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PHARMACOLOGIC TREATMENT OF THE IRRITABLE BOWEL SYNDROME: A COMPREHENSIVE SYSTEMATIC REVIEW

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ABSTRACT

Background: *Abdominal pain and changes in stool frequency are two of the symptoms of Irritable Bowel Syndrome (IBS), a chronic gastrointestinal illness. As there is no known cure, treatment focuses on symptom management. Patients struggle with psychological and emotional issues that lower their quality of life. Clinical trials have demonstrated the therapeutic effects of several therapeutic drugs, which may improve GI symptoms and general quality of life. Effective treatment of IBS requires an understanding of the connection between pharmaceutical medicines and the illness.*

Methods: *Following PRISMA 2020 guidelines, this systematic review concentrated on full-text English literature published between 2014 and 2024. Editorials and review articles that appeared in the same journal as the submission were not accepted without a DOI. The literature was assembled using a variety of online databases, including ScienceDirect, PubMed, and SagePub.*

Result: *The study screened about 20.000 publications using reputable sources including Science Direct, SagePub, and PubMed. Seven papers were found to be pertinent for systematic investigation, after which the entire material was examined in more detail.*

Conclusion: *IBS treatment has shown significant improvement in patients with Minesapride, a novel 5-HT4 receptor agonist, and tenapanor. Tenapanor showed significant improvement in symptoms, treatment metrics, and satisfaction, while geraniol improved the inflammatory profile. Melatonin showed improvement in IBS score and GI symptoms, but no significant improvement in frequency of defecations per week. Amitriptyline showed effectiveness over placebo, while co-micronized PEA/PD improved IBS symptoms in children.*

Keyword: *IBS, treatment, minesapride, geraniol, tenapanor, melatonin, PEA/PD*

INTRODUCTION

Functional gastrointestinal diseases are quite common conditions throughout the world. They are now known as disorders of gut-brain interaction, or DGBI. Based on Rome IV criteria, irritable bowel syndrome (IBS) is one of the most prevalent DGBI globally.[1] The functional bowel illness known as irritable bowel syndrome is characterized by pain in the abdomen that is accompanied by changes in the frequency or form of stools.[2] According to recent studies, the illness is chronic and sporadic, with an incidence of 5% to 10% worldwide.[3,4] There is a large global variation in the prevalence of IBS in children, with estimates ranging from 1% to 23%.[5] IBS can cause major psychological and emotional difficulties for children as well as their families, despite being regarded as a benign ailment. It also has a notable negative impact on children's quality of life.[6] Since there is no known cure its mechanism is not fully understood and it is considered a multifactorial disorder, treatment focuses on managing the symptoms.[6-8]

IBS has a significant impact on people's lives as well as on society. Patients with IBS may experience worse quality of life than those with other chronic non-gastrointestinal diseases like diabetes or heart failure, and impairments comparable to those with other chronic gastrointestinal conditions like Crohn's disease.[9,10] According to available data, IBS is a brain-gut axis condition brought on by intricate interactions between host, environmental, and genetic factors. In genetically predisposed people, several factors (such as nutrition, microbiota, bile acids, etc.) may contribute to the disruption of intestinal barrier function, which permits antigens to pass through the mucosal layer.[11] As a result, modifications in GI sensory-motor function can be triggered, which can then result in mucosal immune responses, including mast cell recruitment and activation, and eventually cause symptoms of irritable bowel syndrome.[6] The incapacitating nature of the symptoms hinders social and occupational functioning.[12] In its most extreme forms, IBS is linked to a substantial financial cost to health care systems because it uses more resources.[13] IBS is expected to cost the UK £1 billion, China ¥123 billion, and the USA more than $10 billion annually in direct and indirect expenses.[9]

