Current view

Irritable bowel syndrome: Current treatment strategies

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SUMMARY

Irritable bowel syndrome, the most common gastrointestinal functional disorder, worsens significantly patients' quality of life and accounts for huge costs for both patients and health-care systems. The treatment of IBS is centred on an excellent doctor–patient relationship along with drugs targeting the predominant symptom, especially during exacerbations. This treatment strategy is unsatisfactory due to the high number of patients complaining of lack of response and/or symptom recurrence. Therefore, a multiple symptom targeting treatment approach is recommended. Components of the approach could be serotonin peripheral receptors agonists and antagonists, water soluble dietary fiber and psychotherapy. Unfortunately, none of the available medications that target serotonin pathways is marketed in Europe yet, usefulness of new forms of fiber needs further confirmation and psychotherapy is still reserved as second-line or as add-on therapy. Wide arrays of potentially useful drugs are currently under consideration in pre-clinical or early phase development trials.

Key words: Irritable bowel syndrome, treatment, tegaserod, alosetron, water-soluble dietary fiber, hypnotherapy, cognitive behavior therapy

1. INTRODUCTION

Irritable bowel syndrome (IBS) is a functional gastrointestinal (GI) disorder characterized by abdominal pain or discomfort and altered bowel habits.[1] IBS is a common disorder, affecting up to 20% of the North American population[2,3] and it accounts for 28% and 12% of diagnoses made by gastroenterologists and primary care physicians, respectively.[4,5] Patient surveys show that IBS has a negative impact on patients' social lives (e.g., affecting personal relationships, travel, and participation in leisure activities) and self-esteem.[6,7] Symptoms can also negatively affect patients' work lives by limiting work-related tasks, thus contributing to the high indirect cost associated with this disorder.[8,9]

The Rome II Committee has defined IBS as the presence of abdominal pain or discomfort for a total of at least 12 weeks (not necessarily consecutive) in the preceding 12 months, with at least two of the following features: relief induced by defecation, onset associated with change in stool frequency and onset associated with change in stool form.[10] This definition is useful for recruiting patients for clinical trials and is an important component of the symptom-based approach to IBS diagnosis in clinical practice, which recommends an evaluation of warning signs and symptoms of possible organic disease.[1,11] During the past two decades, important research strides have enhanced our understanding of the underlying pathophysiology of IBS. The understanding of the critical role of serotonin in maintaining normal GI-tract function and of the vital link between serotonin and the enteric nervous system (ENS), the autonomic nervous system (ANS), and the central nervous system (CNS) [12,13] has resulted in the development of several serotonergic agents as potential therapies for IBS.[1,14,15]

2. CHALLENGES TO ACHIEVE THE GOAL OF TREATMENT

The goal of IBS treatment is to provide rapid, sustained, global relief of the multiple symptoms of IBS with a single, effective, well-tolerated agent. Unfortunately, there is no standard treatment for IBS. Alleviating symp-

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toms is one of the primary challenging goals of care for IBS patients. Rational management is difficult, because we still lack objective criteria for reaching a definite diagnosis, the pathogenesis is not known and there are no specific, effective therapies.

Many drugs are prescribed for IBS and many more are under investigation (Table 1). Not much has changed in the past few decades despite the availability of some new drugs. Whitehead et al. [16] evaluated patients visiting primary care physicians and gastroenterologists. Interestingly, the most common treatment recommendations remained changes in diet (62%), exercise (52%), and lifestyle changes to reduce stress (42%), followed by antidiarrheal drugs, antispasmodics, and laxatives.

