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Mechanism of action, efficacy and adverse events of selected drugs used to treat irritable bowel syndrome (IBS): A Literature Review

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Abstract

Introduction and purpose: Irritable bowel syndrome (IBS) is a prevalent functional gastrointestinal disorder, affecting approximately 11% of the global population, with a higher prevalence in women. It is characterised by recurrent abdominal pain and altered bowel habits, classified into four subtypes according to the Rome IV criteria. Treatment strategies include both non-pharmacological and pharmacological approaches. The aim of this review is to demonstrate the complexity of selected drugs used in IBS, with a particular focus on their mechanism of action, effectiveness, and adverse effects.

Brief description of the state of knowledge: Drug treatment for IBS includes various classes of medications that target specific IBS subtypes. Managing patients is complex and requires familiarity with diverse drug types and their mechanisms of action. In patients with IBS with diarrhoea, commonly used medications include antibiotics, opioid receptor modulators, 5-HT3 antagonists, and peripheral opioid receptor agonists. In contrast, constipation treatment primarily involves guanylate cyclase C agonists, osmotic laxatives, prostaglandin derivatives, and prokinetics. Additionally, antispasmodics and antidepressants are also used in IBS treatment. The appropriateness of certain medications remains a subject of debate. The most common side effects of pharmacotherapy affect the gastrointestinal tract, though adverse effects involving other systems may also occur.

Conclusion: Pharmacological treatment of IBS should be individualized based on the subtype. Given the variability in drug mechanisms, efficacy, and adverse events, a careful assessment of treatment options is essential to optimize therapeutic outcomes.

Key words: irritable bowel syndrome; constipation; diarrhea; abdominal pain

Introduction

Irritable bowel syndrome (IBS) is a chronic and sometimes disabling functional disorder that negatively affects quality of life and reduces productivity at work [1]. IBS belongs to a heterogeneous group of conditions known as functional gastrointestinal disorders (FGIDs), which are now considered disorders of gut-brain interaction and are highly prevalent [2]. Regardless of geographic location, IBS affects approximately 11% of the global population. It is more common in women and is not related to socioeconomic status [3]. There is little likelihood that a single, superior model explains all cases of IBS; rather, multiple factors contribute to the development of symptoms [4]. The classification of IBS is based on the Rome IV criteria, which distinguish four subtypes: IBS with predominant constipation (IBS-C), IBS with predominant diarrhoea (IBS-D), IBS with mixed bowel habits (IBS-M) and, unsubtyped IBS. The Bristol Stool Scale is used to assess improper stool consistency. IBS is characterized by recurrent abdominal pain associated with defecation or changes in bowel habits. Symptoms should begin at least 6 months prior to diagnosis and should be present during the last 3 months [5]. IBS can be treated non-pharmacologically or pharmacologically using a wide range of drugs. The main purpose of this review is to illustrate the complexity of selected pharmacological drugs used in IBS, with a particular focus on their mechanism of action, effectiveness, and adverse effects.

Description of the state of knowledge

PRUCALOPRIDE

Prucalopride is a highly selective serotonin type 4 (5-HT4) receptor agonist with strong prokinetic action that enhances gastrointestinal motility [6]. Serotonin in the gastrointestinal system influences different subtypes of 5-HT receptors. Serotonin antagonists stimulate the

5HT-4 receptors which are G-protein coupled receptors. This stimulation increases production of cyclic adenosine monophosphate (cAMP) which modulates the function of neurotransmitters such as acetylcholine. As a result, the longitudinal muscle layer contracts while the circular muscle layer relaxes, causing the advancement of luminal contents [7].

A placebo-controlled trial involving 620 individuals demonstrated that prucalopride remarkably improved intestinal function and reduced the severity of symptoms with serious chronic constipation [8]. Another study showed that 12 weeks of treatment with 2mg prucalopride once daily effectively mitigated abdominal symptoms of chronic constipation, compared to placebo [9].

Although studies on its efficacy in IBS are limited, prucalopride has been proven effective in treating chronic idiopathic constipation and is an option when laxatives fail [10]. According to the chapter on IBS in „Medycyna Praktyczna", prucalopride is listed among the drugs used for treatment [11].

