traditional pharmacological therapies in children are failing to achieve the desired outcome, whereas new pharmacological and non-pharmacological approaches are showing promising results. The aim of this review is to provide the clinicians an overview and summary of recent literature of pharmacological and non-pharmacological options in management of functional abdominal pain in children and adolescent. This review article discusses about latest evidences which includes randomized controlled trials, retrospective studies, reviews, observational studies and evidence based medicine search on MEDLINE and Cochrane library. Non-pharmacological treatments are as effective as pharmacological treatments in children with functional abdominal pain (FAP) particularly bio-psychosocial modifying therapies and probiotic supplementation with Lactobacillus reuteri DSM 17938 which have shown beneficial actions. Due tosafety and tolerability guidelines, many experts believe that in management of FAP, non-pharmacological interventions should be the first line of treatment in children.

Keywords:*functional abdominal pain; functional gastrointestinal disorders; probiotics; children; adolescent; paediatric; non pharmacological management; review article*

Date of Submission: 30-07-2020 Date of Acceptance: 15-08-2020

Abbreviations:
FGID, functional gastrointestinal disorders; FAP, functional abdominal pain; AP-FGID, Abdominal pain-related functional gastrointestinal disorder; RAP, recurrent abdominal pain; IBS, irritable bowel syndrome; HBT, hydrogen breath test;SIBO, small intestinal bacterial overgrowth; PHGG,partially hydrolysed guar gum;CAP, chronic abdomen pain; LGG,lactobacillus rhamnosus GG; QoL, quality of life; CFU, colony forming units; FAPD, functional abdominal pain disorders; FC, functional constipation; CBT, cognitive behaviour therapy; WGO, world gastroenterology organization

I. Introduction

Functional gastrointestinal disorders (FGIDs) consists of range of disorders which cannot be explained by structural or biochemical abnormalities.Abdominal pain-related functional gastrointestinal disorder (AP-FGID) consist of4 main conditions: functional dyspepsia, irritable bowel syndrome, abdominal migraine and functional abdominal pain. These functional disorders are believed to be associated to gastrointestinal tract, gut microbiota and are seen more commonly from infancy to older school going children. Although benign in nature, these disorders are commonly associated with significant anxiety, school absenteeism, frequent clinic visits, unnecessary testing, and a significant economic burden[1, 2].

Recurrent abdominal pain (RAP) is the most common symptom among children and adolescent. Apley and his colleagues first defined the RAP syndrome in 1958as "at least three episodes of abdominal pain, severe enough to affect their activities over a period longer than 3 months"Through literature review and a consensus process, the working committee of Rome foundation, laid down diagnostic criteria for FGIDs in children. In 1990, first Rome criteria was established but then it was applicable only to adults. The FGIDs diagnostic criteria for children was placed in 1999 which was then revised in 2006 and recently in 2016, called as Rome IV criteria[3].

RAP may include symptoms such as bloating, distension, irregular evacuation, nausea and vomiting. After ruling out all the possible organic causes of RAP, this condition then would be called as functional

abdominal pain (FAP).The pharmacological approaches are often of limited benefit in children presenting with functional abdominal pain and since there is no universally proven method to resolve the symptoms, managing RAP in children can be challenging, frustrating and time consuming for paediatrician and paediatric gastroenterologist[4, 5].

Whereas, the old-fashioned pharmacological management interventions are failing to treat FAP in children, there are new pharmacological and non-pharmacological methods which have shown great potential in managing FAP.

The aim of this review is to provide the clinicians an overview and summary of recent literatures of pharmacological and non-pharmacological options in management of functional abdominal pain in children and adolescent.

II. Search Methodology

MEDLINE and Cochrane library search was conducted between 2005 to November 2018 with no language restriction with the help of following keywords: functional gastrointestinal disorders (FGIDs), recurrent abdominal pain (RAP), functional abdominal pain (FAP), irritable bowel syndrome (IBS), abdominal pain related functional gastrointestinal disorders. Separate search was conducted for keywords such as children, childhood, child, adolescent, toddler, youngster, newborn, neonate, infant, teenager, juvenile, pediatric and paediatric. The intersecting scientific literature of these two separate searches which consists of recent scientific contributions, official medical society guidelines, randomized controlled trials, retrospective studies, reviews, observational studies and evidence based medicine were included in this review. References are provided for more in-depth reading.

III. Diagnosis

Rome IV criteria has set proper sub classification of FAP disorders - functional dyspepsia, irritable bowel syndrome, abdominal migraine and functional abdominal pain.When the child is showing no failure to thrive or any alarming sign and symptoms, the FAP can be clinically diagnosed without undergoing any further investigations, according to the updated ROME IV criteria.However, the most important step of diagnosis in FAP is accurate anamnesis (a detailed history about the abdominal pain and any other associated symptoms, including onset, duration, frequency, site, characteristics, and triggering or relieving factors) and compare symptom concordance with the Rome IV criteria. There is no decisive laboratory or radiological investigations available to make a positive diagnosis of AP-FGID and an attempt should be made to rule out the organic pathologies at the initial visit itself or when there is a presence of any red flag signs and symptoms during physical examination. With no decisive investigation, the medical history becomes an important tool for ruling out others FGIDs such as in IBS where the abdominal pain is relieved after defecation, changes in frequency and appearance of stool, though, this by itself is not the confirmatory diagnosis in IBS or in abdominal migraine where there is presence of nausea, vomiting, headache, photophobia, pallor, and history of cranial migraine in the child or family[6, 7].