Although patients with IBS often describe many stomach and bowel symptoms, those with IBS with diarrhea (IBS-D) say that bloating and abdominal pain are two of the most common and bothersome symptoms.[14] One of the most prevalent symptoms of IBS that leads people to seek medical attention is abdominal pain. Furthermore, patients with IBS who have more severe abdominal pain tend to use healthcare services more frequently. Efficacy endpoints in rifaximin clinical trials thus show a need to comprehend how symptoms affect patients and how payors are impacted by medical care utilization brought on by these symptoms.[8] On the other hand, numerous research have been done on melatonin's therapeutic benefits and its involvement in the pathophysiology of IBS. Melatonin has been shown in clinical trials to have therapeutic benefits, and it may be a promising treatment for IBS patients to improve their GI symptoms and overall quality of life.[15] Owing to its capacity to alter gut microbiota (GM), essential oils (EOs) have gained recognition as viable IBS treatments. Naturally occurring as an acyclic monoterpene component, geraniol is an essential oil obtained from aromatic plants such as lemongrass and roses. Geraniol is a very potent antibacterial molecule with antioxidant and anti-inflammatory qualities, according to several studies on its biological activities.[16]

Understanding the relationship between pharmacologic drugs and IBS is essential to treating IBS patients more successfully. Concerning the pharmacologic therapy of irritable bowel syndrome, this study aims to provide a comprehensive overview of the material that has been published during the last ten years.

METHODS

Protocol

Regarding Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the work's author complied with all requirements. This was done to guarantee that the study complied with all applicable rules. The selected methodology underwent extensive development in order to guarantee the precision and coherence of the research outcomes.

Criteria for Eligibility

In this study, all research conducted in the last 10 years on the pharmacologic treatment of irritable bowel illness is reviewed in detail. Through in-depth data analysis, this project aims to explain and enhance patient care procedures. This thesis' main goal is to highlight the importance of important topics that may be found in a range of literary works.

Strict inclusion and exclusion standards were put in place to ensure that the data utilized in this study was accurate. An item must have been published in English between 2014 and 2024 in order to be considered for inclusion. Among the exclusion criteria include editorials, submissions without a DOI, reviews that have already been published, and multiple journal entries.

Search Strategy

The study's keywords include "pharmacologic, treatment, irritable bowel syndrome". For this research, the following Boolean MeSH keywords were entered into the databases: ((("irritable bowel syndrome"[MeSH Terms] OR "irritable bowel syndrome "[All Fields] AND "pharmacologic"[All Fields]) OR ("irritable bowel syndrome"[MeSH Terms] OR "irritable bowel syndrome"[All Fields] AND "treatment"[All Fields]) AND ("irritable bowel syndrome"[MeSH Terms] OR "IBS"[All Fields] OR "therapy"[All Fields] OR "pharmacologic"[MeSH Subheading] OR "outcomes"[All Fields] OR "therapy"[All Fields])).

Data retrieval

The writers carefully read the title and abstract of each article to determine its significance before starting this arduous examination. Greater weight was only assigned to studies that met the inclusion criteria and bolstered the goals of the article. A recurring pattern produced a definitive answer after several searches. Full-text entries were only accepted in the English language. Content that satisfied all predetermined inclusion criteria and had a clear connection to the study's topic matter was produced through the strictest screening procedure. Studies that deviated from these trends were typically disregarded and their conclusions were not given much weight. During the evaluation, a great deal of information was located and looked over, including factors, titles, authors, publication dates, places, and study methodologies.

Quality Assessment and Data Synthesis

The authors separately assessed the research cited in the titles and abstracts of each article in order to determine whether papers require additional investigation. Examining every document that complied with the prerequisites in advance for review inclusion was the next step. The selection of the papers for the review is based on the evaluation findings. This criterion expedited the selection of publications for additional investigation, enabling a comprehensive appraisal of previous work and the circumstances that qualified it for assessment.

