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ESSENTIALS Symptoms suggestive of disturbed lower gastrointestinal func- tion without adequate explanation are very common in adults in the Western world, up to 15% of whom experience such symp- toms at any one time, although most do not seek medical advice. It is not clear whether the symptoms of those individuals who
do seek medical help have a different pathophysiological basis from those who do not, and whether the seeking of medical advice is more an indication of a worried individual than of disturbed gut function. The currently used terms are best viewed as an attempt to pro- vide some clinically useful, rather than pathophysiologically ac- curate, categorization of patients and their symptoms based on disordered gut–brain interactions. Irritable bowel syndrome is defined according to the Rome IV criteria as recurrent abdominal pain associated with a change in frequency or form of stool that is related to defecation for at least 3 months. Many subtypes are recognized. Routine haematological and biochemical screening is usually performed on the assumption that it will be normal. Features that raise the suspicion of organic disease and indicate a need for fur- ther investigation include the onset of symptoms in middle-aged or older individuals, weight loss, or blood in the stool. Management remains empirical: no single pharmacological agent or group of agents has ever been found to be consistently effective. The principal task of the physician is to provide explan- ation and reassurance (sometimes supplemented by psychological treatments), but particular symptoms are often treated as follows:
(1) constipation—defecation may be eased by supplementary dietary fibre and poorly absorbed fermentable carbohydrates which in- crease faecal bulk and soften the stool; osmotic laxatives and enemas are used for the severely constipated patient, as well as more novel agents;
(2) diarrhoea—attention to diet is often helpful, as are simple antidiarrhoeal agents; and (3) abdominal pain— antispasmodics (e.g. hyoscine butyl bromide) are frequently used, as are antidepressants. Introduction The functional gastrointestinal (GI) disorders are a heterogeneous group of syndromes, which can be defined as ‘variable combin- ations of chronic or recurrent gastrointestinal symptoms which are not explained by structural or biochemical abnormalities’. These disorders are common, accounting for more than 40% of all new referrals to secondary care gastroenterological clinics, although the overwhelming majority of patients are managed in primary

care. However, the multifaceted pathophysiology that underpins symptom genesis and maintenance in functional GI disorders is incompletely understood. As a result, there is a relative paucity of efficacious treatments and long-term patient outcomes are sub- optimal. It is therefore not surprising that the socioeconomic impact is considerable, with healthcare costs estimated to be in the order of $34 billion per annum in the seven largest Western healthcare economies, notwithstanding the impact in terms of the reduction in quality of life. The most commonly encountered functional GI disorder in clin- ical practice is irritable bowel syndrome (IBS), although a variety of terms have been used to describe this disorder in the past such as ‘nervous colitis’ and ‘spastic colon’. Despite a considerable research effort towards identification of objective biomarkers, IBS remains a symptom-based diagnosis in the absence of another ‘organic’ cause. The Rome foundation, an international committee of experts, has sought to systematize the diagnosis of IBS with a focus to improve homogeneity within both the research and clinical spheres. In order to separate IBS from transient gut symptoms, the current diagnostic criteria place an emphasis upon the chronic relapsing–remitting nature of the disorder. IBS is defined according to Rome IV criteria as recurrent abdominal pain associated with a change in frequency or form of stool that is related to defecation for at least 3 months (Box 15.13.1). Despite the Rome classification, it is often helpful to summarize the symptoms of IBS using the ABC mnemonic (Fig. 15.13.1). Considering that abdominal pain and/or discomfort remains a central defining feature of IBS, it is not unsurprising that it is 15.13 Irritable bowel syndrome Adam D. Farmer and Qasim Aziz