Rome IV criteria should help paediatricians to make a positive diagnosis of FAP and avoid needless laboratory investigations. On the other hand, in unmanageable and difficult cases where there is concern regarding some underlying gastrointestinal disease, the child should be referred to paediatric gastroenterologist for further investigations.

IV. Management

The most challenging step in treating a child with functional abdominal pain is to arrive ataccurate diagnosis. If an alarming sign is observed during diagnosis, then the management can be focussed in that direction. Despite, functional abdominal pain is represented with no underlying cause, no abnormal investigational lab reports, and no failure to thrive, it is important to give proper treatment and assurance to the child. Reducing the pain severity, pain episodes and overall improving the child's quality of life such as recommencing of normal lifestyle with regular school attendance, normal sleep pattern and participation in extracurricular activities should be the prime objective of giving any particular interventions. Managing FAP comes with additional challenge of reassuring the parents and explaining the diagnosis to them. Sometimes, the treatment strategies should be based on case-by-case basis i.e. understanding the psychosocial aspects of illness, behaviour habits of diagnosed child and thereby altering the treatment such as indicating of specific diet, modulating the gut micro flora, changing the defecating pattern.

The management consists of pharmacological, placebo and non-pharmacological approach. There is a limited evidence in pharmacological interventions which includes antispasmodics, antidepressants, antihistaminic agents, ant-reflux agents, calcium-channel blockers, serotonin antagonists, laxatives, antibiotics, and melatonin. Apart from low evidence, another issue is children dislike taking medications, hence compliance

becomes a major issue. This leaves the paediatrician with alternative non-pharmacological treatment options such as dietary interventions, probiotic supplementation and bio-psychosocial intervention.

Non-Pharmacological Interventions

Dietary Interventions

Dietary modifications is one of the most commonly accepted intervention in children with FAP. Despite dietary intervention being the most widely used, there are only few studies done in children with FAP. Dietary changes must be done on case-by-case basis which may includerestricting, excluding or increasing the intake of a particular ingredient in the diet.

Fructose

Fructose restricted diet in children and adolescents with recurrent abdominal pain may be of benefit to improve both abdominal pain symptoms.

A study done in 2014 by Escobar et al, which had 222 children with recurrent abdominal pain aged 2 to 19 years out of which 121 patients had positive hydrogen breath test (HBT) for fructose intolerance where they were given a low fructose diet. 76.9% patients reported resolution of symptoms on a low-fructose diet ($P<0.0001$). On the other hand, 55 of 101 patients (54.4%) with negative HBT for fructose reported resolution of symptoms without a low-fructose diet ($P=0.37$). One major limitation of the present study because of its retrospective nature was its inability to differentiate patients with small intestinal bacterial overgrowth (SIBO) from those with fructose intolerance or a combination of both.[8]

In a similar study, done by S.Wirth, 51 paediatric recurrent abdominal pain patients with restricted fructose in-take showed significant improvement in pain scores while 52 patients without any diet restriction in another group did not show any significant change. Moreover, this study also confirmed that a fructose restricted diet may lower the pain intensity irrespective of the HBT outcome.[9]

Also, Wintermeyer in 2012 demonstrated significant decrease in intensity of pain in 75 children (aging 3–14 years) with recurrent abdominal pain followed a fructose restricted diet for 4 weeks ($P<0.001$). Several additional life quality-influencing parameters such as daily stool frequency, nausea, problems to fall asleep, missed school days also improved significantly.[10]

Fibre

Fibres are basically carbohydrates that are not hydrolysed or absorbed in the upper part of gastrointestinal tract. A 2006 studyshowed that fibre intake below the recommended value is a risk factor for recurrent abdominal pain.[11]

A study done by Romano C et al, showed PHGG (Partially hydrolysed guar gum—a water soluble fibre having prebiotic like properties such as modulating microbial flora) to have higher beneficial actions in reducing overall clinical symptoms when compared to control group. This study was a randomized, double-blind pilot study performed in 60 children (8-16 years) with functional bowel disorders such as IBS or chronic abdomen pain (CAP). During the course of study, there was a decrease in the intensity of pain in the group of children given PHGG, which was not seen in the placebo supplemented group. However, this result was not statistically significant ($P > 0.05$), compared with baseline at week 4 and 8.[12]

A systematic review of three randomized control trial was done to evaluate the efficacy of dietary fibres in abdominal pain related FGIDs in children concluded that there is no evidence that fibre rich diet could be beneficialin reducing pain associated with FGIDs. In addition, the 2007 Cochrane review also concludes that fibre enriched diet did not show any significant difference in pain in 136 children with IBS when compared with placebo.[13,14]

Probiotics

Quite a lot of different strains of probiotics have been investigated for therapeutic benefits in children with FGIDs with Lactobacilli species and Bifidobacteria species being the most commonly researched group.