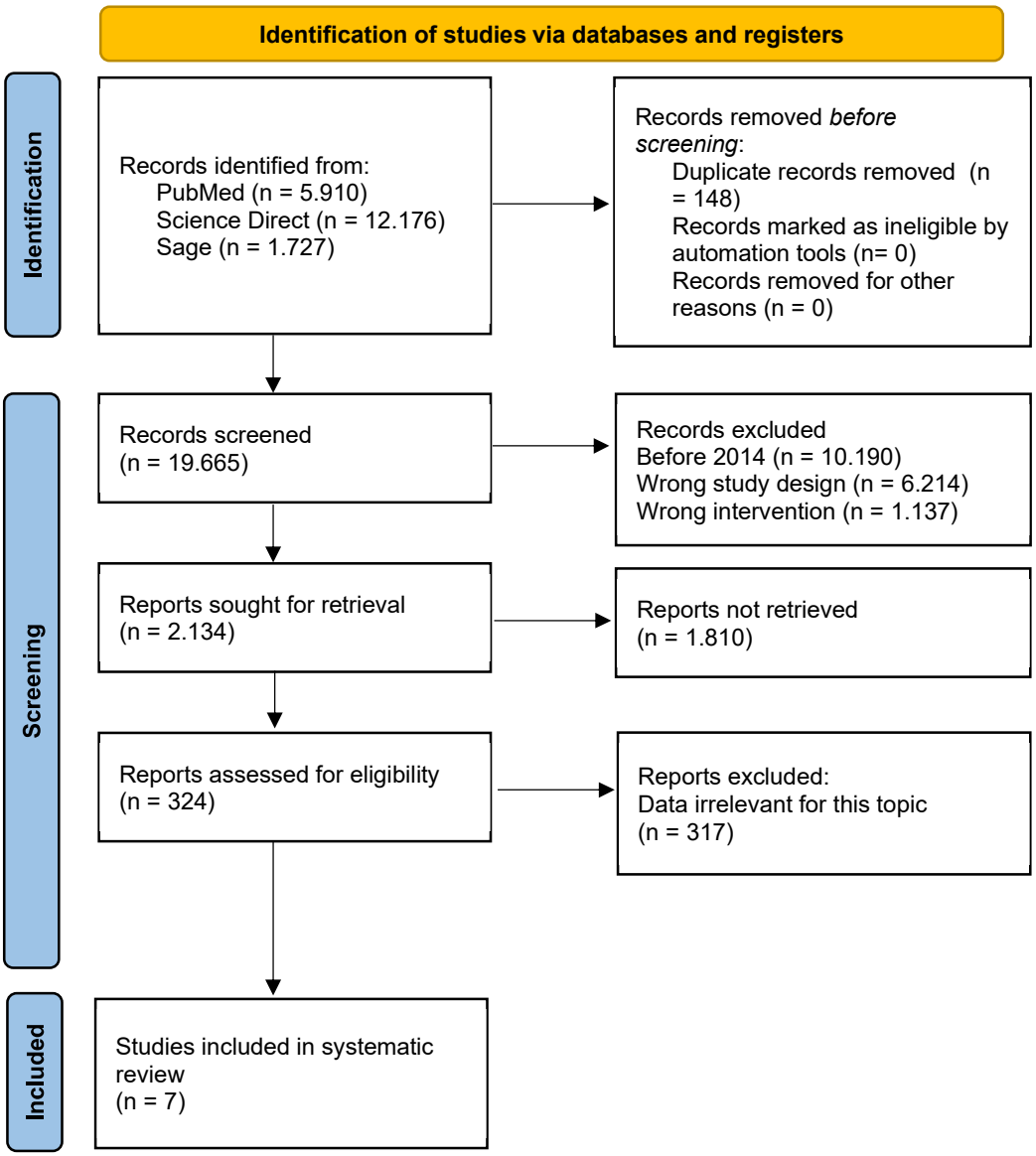

Figure 1. Article search flow chart

RESULT

Our research team first collected almost three thousand publications from reliable sources like PubMed, Science Direct, and SagePub. After a comprehensive three-tier screening procedure, only seven papers were judged to be immediately related to our continuing systematic inquiry. After that, a few passages were chosen for further study and a thorough examination of the whole document. For convenience of viewing, the content that was evaluated for this analysis has been condensed into Table 1.