section 15 Gastroenterological disorders 2952 the symptom most likely to prompt medical consultation, yet it re- mains challenging to manage effectively. IBS accounts for between 40 and 60% of outpatient referrals to gastroenterology clinics and thus, with such a considerable burden of disease, the development of a complete understanding of the underlying pathophysiology of this complex disorder remains the prerequisite step on the road to the development of efficacious treatments. Although this under- standing is in its nascent stages, the last two decades have wit- nessed remarkable progress in unravelling the complexities of this disorder. Pathogenesis and aetiology The pathoaetiology of IBS is complex and multifactorial. A useful approach is to consider it in terms of a construct referred to as the brain–gut axis. This refers to circuitous communication between the GI tract and the brain, which has gained widespread accept- ance as helpful for providing an explanation of both normal GI function, and acute and chronic perturbations thereof. The model has also provided a useful framework to conceptualize the various pathoaetiological factors of IBS, whether they are biological, psy- chological, or social in nature (Fig. 15.13.2). Genetic influences Within families, a number of studies have reported clustering of IBS, and twin studies demonstrate heritability in the order of 40%. Many candidate genes have been investigated in IBS, including those encoding the serotonin transporter SLC6A4, 5-hydroxytryptamine 2A (5-HT2A) receptor, norepinephrine transporter, alpha2A and 2C-adrenergic receptor, and the β3 subunit G protein. However, the results from these studies have been largely disappointing since reproducibility across different cohorts is lacking, most likely re- flecting the problem of these initial underpowered small studies. To combat these limitations, large population-based genome- wide association studies (GWASs) represent one of the most exciting potential avenues. A recently published GWAS of more than 500 IBS cases and 5000 healthy controls has revealed that a locus at 7p22.1 was consistently associated with IBS. This locus includes coding regions for the KDEL endoplasmic reticulum protein retention receptor 2 (KDELR2) and glutamate receptor, ionotropic, delta 2 (Grid2) interacting protein, although the functional significance of these in IBS remains to be fully explored. Another potential application of the GWAS approach is its poten- tial to predict

treatment using pharmacogenetic profiles. Although such an approach is in its infancy, a European collaborative has re- cently been set up to improve homogeneity in sampling and tech- nical methods, from which it is hoped that significant progress will be made (GENes in Irritable Bowel Syndrome Research Network EURope, http://www.GENIEUR.eu). Infection IBS can occur after an enteric infection, where it is termed postinfectious IBS. Although most individuals who develop an infectious gastroenteritis have self-limiting symptoms, approxi- mately 25% develop IBS-like symptoms that outlast the initial infection. Specific personality traits, such as neuroticism and anx- iety, are independent risk factors for postinfectious IBS, which has been documented to occur after infections with a variety of enteric pathogens including campylobacter, salmonella, shigella, and Escherichia coli. Notably, community outbreaks of water-borne infections, such as was seen in Walkerton, Ontario, Canada, when the town's water supply was contaminated with E. coli, have pro- vided the opportunity to prospectively examine the pathophysi- ology and natural history of the postinfectious condition. The outcome of these studies has highlighted the deficiency of ubi- quitous pathophysiological features across patients, suggesting marked intraindividual variability. Visceral hypersensitivity Currently, the favoured hypothesis to account for chronic abdom- inal pain and discomfort in IBS is visceral hypersensitivity. Some patients with IBS have a heightened sensitivity to mechanical disten- sion of the rectum, which is referred to as 'visceral hypersensitivity' (Fig. 15.13.3). This epiphenomenon has resulted in a considerable research effort aimed at identifying the underlying causative mech- anisms. For instance, sensitization of the peripheral and central nervous system, psychological factors, and dysfunction within the stress response systems, namely the autonomic nervous system and the hypothalamic pituitary adrenal axis, have been implicated as co- variant factors. However, testing of rectal distension lacks the pre- requisite sensitivity and specificity for it to become a routine clinical diagnostic test. Psychological factors Psychological comorbidities such as somatization, anxiety, depres- sion, and hypochondriasis have been linked with IBS. In addition, Box 15.13.1 Rome IV Criteria for the diagnosis of Irritable Bowel Syndrome Recurrent abdominal pain, on average, at least 1 day per week in the last 3 months, associated with 2 or more of the following criteria: • Related to defecation • Associated with a change in frequency or form of stool • Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis Bloating Change in bowel habit Abdominal pain or discomfort Fig. 15.13.1 The ABC of IBS. The characteristic symptoms are abdominal pain or discomfort, bloating, and change in bowel habit.

15.13 Irritable bowel syndrome 2953 Genetics Internal factors Hypothalamic- pituitary- adrenal axis response Bidirectional communcation Bidirectional communcation Autonomic nervous system response Gastrointestinal Tract Sensory modulation Neuroendocrine response Emotion, feeling arousal, vigilance External factors Inflammation Infection Adverse life events Fig. 15.13.2 The construct of the brain–gut axis is useful for 'conceptualizing' the pathoaetiological factors in IBS. IBS patients report first sensation and pain at lower distension volumes than healthy controls IBS patients Rectal balloon distension Healthy controls Fig. 15.13.3 Visceral hypersensitivity in IBS. Patients with IBS, in general, report first sensation and pain at lower levels of rectal balloon distension compared with healthy controls.