A symbiotic study containing bacillus coagulans and fructo-oligosaccharides was put out by Saneian et al, in 2015 on Rome 3 diagnosed functional abdominal pain children. This study reported that when compared with placebo, a combination of bacillus coagulans and fructo-oligosaccharides were beneficial during the treatment course (4 weeks), however, these positive effects were not long lasting and had similar results as placebo after 12 weeks.[15]

In 2011, A. Horvath et al, did a meta-analysis to evaluate the effect of Lactobacillus rhamnosus GG (LGG)in abdominal pain related functional gastrointestinal disorder in children. This meta-analysis showed the number of responders to the treatment were significantly higher in IBS when compared with placebo. However, there was no difference in pain intensity and severity in FAP in children.[16]

In 2017, multicenter, randomized, double-blind, placebo-controlled, crossover trial was conducted by Giannetti et al, to investigate the efficacy of mixture of 3 bifidobacteria (Bifidobacterium infantis M-63, B.

breve M-16V, and B. longum BB536) in 48 children with IBS and 25 children diagnosed with functional pain. This mixture of 3 bifidobacteria strains showed improvement in reducing abdominal pain and increased QoL in children with IBS, on the other hand, there was no signs of improvement in children with functional abdominal pain.[17]

Jadresin et al. demonstrated a RCT on 55 children (aged 4-18 years) with FAP or IBS to evaluate the efficacy of Lactobacillus reuteri DSM 17938. These children were randomly assigned to receive 10^8 CFU of L.reuteri or matching placebo for 12 weeks and were followed up for further 4 weeks after intervention. This study reported that in comparison to placebo, L.reuteri was effective in increasing the number of pain free days significantly (median 89.5 vs. 51 days, P=0.029). Also, the severity of abdominal pain was less in second ($p<0.05$) and fourth month ($p<0.01$) significantly after administration of L.reuteri.[18]

Another similar, randomized double-blind placebo controlled trial was conducted in 101children aged 6-15 years with FAP, investigating L.reuteri DSM 17938. This trial showed, L reuteri (n = 47) was significantly superior to placebo (n = 46) in relieving frequency (1.9 +/- 0.8 vs 3.6 +/- 1.7 episodes/wk, P < .02) and intensity (4.3 +/- 2.2 vs 7.2 +/- 3.1 Hicks score/wk, P < .01) of abdominal pain following 4 weeks of supplementation.[19]

Another RCT, performed by Romano which demonstrated beneficial effects on pain intensity at both 4 weeks and 8 weeks as compared to placebo. These 60 FAP children aged 6-18 years were randomized to either receive10^8 CFU of L.reutei DSM 17938 twice daily or matching placebo for 4 weeks. L.reuteri-supplemented children had significantly lower pain intensity at both 4 weeks and 8 weeks compared with placebo. At any point of the study, there was no significant reduction in frequency of pain between the two group, however, pain frequency decreased significantly with time 0–8 weeks in both groups ($p<0.05$).[20]

In 2015, Kambiz et al. conducted double blind randomized control trial in 80 children aged 4-16 years of age divided in to two arms. The first arm received 10^8 CFU daily of L.reuteri for 4 weeks while another arm received a similar placebo. After 8 weeks of follow up, this study shows that there is no significant different in the pain score between the two arms of study, however, there is significant reduction of severity of pain in both the group.[21]

A recent 2018 double blind randomised placebo controlled study published by Sudha MR et al, evaluated the efficacy of Bacillus coagulans Unique IS2 in treatment of irritable bowel syndrome in children. This RCT study was done in 141 children aged between 4-12 years diagnosed with IBS according to the Rome III criteria followed for 8 weeks during treatment and followed by 2 weeks post intervention. This study reported that there was a significant reduction ($P<0.0001$) in pain intensity in the probiotic group (7.6±0.98) as compared to the placebo group (4.2±1.41) by the end of the treatment period (8 weeks). Other symptoms such as consistency of stool, reduction in bloating, abdominal discomfort, staining, urgency, incomplete evacuation and passage of gas showed a significant improvement.[22]

A latest systematic review by Carrie A.M. Wegh et al, investigated the response of probiotics on functional abdominal pain disorders (FAPD) and functional constipation (FC). The authors reported that L. reuteri DSM 17938, a mix of Bifidobacterium infantis, Bifidobacterium breve and Bifidobacterium longum, Bifidobacterium lactis or VSL#3 did not have sufficient evidence for children with FAPD.[23]

Another 2018 article, a systematic review of randomized control trials done by Abbott RA et al, in school aged of recurrent abdominal pain concluded by suggesting probiotic could be considered in management of recurrent abdominal pain, however, effectiveness of different strains of probiotics is currently insufficient to guide clinical practice.[24]

Table 1: Summary of Probiotic studies

Probiotic Strains	Number of studies	Sample Size	Conclusion
Synbiotic (Bacillus coagulans + FOS) vs placebo	1 RCT (FAP)	115	Response rate higher after 4 weeks but similar to placebo after 12 weeks.[15]
Lactobacillus GG	Meta-analysis of 3 RCTs (IBS, FAP, FD)	290	Responded in IBS but no improvement in pain episodes and severity in FAP.[16]
3 billion Bifidobacterium (B). longum, 1 billion B. infantis, 1 billion B. breve	1RCT (IBS, FAP)	73	Improvement in IBS symptoms but not in FAP children.[17]
Lactobacillus reuteri DSM 17938	4 RCTs (FAP, IBS)	296	3 RCTs reported reduction in severity whereas 1 RCT showed similar efficacy as placebo. 2 RCTs showed improvement in pain episodes over placebo.[18,19,20,21]
VSL #3	1 RCT (IBS)	141	Significant reduction in pain intensity after 8 weeks.[22]