Table 1. The literature included in this study

Author	Origin	Method	Sample	Result
Hamatani et al.[17] (2020)	Japan	RCT	411 patients	The FDA composite responder rate, which was 13.6% for the placebo group, 13.6% for the 10 mg group, 19.2% for the 20 mg group, and 14.9% for the 40 mg group, did not show any dose-response relationship. According to the tougher composite evaluation, a higher proportion of patients treated with minesapride 40 mg than those treated with placebo satisfied both responder criteria for ≥ 9/12 weeks ($P < 0.05$). Additionally, compared to a placebo, minesapride 40 mg dramatically raised the frequency of SBM (adjusted $P < 0.001$ at Week 12). A minor case of diarrhea was the most frequent side effect.
Chey et al.[18] (2021)	USA	RCT	620 patients	Tenapanor was found to be a more effective treatment for patients with IBS-C, with a significantly greater proportion of patients being combined responders compared to placebo. Abdominal symptoms and global symptoms of IBS were significantly improved with tenapanor, while diarrhea was the most common adverse event, leading to drug discontinuation for 6.5% and 0.7% of patients, respectively.
Ricci et al.[16] (2022)	Italy	RCT	56 patients	Patients with IBS showed a significant reduction in their symptom severity score (IBS-SSS) with low-absorbable geraniol food supplement (LAGS) treatment, with a higher rate of responders due to the mixed subtype. Geraniol administration also showed notable differences in microbiota composition, with a decrease in the Ruminococcaceae genus Oscillospira, a decrease in Erysipelotrichaceae and Clostridiaceae families, and an increase in other Ruminococcaceae taxa, specifically Faecalibacterium.
Dinevari et al.[15] (2023)	Iran	RCT	136 patients	A significant improvement in IBS score and GI symptoms was observed in patients with and without sleep disorders. However, no significant improvement was observed in defecations per week. Sleep parameters improved significantly in patients with

				sleep disorders, while quality-of-life improvement was observed in melatonin recipients.
Ford et al.[9] (2023)	UK	RCT	463 patients	A study involving 463 participants found a significant difference in IBS-SSS score between low-dose amitriptyline and placebo groups at 6 months. However, 20% discontinued low-dose amitriptyline due to adverse events, while 26% discontinued placebo. Five serious adverse reactions occurred in both groups, with two in the amitriptyline group and three in the placebo group. These adverse events were unrelated to the trial medication.
Lacy et al.[8] (2023)	USA	RCT	1.258 patients	The double-blind trials showed significantly higher percentages of bloating or urgency responders with rifaximin compared to the placebo. Additionally, rifaximin was more effective in treating composite abdominal pain and bloating, as well as tri-symptom composite end-point responders. The results remained consistent for up to 5 weeks post-treatment.
Nardo et al.[6] (2024)	Italy	RCT	70 patients	Seventy IBS children participated in the trial. Of the subjects, 36 were given a placebo and 34 were given co-micronized palmitoylethanolamide (PEA)/polydatin (PD). The co-micronized therapy group had a significantly higher number of patients reaching complete remission after 12 weeks (P = 0.015) as compared to the placebo group, with the IBS-diarrhea subtype benefiting most (P = 0.01). In addition, the intensity and frequency of abdominal pain were significantly lower in the treatment group than in the placebo group. During the study, no untoward incidents were reported.

There was a substantial difference in the frequency of stomach pain and complete spontaneous bowel movements (CSBMs) between the minesapride and placebo groups, according to research by Hamatani et al. From Week 1 to Week 12, there was a higher difference in SBMs and CSBMs in the 40 mg group. There was no discernible difference between the two groups' responses to minesapride medication overall, which was largely good.[17]

According to the study by Chey et al. tenapanor treatment significantly improved patients' response to chronic obstructive pulmonary disease (CSBM) compared to placebo. Patients in the tenapanor treatment group were more likely to be 6/12-week combined responders, with a higher rate of abdominal pain and CSBM responders. Tenapanor treatment also led to a greater mean increase in the average weekly number of CSBMs and a greater decrease in abdominal pain scores from week 1 onward.[18]

The study from Ricci et al. evaluated the impact of LAGS treatment on IBS patients, revealing reduced intensity of mixed bowel habits. The treatment also reduced beta diversity and alpha diversity in fecal samples, with Firmicutes dominated. Both treatment groups showed decreased microbial signatures.[16]

Patients with IBS were divided into two subgroups, receiving either melatonin or placebo in the study by Dinevari et al. in 2023. The study found no significant difference in sleep quality between groups. Melatonin may be an effective treatment for IBS, but further research is needed to determine its effectiveness in treating sleep disorders.[15]

The study from Ford et al. compared amitriptyline and placebo in treating IBS symptoms. Amitriptyline was found to be more effective in providing relief than the placebo at 6 months, with a significant difference in IBS-SSS score. However, it was more effective in reducing abdominal pain severity but not abdominal distension severity. Adverse events were mainly related to its anticholinergic effects.[9]

In the trial by Lacy et al., participants treated with a composite response for bloating and stomach pain demonstrated a significant response to rifaximin. Urgency and stool consistency composite responses were comparable to those obtained from double-blind DB rifaximin trials. Compared to patients receiving a placebo, patients treated with DB rifaximin had a higher likelihood of being composite endpoint responders. The outcomes of the treatment were comparable to those seen with DB rifaximin, with notable variations between the two groups.[8]