In some patients, traditional IBS treatment options are beneficial in relieving single symptoms (e.g., antispasmodics or antidepressants for abdominal pain, laxatives for constipation, and antidiarrheal agents for diarrhea). However, these treatments are often ineffective, and can cause bothersome adverse effects in some patients.[2] Patient surveys also demonstrate general dissatisfaction with these agents.[6,7] Therefore, treatments targeting only single IBS symptoms are considered suboptimal forms of therapy by the Rome II Committee and the American College of Gastroenterology - Functional Gastrointestinal Disorders (ACG FGID) Task Force.[2]

Response of IBS patients to any treatment is widely heterogeneous. Factors that predict the response to treatment of IBS in clinical practice remain largely unexplored, but there has been a general suspicion that psychiatric and psychological comorbidity must be important.[17] Moreover, due to IBS natural history (long lasting with unpredicted exacerbation and remission periods), it is difficult to attribute remission of symptoms to either treatment efficacy or to the natural history of the disorder.[1,13,17]

It is also well known that placebo is an excellent treatment for IBS. Indeed, there have been reports that the placebo response can be maintained for at least 12 months, a finding that remains both surprising and perplexing.[18] It is therefore important to include a placebo arm in all randomized controlled trials that test new therapies for IBS, because the unpredictable placebo response makes any conclusion without a placebo virtually meaningless. Of course, the placebo response is still a contentious entity in medicine, and its further elucidation remains a priority.

Another intriguing methodologic issue is related to the concept of what endpoint is truly most appropriate in treatment trials in IBS. The Rome committees have recommended using a global end point. This has been assumed to be the most suitable means of defining the response to treatment in IBS because it appears to reflect clinical practice (it essentially asks the patient "Are you better?"). In trials concerning the newer serotonin agents, such an endpoint ("adequate relief") provided clear-cut differentiation from the ubiquitous placebo response.[17]

Table 1. Pharmaceutical approach to IBS treatment

Traditional drugs	
Antispasmodics	hyoscyamine, trimebutine, mebeverine, octylonium, pinaverium, cimetropium, dicyclomine, peppermint oil
Tricyclic antidepressants	amitryptiline, nortriptyline, imipramine, doxepine, desipramine
Modern antidepressants (SSRIs)	citalopram, fluoxetine, sertaline, paroxetine
Procinetiks	cisapride
Stool bulking agents	methylcellulose, psyllium
Osmotic laxatives	lactulose, lactitol, polyethylene glycol, milk of magnesia
Anti-diarrheals	loperamide, diphenoxylate, cholestyramine
Modern drugs	
5-HT$_4$ partial agonist	tegaserod
5-HT$_3$ antagonist	alosetron
Drugs in evolution	
5-HT$_4$ agonist	prucalopride
Ανταγωνιστής 5-HT$_3$	cilancetron
5-HT$_4$ agonist + 5-HT$_3$ antagonist	renzapride
Alpha$_2$-adrenergic agonist	clonidine
Cholecystokinin antagonists	loxiglumide, dexloxiglumide
M$_3$ anticholinergic agents	darifenacin, zamifenacin
Opioed antagonist	naltrexone
κ-opioed agonists	fedotozine, asmandoline
μ- opioed agonists	loperamide, alvimopan
Neurokinin antagonists	ezlopitant, nepadutunt

3. TOWARDS THE GLOBAL SYMPTOM RELIEF

3.1 Single-symptom relief

In 2002, both the American Gastroenterology Association and ACG FGID Task Force reviewed all IBS available treatment data on an evidence-based approach (Table 2.) in order to provide clinicians treatment recommendations. Both reviews concluded that evidence-based support is lacking for IBS treatments that target the most bothersome symptom. The methodology in most clinical trials of these agents was flawed. Many studies met the criteria for level II evidence, correlating with a grade B recommendation (Table 3.).[1,2,3] Although bulking agents, antidiarrheals, and tricyclic antidepressants were found to relieve some single symptoms of IBS (constipation, diarrhea, and abdominal pain, respectively), these agents were no more effective than placebo in providing global relief of the multiple symptoms of IBS. In addition, these agents often cause adverse reactions, some of which may mimic or exacerbate IBS symptoms (e.g., constipation from antidepressants and bloating from high doses of fiber).[1,2,3]