Hypnotherapy

The beneficial effects of hypnotherapy have been confirmed by numerous studies in children with FAP. This beneficial affect persisted for up to 5 years after completion of therapy.[25]

According to a systematic review published in 2013 by Rutten et al. which involved three RCTs (n=108) comparing hypnotherapy to control treatment, showed statistically greater improvement in abdominal pain scores of hypnotherapy interventions than the standard medical care in children with FAP and IBS. One

trial in this systematic review showed beneficial effects was persistent even after 1 year of follow-up whereas, one trial demonstrated statistically significant improvement in quality of life in the hypnotherapy group. Another outcome is significant reduction in school absenteeism in children receiving hypnotherapy which was documented in two trials.[26]

Gulewitsch MD et al. performed a RCT in thirty-eight children aged between 6 to 12 years, and were randomly assigned to a standardized hypnotherapeutic–behavioural treatment (n = 20) or to a waiting list condition (n = 18). The authors concluded that the treatment group had significant reductions of pain scores and pain-related disability.[27]

In a RCT which involved 260 children aged 8-18 years with IBS or FAP according to Rome III criteria, were randomized either to receive hypnotherapy performed by a qualified therapist (iHT group) or home based hypnotherapy delivered with the help of self exercises on CD (CD group). This RCT concluded that treatment success rates in both the groups were almost equally effective.[28]

Cognitive Behavioural Therapy

Success rates of psychological interventions particularly cognitive behavioural therapy have been established by a number of RCTs in paediatric FAP. Behavioural interventions may comprise of identification of verbal and non-verbal pain behaviour, reactions of family members, caregivers and teachers, relaxation via physical exercise, breathing exercise and muscle relaxation taught by trained therapist, whereas cognitive interventions may comprise of avoiding pain related thoughts, distracting and encouraging the child to think about pleasant things when pain arises.[29]

A recent RCT conducted in 316 children with FAPD and their parents, investigated the use of social learning and cognitive behavioural therapy in-person (SLCBT) or by phone (SLCBT-R) and education and support condition by phone (ES-R). This study showed that there is no significant difference between the pain scores and QOL, however SLCBT groups showed significantly greater improvements by changing the parents' response to children's pain.[30]

A recent Cochrane in 2017 has concluded that CBT has short term beneficial actions in reducing pain in RAP and adolescent but the evidence remains weak. Longer duration, higher quality trails are needed to confirm the results.[31]

Yoga

A pilot study of 20 children aged 8-18 years, with irritable bowel syndrome (IBS) or functional abdominal pain (FAP) showed significant reduction of pain intensity and frequency after receiving 10 yoga lessons. The effectiveness of yoga was demonstrated by a recent RCT done in sixty-nine patients, aged 8 to 18 years, with AP-FGIDs which showed at 1 year follow up, yoga therapy in addition to standard medical care was significantly superior compared to standard medical care alone according to treatment success, pain intensity scores and reduction in school absence. [32,33]

Based on insufficient evidence, yoga cannot be recommended as treatment of choice for children with FAP, in spite of this, due to its harmless nature yoga can be added along with the standard medical care when requested.

Placebo

In clinical trials, FAPs patients have responded to placebo on several occasions. When a response occurred due to placebo manipulation, it is defined as placebo effect. However, make sure other factors such as natural course of the disease, spontaneous symptoms fluctuations are not involved in the result of the study.[34,35,36]

Hoekman et al. conducted a systematic review and meta-analysis which included 21 RCTs of functional abdominal pain in children. This review demonstrated pooled placebo rates of improvement of 41% (17 studies) and with no pain of 17% (7 studies).[37]

As suggested by few studies, children and adolescent show more response to placebo than in adults. [38,39]

Pharmacological Interventions

Table 2: Summary of Pharmacological studies

Class of Drug	API	No. of Studies (Study group)	Sample Size	Conclusion
Antipasmodics	Peppermint oil	1 RCT (IBS)	50	After 2 weeks, 75% of those receiving peppermint oil had reduced severity of pain associated with IBS[40]
	Peppermint Oil and Synbiotic Lactol (Bacillus coagulans + Fructooligosaccharides)	1 RCT (Functional dyspepsia, IBS, FAP, FAPS)	120	Peppermint oil is more efficacious in reducing pain duration and severity than Lactol.[41]
	Drotaverine hydrochloride	1 RCT (RAP)	132	Pain episodes were reduced. Severity not reported.[42]
	Mebeverine	1 RCT (FAP)	115	No significant improvement on abdominal pain.[43]
	Trimebutine	1 RCT (IBS)	345	Trimebutine is effective for pediatric IBS patients.[44]
Antidepressants	Amitriptyline	2 RCTs (FAP, FD, IBS)	123	No improvement over placebo.[48,49]
	Citalopram	2 RCT (RAP)	140	84% responded in one trial whereas, another trial showed no improvement over placebo.[50]
Antihistamine	Cyproheptadine	1 RCT (FAP)	29	Severity and frequency of pain were significantly improved.[52]
H2 receptor antagonist	Famotidine	1 RCT (RAP, dyspeptic signs)	25	No significant difference in abdominal pain severity in both groups.[54]

Antispasmodics

Peppermint oil are effective in adults with IBS due to its menthol component which is known to block the Ca^{2+} channels leading to reduction in smooth muscle spasms. Kine et al. evaluated the efficacy of peppermint oil in 50 children aged 8-17 years with IBS. In this double blind randomized placebo controlled trial, the children were administered peppermint oil or matching placebo for 2 weeks. After 2 weeks, a significant improvement was reported in severity of symptoms by 76% of children receiving peppermint oil versus 19% of children receiving placebo.[40]