In research comparing 70 IBS children, Nardo et al. found no significant changes between the groups. In contrast to the placebo group, the abdominal discomfort frequency was much lower in the PEA/PD group. This decrease was especially noticeable in the IBS-D subtype. The total IBS-SSS, pain intensity score and life interference score were significantly lower in both groups.[6]

DISCUSSION

The effectiveness and safety of minesapride, a new 5-HT4 receptor agonist, are assessed in patients with Rome IV-defined IBS-C in a research by Hamatani et al. Regarding the CSBM response and abdominal pain relief criteria, the 40-mg minesapride group performed better than the placebo group. Nevertheless, neither the primary endpoint nor CSBMs nor stomach discomfort showed a dose-response connection in the research.[17] By implementing a more stringent composite responder evaluation for nine and twelve weeks, the study was able to successfully lower the placebo responder rate to 3.9%. Minesapride showed a strong improvement in SBMs; the 40 mg group saw an increase in SBMs between 1.46 and 2.08 counts/week, while the placebo group saw an increase in SBMs between 0.34 and 0.95 counts/week. A post-hoc analysis revealed that for the course of the 12-week treatment, a higher number of patients in the 40-mg minesapride group than in the placebo group (22.9% vs. 12.2%) obtained a mean of 3 or more CSBMs per week.[17] In this trial, diarrhea was the most often reported treatment-emergent adverse event, and all cases were mildly severe. In contrast to a different Japanese trial, the placebo group experienced a higher incidence of diarrhea.[19] In general, minesapride at a dose of up to 40 mg for 12 weeks was well tolerated and safe. This study has many limitations, too, including the lack of a dose-response connection in the primary endpoint and the requirement for more long-term safety data to evaluate the risks associated with cardiovascular disease.[17]

According to the research by Chey et al. throughout a 26-week trial, participants receiving tenapanor saw a considerable improvement in their IBS-C symptoms with no hint of diminishing efficacy. There were notable variations in the outcomes for more rigorous objectives, however patients reported less stomach pain and more CSBM frequency. Abdominal symptoms, overall IBS treatment metrics, and treatment satisfaction all improved with tenapanor. Diarrhea occurred in 16.0% of instances, although it was determined to be safe and effective for patients. Despite its limitations, which point to a more severely impacted population, the trial, which was published on ClinicalTrials.gov, did not find any deaths or major adverse events.[18]

The study by Ricci et al. aimed to evaluate the effects of geraniol, a low-adsorbable form of peppermint oil, on the inflammatory profile of IBS patients. The results showed that geraniol treatment improved the GM profile, including blood IL-1β, IL-4, IL-5, IL-6, IL-8, and IL-10, IL-12, IL-17A, IFN-γ, TNF-α, MCP-1, MIP-1β, and CCL28. However, no significant number of patients treated with LAGS reported symptom amelioration or significant changes in these biomarkers compared to the placebo arm.[16] The current first-line pharmacological treatment for IBS is symptoms-based, including spasmolytic or antispasmodic agents, loperamide for diarrhea or mixed-bowel dysfunction, and dietary changes. Peppermint oil has been suggested as an additional first-line therapy for global symptoms and abdominal pain in IBS patients.[16,20] The observed clinical effects could be associated with the antispasmodic effect and some of the GM fluctuations possibly exerted by geraniol. The study showed promising results in improved symptomatology and reduced dysbiosis, especially for the IBS-M subtype.[16]

IBS is a chronic disease with varying clinical manifestations and current treatments not meeting patients' demands.[21] A study compared the effect of melatonin 6 mg daily for 2 months on improving IBS score, GI symptoms, quality of life, and sleep parameters in IBS patients with and without sleep disorders.[15] Melatonin, a hormone secreted by the pineal gland, has anxiolytic, anti-inflammatory, anti-oxidative, and motility-regulatory effects.[21] Sleep disorders are more common among IBS patients than healthy controls, and melatonin may be beneficial in reducing abdominal pain and

improving overall IBS symptom scores.[22] The study included 136 IBS patients, with a dose of 6 mg daily. Results showed a significant improvement in IBS score and GI symptoms, including abdominal pain, bloating, satisfaction with bowel habits, disease impact on the patient's life, and stool consistency. However, no significant improvement was observed in the frequency of defecations per week.[15]

