Drugs of the Future 2011, 36(9): 669-675

CCC: 0377-8282/2011
DOI: 10.1358/dof.2011.36.9.1665562

REVIEW ARTICLE

IRRITABLE BOWEL SYNDROME – PRINCIPLES AND NOVEL TREATMENT OPTIONS

P.M. Hellström and D.-L. Webb

Department of Medical Sciences, Uppsala University, Uppsala, Sweden

CONTENTS

SUMMARY

There is growing interest in the area of irritable bowel syndrome (IBS) in developing tools to separate various subgroups of this disease in order to identify potentially different pathogenetic mechanisms. From such work, the ultimate goal is tailored treatment for the various subtypes of the disease. Among major achievements in this research, the finding of increased gut permeability is of great interest and suggests a luminal factor as a cause of disease, which would be able to maintain low-grade inflammation. There are various treatment options and significant activity in developing drugs that have the capability to inhibit gut motility and increase luminal secretion. The development of analogues to gut peptide hormones, such as glucagon-like peptide 1, is of primary interest, as these drugs rarely give rise to inconvenient adverse reactions at therapeutic doses. Some of these drugs even exert their action directly on the luminal membranes, such as linaclotide, which means that oral administration is favored to diminish the risk of systemic reactions. The concept of IBS is anticipated to evolve into different disease mechanisms that will serve as the basis for customized treatments.

INTRODUCTION

Irritable bowel syndrome (IBS) is considered a chronic gastrointestinal (GI) disorder, which belongs to the group of functional GI disorders defined by the Rome Foundation (1). IBS as a specific disease entity has only recently been recognized by the World Health Organization as separate from other functional GI disorders. Based on epidemiological data and surveys of the population, the prevalence ranges from 3% to 20%, with most studies reporting a prevalence of 10-15% in the general population. Although challenging, the diagnosis today is made according to the Rome III criteria of symptoms (2).

Correspondence: Prof. Per M. Hellström, MD, PhD, Department of Medical Sciences, Uppsala University Hospital, Bldg. 40, SE 751 85 Uppsala, Sweden. E-mail: Per.Hellstrom@medsci.uu.se.

PATHOPHYSIOLOGY OF IBS

The exact underlying pathophysiology of IBS is unclear. As such, "IBS" remains a diagnosis of exclusion, with no clear route to a rationally designed treatment. Modern treatments target selected receptors and enzymes, and are utilized for alleviating IBS symptoms rather than treating the underlying cause. IBS is often associated with different anxiety disorders and undefined food intolerances (3-5). IBS may also occur in the postinfectious phase of gastroenteritis (6).

The paucity of a clear pathophysiological mechanism for IBS makes targeted treatment difficult. Treatment primarily focuses on the dominant symptoms that have the most impact on quality of life. As a consequence, IBS has been separated into a constipation-predominant type (IBS-C), a diarrhea-predominant type (IBS-D) and a mixed type (IBS-M), sometimes also referred to as alternating IBS (IBS-A). Each of the IBS subtypes constitutes about 30% of IBS patients. In addition, a fourth subgroup exists: unsubtyped (IBS-U). In common practice, the treatment of choice for IBS-C is tegaserod or laxatives such as lactulose or polyethylene glycol, and for IBS-D loperamide or codeine. Based on this knowledge, IBS-M is treated according to the presently dominating symptom. For pain as a general symptom of IBS, antispasmodics and antidepressants are often used, albeit with limited success.

DIAGNOSIS OF IBS

Although the diagnosis is primarily based on exclusion criteria and clinical questionnaires, diagnostic biomarkers are emerging. Current knowledge suggests new molecular targets and underlying mechanisms that contribute to symptom profiles in IBS. This might form the basis for new treatments.

IBS is characterized by abdominal pain, altered bowel habits and impaired gut motility in the absence of histopathological changes or inflammatory processes. However, there are reports of low-grade inflammatory activity in patient biopsy specimens, such as increased proteasome activity and decreased tight junction protein ZO-1 (zonula occludens protein 1), but not occludin, expression levels

compared to controls (7, 8). This suggests that increased gut permeability as observed with paracellular permeability of fluorescein isothiocyanate (FITC)–dextran in cultured Caco-2 cell monolayers might be of importance in the pathogenesis of IBS. Patients with the highest pain scores also have the most marked increase in FITC–dextran permeability (8). In agreement with this, a substantial portion of patients with IBS-D have increased intestinal permeability, as shown by an increased lactulose:mannitol ratio (9). Again, these patients demonstrated a higher pain scoring than controls. Along these lines, low expression of tight junction proteins leading to increased gut permeability may cause a local response, with different changes in gene expression of cytokines and chemokines, such as secreted and transmembrane protein 1 (*SECTM1*), C-C motif chemokine 20 (*CCL20*), C-X-C motif chemokine 10 (CXCL-10, *CXCL10*), interleukin-1 beta (IL-1β, *IL1B*) interleukin-10 (IL-10, *IL10*), early growth response protein 1 (EGR-1, *EGR1*) and transforming growth factor beta (TGF-β, *TGFB*), while specifically others, such as interleukin-8 (IL-8), C-C motif chemokine 2 (CCL-2) and C-X-C motif chemokine 9 (CXCL-9) are suggested to be decreased (Tables I and II) (10). This would in turn be associated with dysregulation of the enteric nervous system, with changes in both neurotransmitter levels and expression of their receptors, specifically cholinergic and serotonergic innervation (11, 12). The enteric nervous system releases acetylcholine and serotonin (5-HT) after food intake. 5-HT also signals back to the central nervous system (CNS). The 5-HT_3 receptors are connected through afferent nerves for feedback signaling with the CNS, whereas 5-HT_4 receptors serve to transmit signals to neurons for acetylcholine release at a prejunctional level, leading to increased gut motility (13, 14).