A comparative randomized placebo controlled study was performed on 120 FAP children for 4 weeks to evaluate the effectiveness of pH dependent peppermint oil and Lactol (Bacillus coagulans + Fructooligosaccharides) on FAP in children which revealed peppermint oil to be more efficacy in reducing pain duration and severity. Even so, peppermint oil as well as Lactol were superior to placebo in FGID related abdominal pain in children.[41]

Drotaverine, a selective phosphodiesterase-4 inhibitor was investigated by Narang and his colleagues in 132 children diagnosed with RAP for 4 weeks. This study concluded that there was significant reduction with respect to abdominal pain episodes in children receiving drotravine as compared to children receiving placebo. However, the severity of pain was not reported in this study.[42]

Pourmoghaddas in 2014, conducted the first randomized placebo control trial of Mebeverine (a beta-phenlyethlyamine derivative of reserpine) in 115 children with FAP. This trial reported that after 4 weeks of treatment and 12 weeks of follow up, in comparison with placebo, there is no significant improvement on abdominal pain.[43]

We also found two studies which evaluated trimebutine in children with IBS. Though Karabulut et al, reported significant improvement from trimebutine, this study was neither blinded nor placebo controlled. Likewise, study done by Giannetti et al. had low number of participants.[44,45]

Anti-depressants

Despite the fact, till date, there is lack of convincing data regarding antidepressants role in FAP management in paediatrics. Amitriptyline, a tricyclic antidepressants, in low doses in AP-FGIDs shows its action mainly by inducing pain tolerance through peripheral or central antinociceptive properties and anticholinergic effects.[46]

Adults with IBS and functional dyspepsia have responded to amitriptyline therapy, however, these effects were not confirmed in paediatric setting with AP-FGIDs[47]. A double blind placebo controlled trial done by Saps et al. which included 90 children (8-17 years) with diagnosis of functional abdominal pain, functional dyspepsia and IBS according to the Rome II criteria reported amitriptyline as equally effective as placebo after 4 weeks of treatment. No significant difference was observed between the amitriptyline over placebo. Also, two children in the amitriptyline group discontinued their participation from the study due to adverse events such as fatigue, rashes and headache. Bahar et al, also conducted a double blind placebo study in 33 children with IBS for 8 weeks. Amitriptyline group did not show any statistical improvement in terms of pain or any IBS related symptoms. On the other hand, the overall quality of life scores showed a significant improvement in the amitriptyline group.[48,49]

Campo et al. investigated selective 5-HT-reputake inhibitor- citalopram for 12 weeks in 25 children aged 7-18 years diagnosed with RAP. This small, open label trail showed good results in effectiveness of citalopram where 84% of the patients were responders. On the contrary, these results were not confirmed by another randomized placebo-controlled trial performed by Roohafza et al. in 115 FAP children aged 6-18 years receiving Citalopram for 4 weeks. At the end of 4 week and further 12 week follow period, this study concluded that no significant improvement was observed in response rate between the treatment group and the placebo.[50,51]

Anti-histamine

Cyproheptadine is an anti-histaminic agent and is thought to act by blocking calcium channels and anti 5-HT effects. A double blind placebo control trial was conducted by Sadeghian at al. in 29 FAP children receiving cyproheptadine. Abdominal pain frequency and also the intensity of abdominal pain was significantly improved after 2 weeks of intervention in the cyproheptadine group. Significant global improvement was also seen in the treatment group over placebo. Having said that, relatively low sample size and follow up period of 2 weeks are the limitations of this study.[52]

A retrospective study done by Madani et al. demonstrated that cyroheptadine in patients with abdominal pain related functional gastrointestinal disorders over 7 years as 73% efficacious and 68% safe. Well-designed randomized placebo control multicentre trials with long-term follow-up are needed to further investigate cyroheptadine in AP-FGIDs in children.[53]

Anti-reflux

No recent studies were found on anti-reflux agents' role in treatment of functional abdominal pain in children. We found only a double blind placebo controlled trial of famotidine done in 2001 by See et at, in children with abdominal pain and dyspepsia where 25 children (5-18 years) diagnosed with RAP and dyspeptic signs received famotidine or matching placebo which was assigned for 3 weeks treatment (phase 1) twice daily. If symptoms were not resolved after 3 weeks of phase 1 treatment, the patients underwent crossover and further the treatment continued for 3 weeks. Global improvement for significantly higher in the famotidine group, however, there was no significant difference in abdominal pain severity in both groups.[54]

Laxative

No recent evidence was found on this class of drugs in management of functional abdominal pain.