Prucalopride is generally well tolerated. Probably due to its high selectivity, it has not been associated with an increased risk for cardiovascular effects [12,13]. Additionally, prucalopride was found to be well tolerated and effective in treating constipation regardless of the age of patients. An integrated analysis of 1821 patients (Asian, 26,1%; non-Asian, 73,9%) indicated that prucalopride treatment was associated with diarrhea, headache and nausea. Asian patients were more likely to experience diarrhea than headache, abdominal pain and nausea compared to non-Asians [14].

LUBIPROSTONE

Lubiprostone is a bicyclic fatty acid derived from prostaglandin E1 that stimulates chloride channel type 2 (CIC-2) located on the intestinal apical membrane of epithelium. This activation promotes chloride and water secretion into the lumen of the intestine, increasing the intestinal transit [15].

Several studies have demonstrated the efficacy of lubiprostone. A clinical trial analyzing 1171 patients with a Rome II diagnosis of IBS-C found out that lubiprostone can significantly relieve IBS-C symptoms. In a combined analysis of two phase-3 randomized trials, lubiprostone (8 mcg twice daily for 12 weeks) was more effective than placebo [16]. Another study published in "Neurogastroenterology and Motility" examined 170 patients (42 with IBS

and 128 without IBS) suffering from chronic idiopathic constipation. Patients randomly received a placebo (n=42), 16 mcg (n=41), 32 mcg (n=43) or 48 mcg (n=44) of lubiprostone daily for two weeks. The results demonstrated significant, dose-dependant improvement in the symptoms of chronic idiopathic constipation, regardless of IBS status [17].
As far as the adverse events are concerned, the most frequent side effects are diarrhea (6-14%) and nausea (8-19%), with 11% of patients experiencing both symptoms [18].

LINACLOTIDE AND PLECANATIDE

Linaclotide is 14 amino acid peptide, which is a selective agonist of guanylate cyclase C receptors in the intestinal epithelial cells. When the receptor is activated by linaclotide (pH-independently), the levels of cyclic guanosine monophosphate (c-GMP) increase resulting in secretion of chloride and bicarbonate into the lumen of the intestine. As a consequence, fluid secretion increases, stimulating the intestinal passage [19],[20],[23].
Plecanatide is a synthetic analog of uroguanylin and also acts as an agonist of guanylate cyclase C receptor agonist. However, it has been shown that its optimal activation occurs at a pH of 5. Therefore, the medicine would act properly in the proximal intestine [21]. Similarly, stimulation of the receptor increases c-GMP level [22].
A meta-analysis published in “American Journal of Gastroenterology” showed that both linaclotide and plecanatide were efficacious in treating irritable bowel syndrome with constipation (IBS-C) and were well-tolerated. There were no differences in efficacy or adverse events between plecanatide and linaclotide [23].
It should be noted that the most frequent adverse event is diarrhea [18].

PEG (POLYETHYLENE GLYCOL) - OSMOTIC LAXATIVES

According to the American College of Gastroenterology (ACG) Clinical Guideline, polyethylene glycol (PEG) products are not suggested for use in patients with irritable bowel syndrome with constipation (IBS-C). PEG is shown to be effective and safe for treating chronic constipation, including in vulnerable populations like the elderly and children.

Nevertheless, there is no evidence that PEG relieves abdominal pain or overall symptoms in IBS-C patients. For this reason, PEG alone is not recommended for treating global IBS-C symptoms. Nonetheless, clinicians may still use PEG as a first-line treatment for constipation in IBS because of its affordability and accessibility [18].

ALOSETRON

Alosetron is a highly selective 5-hydroxytryptamine (5-HT3) receptor antagonist that works by blocking the activation of receptors widely located on enteric neurons in the human gastrointestinal tract and nervous system. Alosetron slows intestinal transit, reduces water and chloride secretion, increases rectal compliance and decreases visceral sensitivity. Overall, this mechanism improves motility, secretion and pain in patients with irritable bowel syndrome with diarrhoea (IBS-D) [10],[24].

Alosetron is recommended for use to relieve global symptoms in women with severe IBS-D when other interventions have failed [18].