Table I. *Changes in representative colonic gene expression in subjects with irritable bowel syndrome compared to healthy controls as selected from microarray gene expression (10).*

Activity	Gene expression (qRT-PCR)	Change
Immune	*SECTM1*	↗
Immune	*CXCL10*	↘
Immune	*CCL20*	↘
Immune	*IL1B*	↘
Immune	*IL10*	↘
Immune	*IL12*	0
Transcription	*EGR1*	↘
Differentiation	*TGFB*	↘

↗, increased expression; ↘, decreased expression; 0, unchanged expression; qRT-PCR, quantitative reverse transcription-polymerase chain reaction.

Table II. *Changes in representative protein secretion of the sigmoid colon in patients with irritable bowel syndrome compared to healthy volunteers as selected from microarray gene expression (10).*

Activity	Protein secretion (multiplex cytokine bead array)	Change
Immune	CCL-2	↘
Immune	CXCL-9	↘
Immune	CXCL-10	0
Immune	IL-1β	0
Immune	IL-6	0
Immune	IL-8	↘
Immune	TNF	0

↘, decreased secretion; 0, unchanged secretion.

After its release, 5-HT is removed from the nervous microenvironment around the smooth muscle cells by a reuptake mechanism, thereby terminating its action on the muscle cells. Patients with IBS-D have elevated levels of 5-HT in the intestinal mucosa and fluid, which may serve as an indicator of various dysfunctions connected to 5-HT reuptake in IBS (11).

The hypothalamic–pituitary axis also appears to be involved in elevating plasma levels of adrenocorticotropic hormone and cortisol in patients with IBS compared to healthy volunteers, suggesting dysfunction of the hypothalamic–pituitary–adrenal (HPA) axis, which normally has a permissive effect on transmitter signaling and regulates responses to external stimuli (15). It therefore appears that the interplay between the central and enteric nervous systems and GI motility is involved in IBS. This emphasizes the need for research on the crosstalk between transmitter functions in enteric nerves and hormonal functions of gut enteroendocrine cells that seem to be perturbed in IBS.

THERAPEUTIC APPROACH

The goal of therapy is to alleviate symptoms and optimize quality of life. To this end, possible side effects associated with treatment need to be considered. These include constipating effects of morphine derivatives used as painkillers and diarrheal effects of laxative compounds, which can make bowel movements hard to control. Therefore, the most debilitating symptoms must be the focus of treatment. Task force groups on IBS of the American College of Gastroenterology and the British Society of Gastroenterology have developed guidelines for treatment where a considerable placebo effect in IBS treatment has been recognized (3, 16). The placebo effect might be explained by a more receptive patient–practitioner relationship (17). The high placebo response must be considered with new treatments for IBS and might explain why some medications fail to show significant efficacy (Table III).

Treatments for IBS can be categorized as supportive, alternative and pharmacological. In mild IBS, lifestyle and dietary changes may be helpful, including increased physical exercise, increased intake of soluble fiber, reduced insoluble fiber, probiotic consumption and exclusion of foodstuffs such as lactose, fructose and sorbitol. Although little is known about any true physiological rationale, most IBS patients report improvement with the exclusion of gluten from their diet (18). Of these measures, mainly probiotics have been evaluated in clinical trials to reduce bloating, abdominal pain and frequency of bowel movements. Physical exercise has also been shown to be successful, even if a true placebo is difficult or impossible to define in such a behavioral treatment (19). An effect of physical exercise is, however, not very surprising; many long distance runners are well aware of the phenomenon of "runner's gut" (20). The bacterial