Therefore both AGA and ACG GIFD Task force suggested a comprehensive, multilevel treatment approach, integrating pharmacotherapy with a supportive physician–patient relationship, provision of education and reassurance, close monitoring of symptoms, and dietary adjustments for the treatment of IBS.[1-3]

3.2 Multiple-symptom relief

3.2.1. The role of serotonin

Disruptions in integrated communications among the CNS, ANS, and ENS may contribute to the three key

Table 3. Treatment of IBS. Grade of recommendations[1]

Treatment	Grade of recommendation*
Tegaserod	A
Alosetron	A
Antispasmodicis	B
Fiber	B
Osmotic laxatives	B
Anti-diarrheals	B
Antidepressants	B
Alternative treatments	B

* Grade A recommendations are the only reliable grade for recommending a therapy

pathophysiological features of IBS (altered GI motility, visceral hypersensitivity and altered intestinal secretion).[13,14] Numerous neurotransmitters and neuromodulators are involved in the communication between the intrinsic primary afferent neurons and the effector systems (muscles and secretory and vascular cells) and in the mediation of bidirectional brain-gut communications. Serotonin (5-hydroxytryptamine [5-HT]), a neurotransmitter found mainly in the gut (95%) and the brain is considered to play an important role in the pathophysiological abnormalities observed in IBS.[13,14,19] It appears to be a common link involved in GI motility, intestinal secretion, and pain perception and is involved at multiple levels in the bidirectional interactions between the ENS and the CNS.[13,14,19]

In the GI tract, serotonin acts via intrinsic ENS neurons to initiate motor and secretory reflexes and via extrinsic ENS neurons to initiate the sensations of pain and bloating.[13,14,19] As many as 14 serotonin-receptor subtypes have been identified to date. Of these, the 5-HT_{1p}, 5-HT_3

Table 2. Level of evidence from clinical trials and Grade of therapeutic recommendation (modified from reference 1)

Level I	RCTs with low rate of false positive results, adequate sample size, appropriate methodology
Level II	RCTs with high rate of false positive results, inadequate sample size, inappropriate methodology
Level III	Nonrandomized contemporaneous cohort controls
Level IV	Nonrandomized historical cohort controls
Level V	Case series without controls
Grade A recommendation	Supported by evidence from =2 Level I studies without conflicting evidence from other Level I studies
Grade B recommendation	Supported by evidence from =2 Level I studies with conflicting evidence from other Level I studies or supported by evidence from =2 Level II studies
Grade C recommendation	Supported by evidence from Level III-IV studies

RCTs: Randomized, placebo-controlled clinical trials

and 5-HT$_4$ subtypes are considered the most clinically relevant for lower GI tract function and regulation (e.g., motor, sensory, and secretory functions) and in the underlying pathophysiology of IBS.[13,14]

3.2.1.1. Tegaserod

Tegaserod is a highly selective 5-HT$_4$ receptor partial agonist indicated for women with IBS whose primary altered bowel symptom is constipation (IBS-C). Activation of the 5-HT$_4$ receptor in the GI tract via tegaserod (which mimics the action of serotonin) normalizes impaired intestinal motility, inhibits visceral sensitivity and stimulates intestinal secretion. [13,14,19]

Table 4. summarizes the results of Tegaserod pivotal trials.[20-24] In phase 3 studies,[20,22] tegaserod provided significant global symptom relief of IBS as measured by the primary efficacy measure, the Subject's Global Assessment (SGA) of relief, as well as by secondary efficacy measures (relief of single symptoms [abdominal pain/discomfort, bloating, constipation]) in patients with IBS-C. The SGA is a validated efficacy measure that assesses the impact of treatment on IBS-related symptoms in clinical trials.[25] It captures patient's response to therapy in relation to 3 domains: overall well-being, abdominal pain/discomfort, and altered bowel function. Results showed a 13% to 14% therapeutic gain with tegaserod treatment at 4 weeks and a 5% to 11% therapeutic gain at 12 weeks compared with placebo.[20,22] At the defined end point (completely or considerably relieved for at least 2 of the last 4 weeks of the trial or at least somewhat relieved for the last 4 weeks of the trial), tegaserod response rates ranged from 38% to 46% compared with 30% to 39% for placebo. Efficacy appeared in the first week and lasted for the 12 weeks of treatment.[20,22] By week 12, up to 67% of patients receiving tegaserod achieved overall relief.[20,22]