V. Conclusion

Pharmacological approaches still don't have good quality evidence in reducing severity and intensity of functional abdominal pain in children. In this review, bio-psychosocial approach such as cognitive behavioural therapy and yoga towards managing functionalabdominal pain has shown beneficial effects in children and could be implemented along with standard medical care. On the other hand, these therapies are to be only performed by qualified paediatric therapists and for this reason are often hampered by their absence in majority of centres. Other non-pharmacological interventions such as dietary interventions could play a role in reducing the abdominal pain and should be initiated. However, so as to make sure adequate nutrition particularly in children, dietary interventions in FAP management ought to be initiated and monitored by a professional paediatric dietician. Probiotics has shown promising results in FAP children particularly strain L.reuteri DSM 17938 which were justified with 4 RCTs conducted in children presenting with functional abdominal pain. Also, reduction in intensity of pain was reported in all 4 RCTs.The World Gastroenterology Organization(WGO) Global guidelines for Probiotics and Prebiotics recommends L reuteri DSM 17938 as Level 1 evidence in the management of abdominal pain functional gastrointestinal disorders in children. Hence, L.reuteri DSM 17938 becomes an important intervention in the hands of paediatrician and could be initiated at early stages of functional abdominal pain.Due to its harmless nature, many experts believe that in management of FAP, non-pharmacological interventions should be the first line of treatment in children.Further high quality studies are recommended to confirm the results.

Conflict of Interest:

Authors RCS, LV, and VS did not receive any funding for conceptualisation and review of the article. Authors AGS and KCV are full time employees of Dr Reddy's Laboratories Ltd and are involved in literature search, manuscript preparation, formatting and editing of the review article. The article processing charges are funded by Dr Reddy's Laboratories, India.

Authorship:

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published

References

[1]. Paul SP, Basude D. Non-pharmacological management of abdominal painrelated functional gastrointestinal disorders in 244 A. Brusaferro et al. children. Torquay, UK World J Pediatr, 2016. Available at: http:// www.wjpch.com. Accessed 30 Oct 2018.

[2]. Garber J, Zeman J, Walker LS. Recurrent abdominal pain in children: psychiatric diagnoses and parental psychopathology. J Am Acad Child Adolesc Psychiatry 1990;29:648-56.

[3]. Apley, J. & Naish, N. Recurrent abdominal pains: a field survey of 1,000 school children. Arch. Dis. Child. 33, 165–170 (1958).

[4]. Gomez-Suarez R. Difficulties in the diagnosis and management of functional or recurrent abdominal pain in children. Pediatr Ann. 2016;45:e388–93.

[5]. Tringali A, Thomson M, Dumonceau JM, Tavares M, Tabbers MM, Furlano R, Spaander M, Hassan C, Tzvinikos C, Ijsselstijn H, Viala J, Dall'Oglio L, Benninga M, Orel R, Vandenplas Y, Keil R, Romano C, Brownstone E, Hlava Sˇ, Gerner P, Dolak W, Landi R, Huber WD, Everett S, Vecsei A, Aabakken L, AmilDias J, Zambelli A. Pediatric gastrointestinal endoscopy: European Society of Gastrointestinal Endoscopy (ESGE) and European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) Guideline Executive summary. Endoscopy. 2017;49:83–91.

[6]. Hyams JS, Di Lorenzo C, Saps M, Shulman RJ, Staiano A, van Tilburg M. Childhood functional gastrointestinal disorders: child/ adolescent. Gastroenterology 2016;150:1456-1468.

[7]. Sandhu BK, Paul SP. Irritable bowel syndrome in children: Pathogenesis, diagnosis and evidence-based treatment. World J Gastroenterol 2014;20:6013-6023.

[8]. Escobar MA Jr, Lustig D, Pflugeisen BM, Amoroso PJ, Sherif D, Saeed R, Shamdeen S, Tuider J, Abdullah B. J Fructose intolerance/malabsorption and recurrent abdominal pain in children. Pediatr Gastroenterol Nutr. 2014;58(498–501):7.

[9]. Wirth S, Klodt C, Wintermeyer P, Berrang J, Hensel K, Langer T, Heusch A. Positive or negative fructose breath test results do not predict response to fructose restricted diet in children with recurrent abdominal pain: results from a prospective randomized trial. Klin Padiatr. 2014;226:268–73.

[10]. Wintermeyer P, Baur M, Pilic D, Schmidt-Choudhury A, Zilbauer M, Wirth S. Fructose malabsorption in children with recurrent abdominal pain: positive effects of dietary treatment. Klin Padiatr. 2012;224:17–20.

[11]. Paulo AZ, Amancio OM, de Morais MB, Tabacow KM. Lowdietary fiber intake as a risk factor for recurrent abdominal pain in children. Eur J Clin Nutr. 2006;60:823–7.

[12]. Romano C, Comito D, Famiani A, Calamara` S, Loddo I. Partially hydrolyzed guar gum in pediatric functional abdominal pain. World J Gastroenterol. 2013;19:235–40.

[13]. Horvath A, Dziechciarz P, Szajewska H. Systematic review of randomized controlled trials: fiber supplements for abdominal painrelated functional gastrointestinal disorders in childhood. Ann Nutr Metab. 2012;61:95–101.

[14]. Newlove-Delgado TV, Martin AE, Abbott RA, Bethel A, Thompson-Coon J, Whear R, Logan S. Dietary interventions for recurrent abdominal pain in childhood. Cochrane Database Syst Rev. 2017;3:CD010972.

[15]. Saneian H, Pourmoghaddas Z, Roohafza H, Gholamrezaei A. Synbiotic containing Bacillus coagulans and fructo-oligosaccharides for functional abdominal pain in children. Gastroenterol Hepatol Bed Bench. 2015;8:56–65.

[16]. Horvath A, Dziechciarz P, Szajewska H. Meta-analysis: Lactobacillus rhamnosus GG for abdominal pain-related functional gastrointestinal disorders in childhood. Aliment Pharmacol Ther. 2011;33:1302–10.