Table III. *Therapeutic approaches to treatment in irritable bowel syndrome.*

Compound	Mechanism of action	Target function
Tricyclic antidepressants	Increase 5-HT at receptor level	Pain relief
Selective serotonin reuptake inhibitors	Increase 5-HT at receptor level	Pain relief
Cimetropium	Anticholinergic	Antispasmodic
Pinaverium	Anticholinergic	Antispasmodic
Otilonium	Anticholinergic	Antispasmodic
Mebeverine	Anticholinergic	Antispasmodic
Darifenacin	Anticholinergic	Pain relief, stimulate motility
Zamifenacin	Anticholinergic	Pain relief, antidiarrheal
Loperamide	Stimulation of μ opioid receptors	Antidiarrheal
Asimadoline	Stimulation of κ opioid receptors	Pain relief
Mesalazine	Antiinflammatory	Antidiarrheal
Rifaximin	Antibiotic (broad-spectrum)	Bacterial overgrowth
Alosetron	Blockade of 5-HT_3 receptors	Pain relief, antidiarrheal
Cilansetron	Blockade of 5-HT_3 receptors	Pain relief, antidiarrheal
Ramosetron	Blockade of 5-HT_3 receptors	Pain relief, antidiarrheal
Prucalopride	Stimulation of 5-HT_4 receptors	Pain relief, stimulate motility
Renzapride	Stimulation of 5-HT_4 receptors	Pain relief, stimulate motility
Velusetrag	Stimulation of 5-HT_4 receptors	Pain relief, stimulate motility
Naronapride	Stimulation of 5-HT_4 receptors	Pain relief, stimulate motility
Aprepitant	Blockade of NK_1 receptors	Antispasmodic
Nepadutant	Blockade of NK_2 receptors	Antispasmodic
ROSE-010/GLP-1 analogue	Stimulation of GLP-1 receptors	Pain relief, antispasmodic
Pexacerfont	Blockade of CRF_1 receptors	Pain relief, antidiarrheal
Dexloxiglumide	Blockade of CCK_1 receptors	Pain relief, stimulate motility
Solabegron	Stimulation of β_3-adrenoceptors	Pain relief, antispasmodic
Lubiprostone	Stimulation of chloride channel protein ClC-2	Secretory, laxative
Linaclotide	Stimulation of guanylate cyclase C	Pain relief, secretory
Gabapentin	Sensitizing GABA receptors	Pain relief
Pregabalin	Sensitizing GABA receptors	Pain relief
Dextofisopam	Sensitizing GABA receptors	Pain relief, antispasmodic

GLP-1, glucagon-like peptide 1; NK, neurokinin (tachykinin); CRF, corticotropin-releasing factor; CCK, cholecystokinin; GABA, γ-aminobutyric acid.

species *Bifidobacterium*, *Lactobacillus* and *Streptococcus* all have moderate effectiveness in alleviating IBS symptoms (21). Other supportive means of treatment for IBS include psychotherapy and hypnotherapy, as well as stress management. These measures show the best effect in patients with comorbid stress and anxiety disorders (22, 23).

Alternative treatments for IBS usually employ nutritional supplements and alternative herbal medicines, such as Iberogast® and peppermint oil. Iberogast® is today sold over the counter and praised by many patients, although no physiological principle or specific biochemical mechanism of action is defined. Clinical data on this category are sparse, but a Cochrane review of available clinical trials has concluded that several alternative medicines may provide benefits for IBS patients (24-27). It is reckoned that alternative medicines are used by up to 37% of IBS patients (28).

Since a coexisting mood disorder is likely to be present in IBS patients, tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) have been used as specific therapeutic

pharmacological interventions (29). These agents can alleviate visceral pain and pain perception. A meta-analysis reviewing several randomized, controlled studies (9 with TCAs, 5 with SSRIs and 20 with psychotherapy) found significant benefit for antidepressants and psychotherapy over placebo, with a calculated relative benefit in the range of 0.66 (confidence interval [CI]: 0.57-0.78) and 0.67 (CI: 0.57-0.79), respectively, indicating an improvement in one-third of the patients relative to placebo.

There is, however, an unmet need for the treatment of moderate to severe IBS where pain is the dominating symptom. Pain attacks in IBS have recently been surveyed in an international study by Hellström and collaborators as being surprisingly severe, reaching a level of 7 on a 0-10 visual analog scale (30). The duration of pain attacks lasts on average 2.8 hours. However, some pain attacks persist for 24 hours, indicating a more or less chronic pain syndrome. According to surveys, 35% of IBS patients have reported their pain as so severe and such an interference with their quality of life that they would give up 25% of their remaining life if they could receive a treatment that would eliminate their IBS (28). Hence, IBS patients surprisingly often use antispasmodics and analgesics, and even opioids, most commonly in IBS-D (30).

Antispasmodics serve to reduce abdominal pain and cramping in IBS. Meta-analysis of clinical trials with antispasmodics has shown cimetropium, pinaverium, otilonium and mebeverine to be superior to other anticholinergics (31). The muscarinic M_3 receptor antagonists darifenacin and zamifenacin were shown to have a positive outcome in IBS-C and IBS-D patients (32, 33); however, development of these drugs in IBS was discontinued.

Among other treatments, opioid receptor agonists are used to treat IBS-D. Loperamide, being a μ opioid receptor agonist, has been widely used to treat diarrhea and has been shown to slow intestinal transit in IBS-D. Opioid receptor agonists may also reduce pain perception, but pose the risk of developing drug dependency, as observed with codeine and diphenoxylate (34).

The suggestion of a low-grade inflammatory process with mast cell infiltration of the intestine in IBS would imply treatment with antiinflammatory medications. Mesalazine, as used for Crohn's colitis and ulcerative colitis, has shown some improvement in moderate IBS-D concurrent with a reduced number of mast cells in the mucosa (35). Along these lines, users of oral glucocorticosteroids are found to be less likely to develop IBS (36).

Antibiotics may benefit IBS patients with small bowel bacterial overgrowth. The only antibiotic evaluated for the treatment of IBS with an acceptable response rate and safety profile is rifaximin. Antibiotic treatment may only be considered in patients with confirmed bacterial overgrowth and metabolic derangements and various malnutritional states.