In one of the above trials[22] the effects of a 4-week withdrawal period have been evaluated. In both treatment groups and for all efficacy variables, there was a loss of effect in the first week of this period. The decline continued over weeks 2 and 3, and it stabilized in the third and fourth withdrawal weeks. The therapeutic gain of tegaserod over placebo disappeared within 1-2 weeks of withdrawal. However, at the end of the 4-week withdrawal period, patients' symptoms were less severe than at baseline. This study and the study from Bardhan et al.[26] provide evidence that IBS-C patients experience symptom relapse after tegaserod withdrawal. Re-treatment with tegaserod of patients who initially respond to the medication has been examined. Tegaserod has shown to provide patients with therapeutic response similar to that achieved during initial treatment.[27] Given the periodicity of IBS symptoms, intermittent use of tegaserod represents an attractive treatment option that needs further evaluation.

The results of a multinational, double-blind, randomized, placebo-controlled trial in Scandinavia, confirmed the efficacy, safety, and tolerability of 12 weeks of treatment with tegaserod in more than 600 patients with IBS whose primary altered bowel symptom was not diarrhea.[23] Patients receiving tegaserod experienced significantly greater relief from IBS symptoms in weeks 1-4 and in weeks 1-12 (Table 4.). Adverse-effect profiles were similar between the 2 treatment groups and diarrhea incidence (9.2% vs 1.3% with placebo) was consistent with findings of other studies.[20-24]

The efficacy of tegaserod has also been evaluated in the Asian-Pacific IBS patient population whose primary altered bowel habit was not diarrhea in a randomized, double-blind, 12-week trial. Patients were treated with tegaserod (6 mg twice daily, n = 259) or placebo (n = 261). The primary efficacy end point was patient response during the first 4 weeks to the question: «Over the past

Table 4. Efficacy of Tegaserod in IBS-C

Clinical Trial	N	Women (%)	Response rate (%) for Primary Endpoint Tegaserod	Placebo	Therapeutic gain	Quality of the CT (0-13)
Muller-Lissner et al[20]	881	83	38	30	8	12·
Whorwell et al[21]	799	87	46	33	13	12·
Novick et al[22]	1519	100	44	39	5	13·
Kellow et al[24]	520	88	47	28	19	13·
Nylin et al[23]	647	86	40	29*	11+	

IBS-C: Constipation predominant Irritable Bowel Syndrome, CT: Clinical trial
* Data from week 12, average efficacy ranged between 22% and 29% for weeks 5-12
+ Data from week 12, average therapeutic gain ranged between 5% and 15% for weeks 5-12
· From reference 3

week do you consider that you have had satisfactory relief from your symptoms of IBS?».[24]

Patients who took tegaserod achieved statistically significantly better overall satisfactory relief than patients who took placebo during weeks 1 through 4 (56% vs 35%, respectively, $P < 0.0001$) and weeks 1 through 12 (62% vs 44%, respectively, $P < 0.0001$) of the study. Symptom relief was observed as early as one week after treatment with tegaserod and the effects were maintained compared with placebo throughout the 12-week treatment period. Compared with placebo, tegaserod effected greater reductions in the number of days with at least moderate abdominal pain/discomfort, bloating, no bowel movements and hard/lumpy stools.[24]

Several studies have shown that tegaserod has favorable short- and long-term safety and tolerability profiles.[15,20-24,26-31] Most adverse effects experienced by patients receiving tegaserod were similar in frequency, type and severity to those experienced by patients receiving placebo. The rate of discontinuation attributed to adverse effects was low.[20,22] Long-term safety studies indicate that tegaserod was safe and well tolerated for up to 12 months.[28] Diarrhea was mild and transient and generally resolved with continued treatment. In the pivotal clinical trials, diarrhea occurred in 9% of patients receiving tegaserod 6 mg twice daily compared with 4% receiving placebo.[20,22] No cardiac toxicity or prolongation of the corrected QT interval was observed in phase 3 clinical trials or in a study of healthy subjects.[29] The use of the agent is not associated with increased frequency of abdominal or pelvic surgeries.[30]