[17]. Giannetti E, Maglione M, Alessandrella A, Strisciuglio C, De Giovanni D, Campanozzi A, Miele E, Staiano A. A mixture of 3 Bifidobacteria decreases abdominal pain and improves the quality of life in children with irritable bowel syndrome: a multicenter, randomized, double-blind, placebo-controlled, crossover trial. J Clin Gastroenterol. 2017;51:e5–10.6945.

[18]. Jadresˇin O, Hojsak I, Misˇak Z, Kekez AJ, Trbojevic´ T, Ivkovic´ L, Kolacˇek S. Lactobacillus reuteri DSM 17938 in the treatment of functional abdominal pain in children—RCT Study. J Pediatr Gastroenterol Nutr. 2017;64:925–9.

[19]. Weizman Z, Abu-Abed J, Binsztok M. Lactobacillus reuteri DSM 17938 for the management of functional abdominal pain in childhood: a randomized, double-blind, placebo-controlled trial. J Pediatr. 2016;174(160–164):e1.

[20]. Romano C, Ferrau' V, Cavataio F, Iacono G, Spina M, Lionetti E, et al. Lactobacillus reuteri in children with functional abdominal pain (FAP). J Paediatr Child Health. 2014;50:E68–71.

[21]. Kambiz Eftekhari, Zahra Vahedi, Mojtaba Kamali Aghdam and Diana Noemi Diaz. A Randomized Double-Blind Placebo-Controlled Trial of Lactobacillus reuteri for Chronic Functional Abdominal Pain in Children. Iran J Pediatr. 2015 December; 25(6): e2616. doi: 10.5812/ijp.2616

[22]. Sudha MR, Jayanthi N, Aasin M, Dhanashri RD, Anirudh T. Efficacy of Bacillus coagulans Unique IS2 in treatment of irritable bowel syndrome in children: a double blind, randomised placebo controlled study. Benef Microbes. 2018 Jun 15;9(4):563-572. doi: 10.3920/BM2017.0129. Epub 2018 Apr 26.

[23]. Wegh CAM, Benninga MA, Tabbers MM. Effectiveness of Probiotics in Children With Functional Abdominal Pain Disorders and Functional Constipation: A Systematic Review. Journal of Clinical Gastroenterology. 52():S10–S26, NOV 2018

[24]. Abbott RA, Martin AE, Newlove-Delgado TV, Bethel A, Whear RS, Thompson Coon J, Logan S. Recurrent Abdominal Pain in Children: Summary Evidence From 3 Systematic Reviews of Treatment Effectiveness. J Pediatr Gastroenterol Nutr. 2018 Jul;67(1):23-33. doi: 10.1097/MPG.0000000000001922.

[25]. Vlieger AM, Rutten JM, Govers AM, Frankenhuis C, Benninga MA. Long-term follow-up of gut-directed hypnotherapy vs. standard care in children with functional abdominal pain or irritable bowel syndrome. Am J Gastroenterol. 2012;107:627–31.

[26]. Rutten JM, Reitsma JB, Vlieger AM, Benninga MA. Gut-directed hypnotherapy for functional abdominal pain or irritable bowel syndrome in children: a systematic review. Arch Dis Child. 2013;98:252–7.

[27]. Gulewitsch MD, Mu¨ller J, Hautzinger M, Schlarb AA. Brief hypnotherapeutic-behavioral intervention for functional abdominal pain and irritable bowel syndrome in childhood: a randomized controlled trial. Eur J Pediatr. 2013;172:1043–51.

[28]. Rutten JM, Vlieger AM, Frankenhuis C, George EK, Groeneweg M, Norbruis OF, et al. Home-based hypnotherapy self-exercises vs individual hypnotherapy with a therapist for treatment of pediatric irritable bowel syndrome, functional abdominal pain, or functional abdominal pain syndrome: a randomized clinical trial. JAMA Pediatr. 2017. https://doi.org/10.1001/jamapediatrics. 2017.0091 (Epub Mar 27).

[29]. Huertas-Ceballos A, Logan S, Bennett C, Macarthur C. Psychosocial interventions for recurrent abdominal pain (RAP) and irritable bowel syndrome (IBS) in childhood. Cochrane Database Syst Rev 2008;(1):CD003014.

[30]. Levy RL, Langer SL, van Tilburg MA, Romano JM, Murphy TB, Walker LS, Mancl LA, Claar RL, DuPen MM, Whitehead WE, Abdullah B, Swanson KS, Baker MD, Stoner SA, Christie DL, Feld AD. Brief telephone-delivered cognitive behavioral therapy targeted to parents of children with functional abdominal pain: a randomized controlled trial. Pain. 2017;158:618–28.

[31]. Abbott RA, Martin AE, Newlove- Delgado TV, Bethel A, Thompson- Coon J, Whear R, Logan S. Psychosocial interventions for recurrent abdominal pain in childhood. Cochrane Database of Systematic Reviews 2017, Issue 1. Art. No.: CD010971. DOI: 10.1002/14651858.CD010971.pub2.

[32]. Brands MM, Purperhart H, Deckers-Kocken JM. Complement Ther Med. 2011 Jun;19(3):109-14. doi: 10.1016/j.ctim.2011.05.004. Epub 2011 May 26.