5-HT_3 receptor antagonists benefit IBS patients with moderate to severe IBS-D by reducing GI motility and visceral pain perception (37). Evaluation of a meta-analysis comprising 14 randomized, controlled trials showed alosetron and cilansetron to be superior in achieving global symptom improvement in IBS-D and non-constipated IBS, with a 60% improvement calculated as risk ratio 1.6 (CI: 1.49-2.72) (38). The use of alosetron has, however, been restricted due to the severe risk of ischemic colitis (39).

EMERGING THERAPIES AGAINST IBS

Newly discovered targets are in high demand to alleviate symptoms characteristic of IBS (Table III). One major hurdle in the development of drugs is that animal models may not typically translate to the human conditions. In animals, motility can be studied with foreseeable effects in man, while effects on visceral pain perception are more difficult and bloating as a symptom of IBS cannot be studied at all.

Tachykinins are of major interest in IBS since these endogenous neuropeptides are often co-localized with acetylcholine in the enteric nervous system. Tachykinins are powerful in contracting intestinal smooth muscle cells via NK_1, NK_2 and NK_3 receptors. These receptors are considered major targets for antispasmodics. Aprepitant (an NK_1 receptor antagonist) and nepadutant (an NK_2 receptor antagonist) have been reported to be effective in reducing GI motility and visceral pain sensitization. However, an earlier NK_3 receptor antagonist, talnetant, showed no benefit in IBS (40). To this end, new NK_2 receptor blockers are in development as candidate drugs against IBS.

The gut hormone glucagon-like peptide 1 (GLP-1) is a prominent inhibitor of upper GI motor activity, and as such has an added benefit (beyond stimulating insulin secretion and inhibiting glucagon secretion) in the treatment of type 2 diabetes, where postprandial hyperglycemia is also prevented and/or delayed by slowed gastric emptying. GLP-1 also reduces appetite and causes moderate weight loss. Actions of GLP-1 are mediated through a single G protein-coupled receptor. In addition to the inhibitory effect of GLP-1 on gastric emptying, GLP-1 also reduces intestinal motility (41-43), which is why the GLP-1 analogue ROSE-010 was studied for analgesic effects during pain attacks in IBS (44). In this randomized, controlled trial with blinded subcutaneous injections, ROSE-010 was found to reduce pain attacks by about 50% (Fig. 1). There is preclinical and clinical evidence that GLP-1 relaxes gut smooth muscle, which should relieve pain attacks associated with IBS (41-43).

Antagonism of the corticotropin-releasing factor receptor CRF_1 is of interest because corticotropin-releasing factor (CRF) has a direct stimulating effect on intestinal motility under stressful conditions.

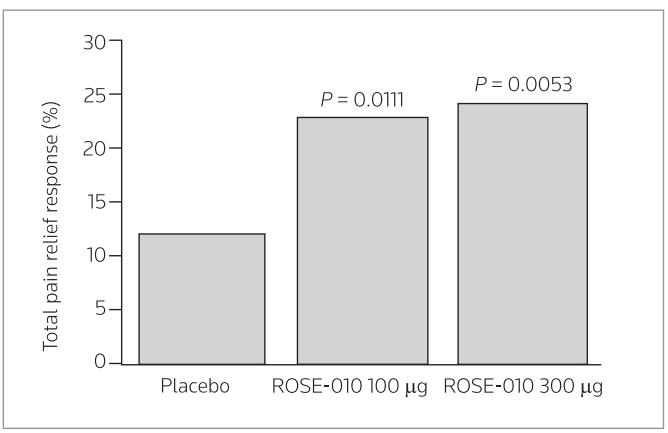

Figure 1. Total pain relief in irritable bowel syndrome pain attacks after an injection of the glucagon-like peptide 1 analogue ROSE-010 at two different doses, 100 and 300 μg subcutaneously (44).

This also appears to be related to visceral pain sensation (6, 45). Studies with the CRF_1 receptor antagonists pexacerfont and GW-876008 (emicerfont) have not shown significant improvements in intestinal motility or pain perception using global assessment scales (46, 47). The immense complexity of the interactions between the HPA axis and gut motility is the most likely cause for the lack of efficacy of CRF_1 receptor antagonists in IBS.

Stimulation of the cholecystokinin CCK_1 receptor dampens GI motility, which is why CCK_1 receptor antagonists should increase colonic motility, predictably benefiting the IBS-C subgroup. Phase III clinical studies with the CCK_1 receptor antagonist dexloxiglumide have shown either mixed results for pain relief and distension (48) or no benefits over placebo (49). Due to the clear role of CCK_1 receptors in motility, antagonists nonetheless deserve further investigation.

Agonist stimulation of β_3-adrenoceptors reduces motility and relieves pain and discomfort in IBS. An interesting example of this may be solabegron, which is known to release somatostatin from adipocytes and has shown promising results in clinical trials (50).

Exploiting the hypothesized low-grade inflammatory process as a target for IBS treatment, a direct application of adenosine triphosphate (ATP) has been used to act on purinoceptor P2X and P2Y receptors in the gut. Activation of P2X receptors on immune cells has proinflammatory properties, while P2Y receptors and potassium–ATP exert antiinflammatory effects and relaxation of intestinal smooth muscle (51). So far, experimental data are meager and further clinical trials should be carried out with ATP or similar analogues.