Several studies have demonstrated the efficacy of the alosetron treatment. A meta-analysis of randomized controlled trials evaluating the effectiveness and safety of 5-hydroxytryptamine (5-HT3) receptor antagonists concluded that alosetron is an effective treatment for non-constipated IBS and IBS-D [25]. In addition to this, another network meta-analysis performed in “Annals of Gastroenterology” has shown that 5-HT3 receptor antagonists are effective in alleviating the debilitating symptoms of non-constipated IBS, particularly IBS-D, by reducing urgency and episodic incontinence [26].

The most common adverse events of alosetron treatment is constipation, with other frequently reported side effects including nausea, abdominal discomfort, abdominal distension, reflux, hemorrhoids, headache and fatigue. Although infrequent, ischemic colitis has been documented in some patients using alosetron for IBS treatment [27].

ELUXADOLINE

Eluxadoline is a mixed mu-opioid receptor agonist, kappa-opioid receptor agonist and delta-opioid receptor antagonist. The stimulation of the mu- and kappa- receptors contributes to increased muscle tone, reduced secretion of enterocytes, contraction and peristalsis.

Furthermore, blocking the delta-opioid receptor results in reduction of the excessive slowing of motility and affects the action of mu- and kappa-opioid receptors in visceral sensation by enhancing them [28].

The two phase 3 trials conducted by Anthony J. Lembo and his team, published in “The New England Journal of Medicine, indicated that eluxadoline reduces IBS with diarrhoea symptoms in both men and women. This study, involving 2427 adults, revealed that the drug outperforms a placebo in improving symptoms, highlighting its efficacy in the treatment [29].

Adverse events of eluxadoline include constipation, nausea and abdominal pain. Admittedly, more severe, albeit rare, side effects may occur, including severe abdominal pain due to sphincter of Oddi spasm or pancreatitis. These symptoms are associated mainly with patients without a gallbladder or with existing pancreatic or hepatobiliary disease [30].

LOPERAMIDE

Loperamide is a mu-opioid receptor agonist which affects gastrointestinal musculature by increasing water absorption. Trials have shown that loperamide reduces diarrhoea without any impact on global IBS symptoms or abdominal pain. For this reason, loperamide is not recommended as a first-line therapy for treating patients with IBS-D [18],[31].

RIFAXIMIN

Rifaximin alpha (rifamycin derivative) is a non-absorbed antibiotic that inhibits the expression of bacterial genes. Concentration of the drug in the intestinal lumen makes it beneficial for fighting pathogenic bacteria (e.g, Clostridium, Escherichia, Peptostreptococcaceae) and has the effect of modulating the microbiota. Additionally, low bioavailability minimizes the risk of systemic immune hypersensitivity, which can be a serious outcome. Treatment with rifaximin for 14 days leads to an increase in beneficial bacteria, including Bifidobacterium, Lactobacillus, and anti-inflammatory Faecalibacterium prausnitzii. Furthermore, it is shown that it restores intestinal barrier tightness, affects the pregnane-X receptor and has an immunomodulatory effect [32],[33].

A meta-analysis of randomized, placebo-controlled trials determined effects of treating with rifaximin. The study showed that patients treated with this antibiotic experienced significant relief of overall IBS symptoms compared to those receiving placebo. Moreover, the drug appeared to be well tolerated. Although there was major relief of abdominal bloating at the follow-up endpoint, it was not significant at the treatment endpoint [33]. In another analysis, published in ”Clinical Therapeutics”, analyzed 1258 patients from double-blind trials and 2438 from an open-label trial, indicating that 14-day treatment with rifaximin improves multiple symptoms in adult patients with IBS-D [34].

Rifaximin is considered a safe drug with placebo-like tolerability. The most frequently reported side effects of treatment were mild to moderate including nausea, diarrhea, infections (upper respiratory and urinary tract infections), headache, and arthralgia [35].

ANTIDEPRESSANTS

Antidepressants can affect the release of endorphins, block norepinephrine, which strengthens descending inhibitory pain pathways and blocks the pain neuromodulator serotonin [31]. In abdominal symptoms, disturbances in nerve conduction cause hypersensitivity to stimuli and a hyper-reactive neuronal response. Patients with IBS may experience emotional disorders, which is why medications with a central effect are considered [32].