A large trial of low-dose amitriptyline, a tricyclic antidepressant, was conducted to evaluate its effectiveness in treating IBS.[23] The primary outcome was a decrease in IBS-SSS by almost 100 points, and the secondary outcome for effectiveness was met. Adverse events were more frequent with low-dose amitriptyline, but most participants found them mild. The study aligned with European Medicines Agency recommendations for IBS treatment trials, ensuring its effectiveness in primary care. The primary outcomes included a 30% or greater improvement in abdominal pain on the IBS-SSS and adequate relief of IBS symptoms in 50% of weeks. The trial was primarily White, with over 30% of recruited participants being male.[9] The Rome IV criteria led to a group of patients with higher symptom severity, and the 6-month treatment duration resulted in high placebo response rates. However, the study found a significant difference in effectiveness with amitriptyline over placebo, indicating that amitriptyline may be a more effective treatment option for IBS patients.[9,24]

Using the most recent clinically relevant definitions of therapy response, post hoc analyses of three Phase III clinical studies have demonstrated that a 2-week dose of rifaximin is effective for concurrently and significantly relieving various IBS-D symptoms.[25] When compared to DB placebo, a 2-week course of DB rifaximin significantly reduced both individual and multiple symptoms for as long as 10 weeks following therapy. The efficacious results of OL rifaximin were comparable to those of DB rifaximin, indicating the possible advantages of a two-week rifaximin course for the management of IBS-D.[8] According to FDA guidelines, a clinically significant abdominal pain response is defined as an improvement in the mean weekly abdominal pain score of at least 30% from the baseline.[26] Treatments with DB and OL rifaximin for two weeks both reduced bloating at thresholds of ≥30%, ≥40%, and ≥50%, and similar proportions of patients responded to DB or OL treatment. Likewise, following DB and OL rifaximin treatment, a similar proportion of patients experienced fecal urgency responses.[8] But the study had certain drawbacks, such the patients who were included who didn't improve after trying other IBS-D treatments or who had less severe symptoms. Rome IV criteria for IBS diagnosis tends to result in less severe symptoms than Rome II criteria for the same condition, therefore it's possible that the criteria used to classify the patient groups also influenced the outcome.[8]

The results of this trial showed that co-micronized PEA/PD is a safe and useful treatment for children with IBS symptoms related to the abdomen. Compared to 22% in the placebo group, 50% of patients who received the active medication experienced complete remission, which was the primary result. Along with a number of other indicators of IBS symptoms, co-micronized PEA/PD also satisfactorily satisfied secondary outcome measures for effectiveness.[6] Clinical interest in PEA has grown as a result of the mounting evidence for neuroinflammation and the potential therapeutic options for the treatment and prevention of chronic pain problems. A possible function for these nutraceuticals in IBS was indicated by a proof-of-concept trial involving individuals with IBS, which demonstrated a substantial effect of PEA/PD on relieving stomach pain.[6,27] The present study confirmed the efficacy data shown by Cremon et al. in a population of 54 adult IBS patients versus 12 healthy controls.[27] Nevertheless, there was also a large variation in frequency, which may have resulted from the immunologic immaturity of the juvenile patients' digestive systems and the microbiota's notable compositional variations when compared to adults.[28] Compared to adult patients with a longer history of IBS, children have a less developed neuroinflammation phenomena' temporal development, which may allow for a potential therapy window and more satisfying and long-lasting treatment outcomes.[6]

CONCLUSION

IBS treatment has shown significant improvement in patients with IBS-C and tenapanor, with Minesapride showing better outcomes in reducing CSBM response and abdominal pain compared to the placebo group. Tenapanor showed significant improvement in symptoms, treatment metrics, and treatment satisfaction, but diarrhea occurred in 16.0% of instances. Geraniol improved the GM profile in IBS patients, while melatonin showed improvement in IBS score and GI symptoms. Low-dose amitriptyline showed significant effectiveness over the placebo, while Rifaximin improved multiple symptoms of IBS-D. Co-micronized PEA/PD significantly improved IBS symptoms in children, showing promising potential for treating chronic painful conditions like IBS.

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