Serotonergic compounds in the form of $5\text{-}HT_4$ receptor agonists (prucalopride, renzapride, velusetrag, naronapride) have recently shown clinical improvement in patients with moderate IBS-C, increasing motility and improving visceral pain perception (52-55). Furthermore, the $5\text{-}HT_3$ receptor antagonist ramosetron has shown benefit in patients with IBS-D, alleviating diarrhea and pain, as well as normalizing GI motility (56). The results are in line with the general view of 5-HT being the main transmitter for motility in the gut.

For the treatment of IBS-C, secretagogues such as lubiprostone, which acts on the chloride channel protein ClC-2 on the apical membrane of enterocytes, have been tested. Lubiprostone stimulates enterocytes to increase water secretion and decrease intestinal transit time, pain perception and distension (57). This drug was approved by the FDA in 2006 for the treatment of chronic idiopathic constipation, but beneficial effects in mild to moderate IBS-C have also been found.

The guanylate cyclase C agonist linaclotide is a 14-amino-acid residue that binds to the receptor on gut epithelial cells and increases the secretion of chloride and bicarbonate together with water to the luminal side of the intestine. Phase II clinical studies have shown this drug to improve visceral pain perception, stool consistency and abdominal pain, as well as quality of life, in IBS-C patients (58). This drug is particularly interesting since it acts locally on the mucosal membranes in the gut and does not cross the mucosa to reach the bloodstream for widespread distribution in the body.

The common opioids codeine, morphine and loperamide have been used for a very long time in moderate to severe IBS-D to ameliorate pain perception and reduce intestinal motility and secretion. Among newer compounds in this class of drugs, asimadoline has been evaluated for the treatment of IBS (59). Asimadoline has the advantage of acting only on peripheral κ opioid receptors. Recently, benzodiazepine receptor modulators received attention due to their ability to influence intestinal motility and pain perception. Gabapentin and pregabalin, which are regularly used for epilepsy, are also active in neuralgia and chronic pain syndromes. These drugs act on the γ-aminobutyric acid receptor in the brain to increase binding of the endogenous ligand and promote efflux of chloride ions, which prevents signal propagation. Gabapentin and pregabalin have been shown to reduce visceral pain perception in IBS patients (60, 61). A new benzodiazepine derivative, dextofisopam, has been developed for use in IBS. An early study showed this drug to reduce gut motility, but surprisingly, also increase abdominal pain compared to placebo (62).

CONCLUSIONS

New targets for the treatment of IBS symptoms are continuously being identified and new drugs are being evaluated in preclinical and clinical trials for use in the treatment of IBS. Apart from drugs recognized for their actions on $5\text{-}HT_3$ and $5\text{-}HT_4$ receptors with effects in IBS-D and IBS-C, gut peptide analogues of tachykinins and GLP-1 have found their way into clinical trials, mainly acting as antispasmodics. Drugs that target chloride channels and stimulate water secretion have found an indication in chronic constipation, but may also relieve symptoms in IBS. Antiinflammatory pharmaceuticals and immunomodulators have yet to show effectiveness in IBS, whereas opioid receptor agonists and benzodiazepine receptor modulators might affect pain perception. The array of new pharmaceuticals for the treatment of IBS requires special attention in terms of profiling clinical studies in relation to the dominant symptom of IBS to be studied. Perhaps further subtyping in relation to objective biomarkers such as transit time or permeability in various parts of the gut will be needed in order to disentangle the IBS spectrum and find treatable symptoms within sharply defined disease entities. In line with this, once a single symptom of IBS is remedied, the impact of disease on patients' general health and quality of life will improve.

ACKNOWLEDGMENTS

Supported by the Swedish Research Council and Uppsala University.

DISCLOSURES

The authors state no conflicts of interest.

REFERENCES

1. Drossman, D.A. *Introduction. The Rome Foundation and Rome III.* Neurogastroenterol Motil 2007, 19(10): 783-6.
2. Drossman, D.A., Douglas, A., (Eds.). Rome III: The Functional Gastrointestinal Disorders. Third Edition. Degnon Associates, Inc.,: MacLean, VA 2006.
3. Sagami, Y., Shimada, Y., Tayama, J. et al. *Effect of a corticotropin releasing hormone receptor antagonist on colonic sensory and motor function in patients with irritable bowel syndrome.* Gut 2004, 53(7): 958-64.