An article published in “Pharmacological Reports” by Agnieszka Kułak-Bejda and her team, analyzed 6 meta-analyses, 18 randomized controlled trials, and 5 studies without randomization. The study showed that antidepressants relieved IBS symptoms and worked more effectively with patients with IBS-D subtype. Compared to placebo, tricyclic antidepressants (TCAs) demonstrated greater effectiveness than selective serotonin reuptake inhibitors (SSRIs). Nonetheless, SSRIs improved IBS manifestations such as pain, severity, bloating and quality of life compared to placebo [36]. As far as the American Gastroenterology Association (AGA) Practice Guideline is concerned, TCAs are recommended due to a greater response in terms of adequate relief and abdominal pain

compared to placebo. However, the AGA suggests against treatment with SSRIs in patients with IBS, as they did not significantly improve global symptoms or abdominal pain [37]. Potential adverse events of TCAs to consider include dry mouth, dry eyes, urinary retention, constipation, and cardiac arrhythmias [18].

ANTISPASMODICS

Antispasmodics are a heterogeneous group of drugs that reduce defecation-related symptoms and include preparations with varied mechanisms of action. Some drugs act as direct smooth muscle relaxants by inhibiting sodium and calcium transport (e.g., dicyclomine, mebeverine). Other antispasmodics are anticholinergic/antimuscarinic agents (e.g., hyoscine, hyoscyamine, cimetropium bromide), which inhibit smooth muscle contraction. Another category consists of calcium channel inhibitors, which block calcium transport to gastrointestinal smooth muscle (e.g., alverine, pinaverium). Moreover, some drugs often have mixed mechanisms of action [38],[39].

The ACG Clinical Guidelines do not recommend using antispasmodics currently available in the United States to treat global IBS symptoms. Furthermore, they suggest that specific therapies should be evaluated based on individual drugs rather than the entire group. Studies evaluating hyoscine, hyoscyamine, and dicyclomine, which are available in the U.S., are limited. The studies are of poor quality and outdated, with methodological flaws, such as sample sizes, inconsistent enrolment criteria, non-identical trial design, and different endpoints [18]. On the other hand, the American Gastroenterological Association (AGA) recommends the use of antispasmodics in patients struggling with IBS. Although their guidelines also highlight the inadequacies and poor quality of existing studies, they indicate that antispasmodics have been associated with significant relief of global symptoms and abdominal pain [37]. According to the Polish guidelines for IBS treatment by the Polish Society of Gastroenterology, the use of specific preparations (e.g. drotaverine, hyoscine, otilonium, cimetropium, pinaverium, and dicyclomine) is suggested, rather than recommending antispasmodics as a whole group. However, this recommendation is considered weak and the quality of evidence is very low. Additionally, the authors also point out that combined analysis of the entire group of antispasmodics is problematic and the number of studies examining individual drugs is limited or has too few subjects [32].

A meta-analysis conducted by Alexander C. Ford in “the BMJ” demonstrated that the most common side effects experienced by patients were dry mouth, dizziness, and blurred vision, with no serious adverse effects reported [40]. Another article indicates that antispasmodics cause more side effects than placebo and additionally mentions constipation as a side effect [41].

Conclusion

Various medications are used to treat irritable bowel syndrome (IBS), depending on the subtype of IBS and the symptoms present. The mode of action, mechanisms, adverse events and efficacy of these drugs vary, so it is important to carefully evaluate the possible treatment options and exercise caution when choosing a therapy for IBS.

Disclosure

Author’s contribution

- Conceptualization: Mikołaj Łabuda, Agnieszka Szema
- Methodology: Agnieszka Szema, Jakub Sikora, Adrianna Bogucka
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- Writing - review and editing: Mikołaj Łabuda, Agata Kotkowiak
- Visualization: Adrianna Bogucka, Jakub Sikora, Teresa Sowińska
- Supervision: Aleksandra Słojewska, Teresa Sowińska,
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