[33]. Korterink JJ, Ockeloen LE, Hilbink M, Benninga MA, DeckersKocken JM. Yoga therapy for abdominal pain-related functional gastrointestinal disorders in children: a randomized controlled trial. J Pediatr Gastroenterol Nutr. 2016;63:481–7.

[34]. Spiller RC. Problems and challenges in the design of irritable bowel syndrome clinical trials: experience from published trials. Am J Med. 1999;107:91S–7S.

[35]. Kirsch I. The placebo effect revisited: lessons learned to date. Complement Ther Med. 2013;21:102–4.

[36]. Elsenbruch S, Enck P. Placebo effects and their determinants in gastrointestinal disorders. Nat Rev Gastroenterol Hepatol. 2015;12:472–85.

[37]. Hoekman DR, Zeevenhooven J, van Etten-Jamaludin FS, Dekker ID, Benninga MA, Tabbers MM, Vlieger AM. The placebo response in pediatric abdominal pain-related functional gastrointestinal disorders: a systematic review and meta-analysis. J Pediatr. 2017;182:155-163.e7.

[38]. Weimer K, Gulewitsch MD, Schlarb AA, Schwille-Kiuntke J, Klosterhalfen S, Enck P. Placebo effects in children: a review. Pediatr Res. 2013;74:96–102.

[39]. Rheims S, Cucherat M, Arzimanoglou A, Ryvlin P. Greater response to placebo in children than in adults: a systematic review and metaanalysis in drug-resistant partial epilepsy. PLoS Med. 2008;5:e166.

[40]. Kline RM, Kline JJ, Di Palma J, Barbero GJ. Enteric-coated, pH dependent peppermint oil capsules for the treatment of irritable bowel syndrome in children. J Pediatr. 2001;138:125–8.

[41]. Asgarshirazi M, Shariat M, Dalili H. Comparison of the effects of pH-dependent peppermint oil and synbiotic lactol (Bacillus coagulans ? Fructooligosaccharides) on childhood functional abdominal pain: a randomized placebocontrolled study. Iran Red Crescent Med J. 2015;17:e23844.

[42]. Narang M, Shah D, Akhtar H. Efficacy and safety of drotaverine hydrochloride in children with recurrent abdominal pain: a randomized placebo controlled trial. Indian Pediatr. 2015;52:847–51.

[43]. Pourmoghaddas Z, Saneian H, Roohafza H, Gholamrezaei A. Mebeverine for pediatric functional abdominal pain: a randomized, placebo-controlled trial. BioMed Res Intern. 2014;2014:191026.

[44]. Karabulut GS, Beer OF, Ergino¨z E, Kutlu T, Coku ra FC¸ , Erkan T. The incidence of irritable bowel syndrome in children using the Rome III criteria and the effect of trimebutine treatment. J Neurogastr Motil. 2013;19:90–93.

[45]. Giannetti E, Maglione M, Sciorio E, Coppola V, Miele E, Staiano A. Do children just grow out of irritable bowel syndrome? J Pediatr. 2017;183(122–126):e1.

[46]. Rajagopalan, M., Kurian, G. & John, J. Symptom relief with amitriptyline in the irritable bowel syndrome. J. Gastroenterol. Hepatol. 13, 738–741 (1998).

[47]. Ford, A. C., Talley, N. J., Schoenfeld, P. S., Quigley, E. M. & Moayyedi, P. Efficacy of antidepressants and psychological therapies in irritable bowel syndrome: systematic review and meta-analysis. Gut 58, 367–378 (2009).

[48]. Saps M, Youssef N, Miranda A, Nurko S, Hyman P, Cocjin J, et al. Multicenter, randomized, placebo-controlled trial of amitriptyline in children with functional gastrointestinal disorders. Gastroenterology. 2009;137:1261–9.

[49]. Bahar RJ, Collins BS, Steinmetz B, Ament ME. Double-blind placebo controlled trial of amitriptyline for the treatment of irritable bowel syndrome in adolescents. J Pediatr. 2008;152:685–9. 55.

[50]. Campo JV, Perel J, Lucas A, Bridge J, Ehmann M, Kalas C, et al. Citalopram treatment of pediatric recurrent abdominal pain and comorbid internalizing disorders: an exploratory study. J Am Acad Child Adolesc Psychiatry. 2004;43:1234–42.

[51]. Roohafza H, Pourmoghaddas Z, Saneian H, Gholamrezaei A. Citalopram for pediatric functional abdominal pain: a randomized, placebo-controlled trial. Neurogastr Motil. 2014;26:1642–50.

[52]. Sadeghian M, Farahmand F, Fallahi GH, Abbasi A. Cyproheptadine for the treatment of functional abdominal pain in childhood: a doubleblinded randomized placebo-controlled trial. Minerva Pediatr. 2008;60:1367–74.

[53]. Madani S, Cortes O, Thomas R. Cyproheptadine use in children with functional gastrointestinal disorders. J Pediatr Gastroenterol Nutr. 2016;62:409–13.

[54]. See MC, Birnbaum AH, Schechter CB, Goldenberg MM, Benkov KJ. Double-blind, placebo-controlled trial of famotidine in children with abdominal pain and dyspepsia: global and quantitative assessment. Dig Dis Sci. 2001;46:985–92.

Ashley George Suares, et. al. "Consolidated Summary of Current Treatment Modalities of Childhood Functional Abdominal Pain ." *IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*, 19(8), 2020, pp. 49-57.