4. Jones, J., Boorman, J., Cann, P. et al. *British Society of Gastroenterology guidelines for the management of the irritable bowel syndrome.* Gut 2000, 47(Suppl. 2): ii1-19.
5. Lee, V., Guthrie, E., Robinson, A., Kennedy, A., Tomenson, B., Rogers, A., Thompson, D. *Functional bowel disorders in primary care: Factors associated with health-related quality of life and doctor consultation.* J Psychosom Res 2008, 64(2): 129-38.
6. Lea, R., Whorwell, P.J. *The role of food intolerance in irritable bowel syndrome.* Gastroenterol Clin North Am 2005, 34(2): 247-55.
7. Coeffier, M., Gloro, R., Boukhettala, N. et al. *Increased proteasome-mediated degradation of occludin in irritable bowel syndrome.* Am J Gastroenterol 2010, 105(5): 1181-8.
8. Piche, T., Barbara, G., Aubert, P. et al. *Impaired intestinal barrier integrity in the colon of patients with irritable bowel syndrome: Involvement of soluble mediators.* Gut 2009, 58(2): 196-201.
9. Zhou, Q., Zhang, B., Verne, G.N. *Intestinal membrane permeability and hypersensitivity in the irritable bowel syndrome.* Pain 2009, 146(1-2): 41-6.
10. Macsharry, J., O'Mahony, L., Fanning, A. et al. *Mucosal cytokine imbalance in irritable bowel syndrome.* Scand J Gastroenterol 2008, 43(12): 1467-76.
11. Coates, M.D., Mahoney, C.R., Linden, D.R. et al. *Molecular defects in mucosal serotonin content and decreased serotonin reuptake transporter in ulcerative colitis and irritable bowel syndrome.* Gastroenterology 2004, 126(7): 1657-64.
12. Leng, Y.X., Wei, Y.Y., Chen, H., Zhou, S.P., Yang, Y.L., Duan, L.P. *Alteration of cholinergic and peptidergic neurotransmitters in rat ileum induced by acute stress following transient intestinal infection is mast cell dependent.* Chin Med J (Engl) 2010, 123(2): 227-33.
13. Nagakura, Y., Kontoh, A., Tokita, K., Tomoi, M., Shimomura, K., Kadowaki, M. *Combined blockade of 5-HT3- and 5-HT4-serotonin receptors inhibits colonic functions in conscious rats and mice.* J Pharmacol Exp Ther 1997, 281(1): 284-90.
14. Taniyama, K., Makimoto, N., Furuichi, A., Sakurai-Yamashita, Y., Nagase, Y., Kaibara, M., Kanematsu, T. *Functions of peripheral 5-hydroxytryptamine receptors, especially 5-hydroxytryptamine4 receptor, in gastrointestinal motility.* J Gastroenterol 2000, 35(8): 575-82.
15. Locatelli, V., Bresciani, E., Tamiazzo, L., Torsello, A. *Central nervous system-acting drugs influencing hypothalamic-pituitary-adrenal axis function.* Endocr Dev 2010, 17: 108-20.
16. Brandt, L.J., Chey, W.D., Foxx-Orenstein, A.E. et al. *An evidence-based position statement on the management of irritable bowel syndrome.* Am J Gastroenterol 2009, 104(Suppl. 1): S1-35.
17. Dhaliwal, S.K., Hunt, R.H. *Doctor-patient interaction for irritable bowel syndrome in primary care: A systematic perspective.* Eur J Gastroenterol Hepatol 2004, 16(11): 1161-6.
18. Biesiekierski, J.R., Newnham, E.D., Irving, P.M. et al. *Gluten causes gastrointestinal symptoms in subjects without celiac disease: A double-blind randomized placebo-controlled trial.* Am J Gastroenterol 2011, 106(3): 508-14.
19. Johannesson, E., Simren, M., Strid, H., Bajor, A., Sadik, R. *Physical activity improves symptoms in irritable bowel syndrome: A randomized controlled trial.* Am J Gastroenterol 2011, 106(5): 915-22.
20. Gil, S.M., Yazaki, E., Evans, D.F. *Aetiology of running-related gastrointestinal dysfunction. How far is the finishing line?* Sports Med 1998, 26(6): 365-78.
21. Barbara, G., Stanghellini, V., Cremon, C. et al. *Probiotics and irritable bowel syndrome: Rationale and clinical evidence for their use.* J Clin Gastroenterol 2008, 42(Suppl. 3, Pt. 2): S214-7.
22. Drossman, D.A., Camilleri, M., Mayer, E.A., Whitehead, W.E. *AGA technical review on irritable bowel syndrome.* Gastroenterology 2002, 123(6): 2108-31.