In evidence-based systematic reviews tegaserod was more effective than placebo in providing global symptom relief in women with IBS-C.[1,3,31] In addition, based on the high quality of the tegaserod clinical trials, tegaserod received a grade A recommendation from these panel of experts.[1,3] Further more, in the latest Cohrane database systematic review of tegaserod in IBS-C female patients, the Number Needed to Treat (NNT) was calculated to 17, and as far diarrhea is concerned the Number Needed to Harm (NNH) was 20.[31] While the efficacy and safety of tegaserod has been adequately examined in IBS-C female patients, its use in male IBS-C patients warrants further evaluation since male patients have been underrepresented in tegaserod pivotal trials.

In August 2004, the package labeling for tegaserod was revised to warn that rare cases of serious diarrhea (requiring hospitalization) have been reported in clinical trials (occurring in 0.04% of patients in randomized clinical trials), and post-marketing reports of ischemic colitis and other forms of ischemia, although rare, have been received. However, in most cases, diarrhea resolved without complication.[32]

Unfortunately, on December 2005, The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency has not been convinced by the data the authorisation marketing holder of tegaserod has submitted and was concerned that the results of the studies would not translate into real benefit to the patient treated to relieve the symptoms of this disorder in standard health care setting.[33]

Hence although tegaserod is marketed in more than 50 countries worldwide (USA included), the CHMP did not approve tegaserod's marketing authorization in European countries.

3.2.1.2 Alosetron

Alosetron is a selective 5-HT$_3$ antagonist that slows small-bowel and overall colonic transit time, enhances basal sodium and fluid absorption (in humans) and modifies visceral hypersensitivity in many different ways.[34]

Efficacy of alosetron in patients with IBS with diarrhea (IBS-D) has been evaluated in four multicenter, randomized, double-blind, placebo-controlled, parallel group studies listed in Table 5.[35-38] In a fifth study alosetron has been compared to mebeverin.[39]

All of the studies had treatment periods of 12 weeks and the optimal dose of alosetron was found to be 1 mg twice daily given orally. Over 3000 patients were enrolled and women comprised the study population in all except one[35] of these trials. Three of the four studies used adequate relief of IBS pain and discomfort for at least two of the four weeks in the past month as primary efficacy endpoint.[35-37] The fourth one enrolled women with IBS-D who lacked satisfactory control of urgency on at least 50% of the days.[38] In this study, a 7-point scale was used in order to measure the relief ranging from substantially worse to substantially improved. Patients were asked to rate the degree of relief they experienced over the previous four weeks compared with the three months prior to the trial.

In clinical trials, the 1 mg twice daily dose of alosetron induced constipation to approximately 28% of patients and constipation caused approximately 11% of patients to prematurely withdraw from the studies. The incidence of serious complications of constipation in women was 1 in 1000. Patients who are elderly, debilitated or taking medications that decrease GI motility may

Table 5. Efficacy of Alosetron in IBS-D

Κλινική μελέτη	N	Women (%)	Response rate (%) for Primary Endpoint Alosetron	Placebo	Therapeutic gain	Quality of the CT (0-13)
Camilleri et al[35]	370	53	60	33	27	12·
Camilleri et al[36]	647	100	41	29	12	12·
Camilleri et al[37]	626	100	43	26	17	
Lembo et al[38]	801	100	73	57	16	12·
Jones et al[39]	623	100	58	48*	10	12·

IBS-D: Diarrhea predominant Irritable Bowel Syndrome, CT: Clinical Trial
* Mebeverin as control treatment
· From reference 3

be at greater risk for complications. Ischemic colitis is another adverse event associated with alosetron that has been reported during clinical trials and in the post-marketing period.