23. Halpert, A., Dalton, C.B., Diamant, N.E. et al. *Clinical response to tricyclic antidepressants in functional bowel disorders is not related to dosage.* Am J Gastroenterol 2005, 100(3): 664-71.
24. Liu, J.P., Yang, M., Liu, Y.X., Wei, M.L., Grimsgaard, S. *Herbal medicines for treatment of irritable bowel syndrome.* Cochrane Database Syst Rev 2006(1): CD004116.
25. Bensoussan, A., Talley, N.J., Hing, M., Menzies, R., Guo, A., Ngu, M. *Treatment of irritable bowel syndrome with Chinese herbal medicine: a randomized controlled trial.* JAMA 1998, 280(18): 1585-9.
26. Madisch, A., Holtmann, G., Plein, K., Hotz, J. *Treatment of irritable bowel syndrome with herbal preparations: Results of a double-blind, randomized, placebo-controlled, multi-centre trial.* Aliment Pharmacol Ther 2004, 19(3): 271-9.
27. Shen, Y.H., Nahas, R. *Complementary and alternative medicine for treatment of irritable bowel syndrome.* Can Fam Physician 2009, 55(2): 143-8.
28. Drossman, D.A., Morris, C.B., Schneck, S. et al. *International survey of patients with IBS: Symptom features and their severity, health status, treatments, and risk taking to achieve clinical benefit.* J Clin Gastroenterol 2009, 43(6): 541-50.
29. Henningsen, P., Zimmermann, T., Sattel, H. *Medically unexplained physical symptoms, anxiety, and depression: A meta-analytic review.* Psychosom Med 2003, 65(4): 528-33.
30. Hellstrom, P.M., Saito, Y.A., Bytzer, P., Tack, J., Mueller-Lissner, S., Chang, L. *Characteristics of acute pain attacks in patients with irritable bowel syndrome meeting Rome III Criteria.* Am J Gastroenterol 2011, 106(7): 1299-307.
31. Ford, A.C., Talley, N.J., Spiegel, B.M., Foxx-Orenstein, A.E., Schiller, L., Quigley, E.M., Moayyedi, P. *Effect of fibre, antispasmodics, and peppermint oil in the treatment of irritable bowel syndrome: Systematic review and meta-analysis.* BMJ 2008, 337: a2313.
32. Kobayashi, S., Ikeda, K., Suzuki, M., Yamada, T., Miyata, K. *Effects of YM905, a novel muscarinic M3-receptor antagonist, on experimental models of bowel dysfunction in vivo.* Jpn J Pharmacol 2001, 86(3): 281-8.
33. Wallis, R.M. *Pre-clinical and clinical pharmacology of selective muscarinic M3 receptor antagonists.* Life Sci 1995, 56(11-12): 861-8.
34. Palmer, K.R., Corbett, C.L., Holdsworth, C.D. *Double-blind cross-over study comparing loperamide, codeine and diphenoxylate in the treatment of chronic diarrhea.* Gastroenterology 1980, 79(6): 1272-5.
35. Corinaldesi, R., Stanghellini, V., Cremon, C. et al. *Effect of mesalazine on mucosal immune biomarkers in irritable bowel syndrome: A randomized controlled proof-of-concept study.* Aliment Pharmacol Ther 2009, 30(3): 245-52.
36. Huerta, C., Garcia Rodriguez, L.A., Wallander, M.A., Johansson, S. *Users of oral steroids are at a reduced risk of developing irritable bowel syndrome.* Pharmacoepidemiol Drug Saf 2003, 12(7): 583-8.
37. Goldberg, P.A., Kamm, M.A., Setti-Carraro, P., van der Sijp, J.R., Roth, C. *Modification of visceral sensitivity and pain in irritable bowel syndrome by 5-HT3 antagonism (ondansetron).* Digestion 1996, 57(6): 478-83.
38. Andresen, V., Montori, V.M., Keller, J., West, C.P., Layer, P., Camilleri, M. *Effects of 5-hydroxytryptamine (serotonin) type 3 antagonists on symptom relief and constipation in nonconstipated irritable bowel syndrome: A systematic review and meta-analysis of randomized controlled trials.* Clin Gastroenterol Hepatol 2008, 6(5): 545-55.
39. Rahimi, R., Nikfar, S., Abdollahi, M. *Efficacy and tolerability of alosetron for the treatment of irritable bowel syndrome in women and men: A meta-analysis of eight randomized, placebo-controlled, 12-week trials.* Clin Ther 2008, 30(5): 884-901.

40. Houghton, L.A., Cremonini, F., Camilleri, M. et al. *Effect of the NK(3) receptor antagonist, talnetant, on rectal sensory function and compliance in healthy humans.* Neurogastroenterol Motil 2007, 19(9): 732-43.
41. Tolessa, T., Gutniak, M., Holst, J.J., Efendic, S., Hellstrom, P.M. *Glucagon-like peptide-1 retards gastric emptying and small bowel transit in the rat: Effect mediated through central or enteric nervous mechanisms.* Dig Dis Sci 1998, 43(10): 2284-90.
42. Tolessa, T., Gutniak, M., Holst, J.J., Efendic, S., Hellstrom, P.M. *Inhibitory effect of glucagon-like peptide-1 on small bowel motility. Fasting but not fed motility inhibited via nitric oxide independently of insulin and somatostatin.* J Clin Invest 1998, 102(4): 764-74.
43. Hellstrom, P.M., Naslund, E., Edholm, T. et al. *GLP-1 suppresses gastrointestinal motility and inhibits the migrating motor complex in healthy subjects and patients with irritable bowel syndrome.* Neurogastroenterol Motil 2008, 20(6): 649-59.
44. Hellstrom, P.M., Hein, J., Bytzer, P., Bjornsson, E., Kristensen, J., Schambye, H. *Clinical trial: the glucagon-like peptide-1 analogue ROSE-010 for management of acute pain in patients with irritable bowel syndrome: A randomized, placebo-controlled, double-blind study.* Aliment Pharmacol Ther 2009, 29(2): 198-206.
45. Wallon, C., Yang, P.C., Keita, A.V. et al. *Corticotropin-releasing hormone (CRH) regulates macromolecular permeability via mast cells in normal human colonic biopsies in vitro.* Gut 2008, 57(1): 50-8.
46. Sweetser, S., Camilleri, M., Linker Nord, S.J. et al. *Do corticotropin releasing factor-1 receptors influence colonic transit and bowel function in women with irritable bowel syndrome?* Am J Physiol Gastrointest Liver Physiol 2009, 296(6): G1299-306.
47. Dukes, G.E., Mayer, E.A., Kelleher, D.L., Hicks, K.J., Boardley, R.L., Alpers, D.H. *A randomised, double blind, placebo (PLA) controlled, crossover study to evaluate the efficacy and safety of the corticotrophin releasing factor 1 (CRF1) receptor antagonist (RA) GW876008 in irritable bowel syndrome (IBS) patients (pts).* Neurogastroenterol Motil [3rd Intl Meet Neurogastroenterol Motil (Aug 27-30, Chicago) 2009] 2009, 21(Suppl. s1): Abst 279.
48. Whorwell, P.J., Pace, F., D'Amato, M. et al. *A phase III, 6-month, double-blind, placebo-controlled, randomized withdrawal trial of the selective CCK-1 antagonist dexloxiglumide in constipation-predominant IBS: the Darwin study.* Gastroenterology [Dig Dis Week (May 17-22, San Diego) 2008] 2008, 134(4, Suppl. 1): Abst 1051.
49. Cremonini, F., Camilleri, M., McKinzie, S. et al. *Effect of CCK-1 antagonist, dexloxiglumide, in female patients with irritable bowel syndrome: A pharmacodynamic and pharmacogenomic study.* Am J Gastroenterol 2005, 100(3): 652-63.
50. Kelleher, D.L., Hicks, K.J., Cox, S., Williams, R.R., Alpers, D.H., Dukes, G.E. *Randomized, double-blind, placebo (PLA)-controlled crossover study to evaluate efficacy and safety of the beta 3-adrenergic receptor agonist solabegron (SOL) in patients with irritable bowel syndrome (IBS).* Neurogastroenterol Motil [2nd Intl Meet Neurogastroenterol Motil (Nov 6-9, Lucerne) 2008] 2008, 20(Suppl. s1): Abst SAT157.
51. Salari, P., Abdollahi, M. *Current opinion in the pharmaceutical management of irritable and inflammatory bowel diseases: Role of ATP.* Recent Pat Endocr Metab Immune Drug Discov 2009, 3(1): 69-75.
52. Bouras, E.P., Camilleri, M., Burton, D.D., Thomforde, G., McKinzie, S., Zinsmeister, A.R. *Prucalopride accelerates gastrointestinal and colonic transit in patients with constipation without a rectal evacuation disorder.* Gastroenterology 2001, 120(2): 354-60.
53. Manini, M.L., Camilleri, M., Goldberg, M. et al. *Effects of velusetrag (TD-5108) on gastrointestinal transit and bowel function in health and pharmacokinetics in health and constipation.* Neurogastroenterol Motil 2010, 22(1): 42-9.
54. Camilleri, M., Vazquez-Roque, M.I., Burton, D., Ford, T., McKinzie, S., Zinsmeister, A.R., Druzgala, P. *Pharmacodynamic effects of a novel prokinetic 5-HT receptor agonist, ATI-7505, in humans.* Neurogastroenterol Motil 2007, 19(1): 30-8.
55. George, A.M., Meyers, N.L., Hickling, R.I. *Clinical trial: renzapride therapy for constipation-predominant irritable bowel syndrome—Multicentre, randomized, placebo-controlled, double-blind study in primary healthcare setting.* Aliment Pharmacol Ther 2008, 27(9): 830-7.
56. Matsueda, K., Harasawa, S., Hongo, M., Hiwatashi, N., Sasaki, D. *A randomized, double-blind, placebo-controlled clinical trial of the effectiveness of the novel serotonin type 3 receptor antagonist ramosetron in both male and female Japanese patients with diarrhea-predominant irritable bowel syndrome.* Scand J Gastroenterol 2008, 43(10): 1202-11.
57. Sweetser, S., Busciglio, I.A., Camilleri, M. et al. *Effect of a chloride channel activator, lubiprostone, on colonic sensory and motor functions in healthy subjects.* Am J Physiol Gastrointest Liver Physiol 2009, 296(2): G295-301.
58. Andresen, V., Camilleri, M., Busciglio, I.A. et al. *Effect of 5 days linaclotide on transit and bowel function in females with constipation-predominant irritable bowel syndrome.* Gastroenterology 2007, 133(3): 761-8.
59. Mangel, A.W., Bornstein, J.D., Hamm, L.R., Buda, J., Wang, J., Irish, W., Urso, D. *Clinical trial: asimadoline in the treatment of patients with irritable bowel syndrome.* Aliment Pharmacol Ther 2008, 28(2): 239-49.
60. Lee, K.J., Kim, J.H., Cho, S.W. *Gabapentin reduces rectal mechanosensitivity and increases rectal compliance in patients with diarrhoea-predominant irritable bowel syndrome.* Aliment Pharmacol Ther 2005, 22(10): 981-8.
61. Houghton, L.A., Fell, C., Whorwell, P.J., Jones, I., Sudworth, D.P., Gale, J.D. *Effect of a second-generation alpha2delta ligand (pregabalin) on visceral sensation in hypersensitive patients with irritable bowel syndrome.* Gut 2007, 56(9): 1218-25.
62. Leventer, S.M., Raudibaugh, K., Frissora, C.L., Kassem, N., Keogh, J.C., Phillips, J., Mangel, A.W. *Clinical trial: Dextofisopam in the treatment of patients with diarrhoea-predominant or alternating irritable bowel syndrome.* Aliment Pharmacol Ther 2008, 27(2): 197-206.