Both AGA and ACG FGID Task Force considered that alosetron was more effective than placebo in providing global symptom relief in women with IBS-D and they granted a grade A recommendation for it's use.[1,3]

In 2000, the Marketing Authorization Holder of alosetron withheld the drug from the marked voluntarily, due to concerns on the reported cases of ischemic colitis and of serious complications of constipation. In June 2002, alosetron was reintroduced in the USA market with sever restrictions for the treatment of women with severe IBS-D unresponsive to any other treatment. The medication must be prescribed by experts, at half the approved dose and the patients should be closely monitored.[40] Currently alosetron is not approved in Europe.

3.2.1.3 Cilansetron

Cilansetron is a novel serotonin 5-HT$_3$ receptor antagonist currently being evaluated for the treatment of female and male patients with irritable bowel syndrome with diarrhea.[41] Results from two large, randomized, double-blind, placebo-controlled, parallel-group Phase III clinical trials[42,43] showed that cilansetron was more effective than placebo at improving overall, as well as individual symptoms, including abdominal pain and diarrhea in female and male IBS-D patients. The most common side effect with cilansetron has been constipation. Although rare, the most concerning side effect observed with cilansetron has been suspected ischaemic colitis. The event rate for suspected ischaemic colitis associated with cilansetron from clinical trials is 3.77 per 1000 person years of exposure.[41] This rate appears to be greater than that expected in the IBS population[44,45] and similar to that observed with alosetron. All of the cases

of suspected ischaemic colitis reported with cilansetron have resolved without serious sequelae. However, issues surrounding the safety of cilansetron will affect the approval process in various countries.

3.2.2. Water-soluble dietary fiber

The multiple limitations of dietary fiber supplementation for the treatment of IBS symptoms have been described elsewhere.[1,2,3] Although fibre is still recommended as first line treatment,[16,46] it's use is some times associated with symptoms exacerbation, the effect is not predicted and some times it is not easy to consume the different forms of available dietary fibre.[46]

In recent years, the beneficial effects of water-soluble dietary fibers have received much attention. Guar gum is a water-soluble polysaccharide found in the seeds of guar, a plant indigenous to India and Pakistan. Because guar gum is extremely viscous, it is very difficult to incorporate in food in quantities large enough to obtain a physiological effect, so partially hydrolyzed guar gum (PHGG) is used in beverage form. PHGG has proved effective in softening and improving the output of feces and increasing bulking capacities (fecal weight, frequency of defecation and fecal excretory feeling).[47-49] In a previous investigation (50), 188 IBS patients were treated with high-fiber diet supplementation (30 g/day of wheat bran) or PHGG (5 g/day) for 12 weeks. Improvements in core IBS symptoms (abdominal pain and bowel habits) were observed with both bran and PHGG, but the latter was better tolerated and preferred by patients.

The effects of partially hydrolyzed guar gum (PHGG) were compared in patients with irritable bowel syndrome, at 10 g/day (N = 40) and 5 g/day (N = 46) for 12 weeks. Gastrointestinal symptoms, quality of life, and psychological symptoms were evaluated at baseline, during treatment (months 1 and 3), and at follow-up (month 6) using validated generic and disease specific scales.[51] In

both groups symptoms and quality of life improved significantly after the first month of administration until follow-up compared to those at baseline. However, the improvement was significantly reduced at follow-up compared to the end of treatment. PHGG was effective for improving somatic and psychological symptoms over the short term.[51] Given the lack of symptoms exacerbations, the patient attractive liquid form of the product and the global effect of PHGG in IBS, this product deserves further long term evaluation to examine potential benefits at maintenance dosage.

3.2.3 Hypnotherapy

Gut directed hypnotherapy has been shown to be effective in the treatment of IBS, with the majority of patients showing improvement in symptoms, associated extra-colonic features and quality of life, findings which have been confirmed by independent studies.[15,52-57] Gut directed hypnotherapy comprises a course of up to 12 weekly 1 hr sessions.[52-57] Each session consists of induction of the hypnotic state and deepening procedures, followed by "ego strengthening" suggestions relevant to the individual.

These are accompanied by further suggestions and interventions, such as inducing warmth in the abdomen, directed towards controlling and normalizing gut function.

This work led to the establishment of the first hypnotherapy unit in the National Health Service in the UK devoted to the treatment of IBS patients. The team from South Manchester University Hospital initially have published an audit on the first 250 patients treated at this unit, confirming the beneficial short-term effects of hypnotherapy in a large number of patients.[57] These patients were followed prospectively by completing questionnaires scoring symptoms, quality of life, anxiety, and depression before, immediately after and up to six years following hypnotherapy.[58] 81% of the initially responders maintained their improvement over time while the majority of the remaining claimed that deterioration of symptoms had only been slight. With respect to symptom scores, all items at follow up were significantly improved compared to pre-hypnotherapy levels and showed little change from post-hypnotherapy values. There were no significant differences in the symptom scores between patients assessed at any year post treatment.[58]

Improvement of quality of life and anxiety or depression scores, although showed some deterioration were still significant at follow up. Patients also reported less consultation rates and medication consumption following the completion of hypnotherapy.[58]

These amazing results must be interpreted with caution, because of lack of data from big controlled studies, inability to perform blinded studies and the unknown mechanism of hypnotherapy action in IBS. However, available data show that hypnotherapy should be considered as a complementary treatment for IBS symptoms.

3.2.4 Cognitive Behavior Therapy

Cognitive Behavioral Therapy (CBT) is a broad term and the interventions described in the literature have differed in their composition. However, each of the following components is normally included to some degree: Education about IBS and the CBT model, monitoring of thoughts, emotions and IBS symptoms to consider how they might be related, identifying and testing out thoughts and underlying assumptions, stress management and planning activities.[59]

In general, CBT is most appropriate for patients who are significantly distressed by their symptoms, are open to the idea that psychological factors play some role in their difficulties, are willing to take part in an intervention that requires their active participation and have already had reasonable medical investigations and interventions. The study of Jones et al.[60] contributed to the increasing evidence for the effectiveness of CBT in alleviating the physical and psychological symptoms of IBS.[61,62] This study was the first cognitive behavior intervention in primary care settings. Investigators randomized IBS patients not responding to 4-weeks mebeverine treatment to either 6 sessions of CBT + mebeverine (n=72) or to the antispasmodic alone (n=77). Significant symptom improvement has been observed in the psychological intervention group, lasting up to one year after the end of treatment. The major limitation of the study was the lack of placebo group.[60]

CBT seems most appropriate as complementary treatment for patients who have already had reasonable medical investigations and interventions, remain significantly distressed and are interested in taking an active part in achieving greater control over their symptoms.

3.2.5 Medications under development

There are two promising categories of compounds that are under intense development for the treatment of IBS.[15] Compounds targeting serotonin receptors[63,64] and compounds targeting mechanisms implicated in the development and the perception of abdominal pain.[65-69] Although pharmaceutical companies struggle to fill the existing gap on the needs of both IBS suffers and physi-

cians, none of these compounds is expected to be marketed in the forthcoming years.

3.3 Conclusions

Current pharmacological remedies targeting single predominant IBS symptom are largely unsatisfactory. More holistic approaches, such as compounds targeting serotonin pathways have given persuasive results and they will be under investigation for the next years, hoping that they will soon reach European market. At the same time, numerous compounds (some of them are listed in Table 1) targeting peripheral and/or central mechanisms of visceral pain are either in preclinical phases or in early stages of their development.

Until the development of more conclusive guidelines, IBS symptoms treatment will be still centered on an excellent doctor-patient relationship as long as drugs and life-style modifications target the suffering patient, not the specific symptom. Data from recent studies promise that psychotherapy can be another powerful option in the armament of the IBS treating physician.

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