section 15 Gastroenterological disorders 2954 adverse life events, such as sexual and physical abuse, are linked with the disorder. Increased levels of psychiatric comorbidity are seen in tertiary care IBS clinics compared to community populations. Gut microbiota Advances in culture- independent techniques have facilitated both quantification and qualitative evaluation of the

microbiological population residing within the GI tract, hereinafter referred to as the GI microbiota. The GI microbiota is a diverse ecosystem that inhabits the entire length of the GI tract, with microbial cells outnumbering human cells by approximately 10 to 1. Most of the microbiota resides within the colon (approximately 1014 organisms). Prior to birth, the GI tract is largely sterile, but is vertically in- oculated from the mother's vagina during delivery, with subsequent establishment of the diverse microbiota ecosystem during the first year of life. During early life, the GI microbiota becomes increas- ingly diverse and is influenced by the external environment, dietary components, genetic factors, and ethnicity. The relationship between the GI tract and the microbiota is complex and symbiotic. While arguably the main function of the GI microbiota is to protect against external pathogens, it has also been shown that it influences and modulates cognition, including learning and memory. Studies have demonstrated that germ-free animals, inoculated with the GI microbiota from IBS patients, can induce a state of visceral hypersensitivity and alterations in GI transit. Moreover, recent studies in IBS patients have demonstrated two species-specific subtypes of IBS, which were independent of symptom-based/Rome classifications. The first of these showed a microbial composition similar to normal, while the second was characterized by an increase in firmicutes-associated taxa, with a relative depletion of bacteroides-related taxa. The implication of these data suggests GI microbial enterotyping may facilitate strati- fication of IBS subpopulations, which may lead to individualization of treatment. However, such techniques remain resource intensive, thereby limiting their utility in routine clinical practice. Recent data have suggested that nonabsorbable antibiotics, such as rifaximin, are associated with a moderate improvement in global symptoms and also abdominal pain and bloating. Further studies are needed to replicate these initial findings and to ascer- tain whether patients need regular retreatment to maintain the therapeutic effect. Faecal microbiota transplantation has received considerable attention recently, particularly in the treatment of pseudomem- branous colitis caused by Clostridium difficile. It has been shown to be more effective for the treatment of recurrent C. difficile infection than the use of oral antimicrobials, such as vancomycin. Given the role of the microbiota in IBS, a number of preliminary case reports and retrospective studies examining the efficacy of faecal microbiota transplantation in the treatment of IBS have been reported. These have shown promising results, although to date there are no pro- spective, randomized, double-blinded, placebo-controlled trials. Epidemiology Worldwide, IBS affects approximately 5 to 20% of individuals, depending on the definition of IBS used. One large United Kingdom- based study of 580 000 primary care patients has estimated that the incidence of IBS is approximately four new cases per 1000 population per annum, with the peak occurring in the 18 to 34 years age group, declining with increasing age thereafter. The prevalence is around 25 times that of the incidence, hence IBS can be regarded as a chronic disorder. Several risk factors have been identified, the most reprodu- cible of which is female sex, with an odds ratio of 1.67. IBS is frequently associated with other disorders including gastro-oesophageal reflux disease, functional dyspepsia, and psy- chiatric comorbidity such as anxiety, depression, and somatiza- tion. Furthermore, IBS is also associated with other medically unexplained disorders/functional somatic syndromes such as fibro- myalgia, chronic fatigue syndrome, and migraine. Clinical features Current guidelines recommend that the diagnosis of IBS should be positively made, based on characteristic symptoms, rather than by exclusion based on a battery of (negative) investigations. While there is no clinically applicable biomarker for IBS, the diagnosis is based upon the patient fulfilling the diagnostic criteria in conjunc- tion with a small number of targeted investigations. The central defining clinical features of IBS are recurrent ab- dominal discomfort and/or pain associated with a change in in stool frequency or consistency (Fig. 15.13.4). In many patients, the abdominal discomfort is sometimes relieved following defe- cation.

IBS is frequently associated with a plethora of extra-GI manifestations including tiredness, headache, dysmenorrhoea, and dyspareunia in females. While symptoms characteristically change over time, patients typically report pain or discomfort on approximately 3 days per week, frequently occurring in clusters. Although IBS is currently subdivided based upon predominant bowel habit, patients frequently move from one subtype to an- other over time. IBS with diarrhoea (IBS-D) is reportedly the 100 75 50 25 0 0 25 50 Percentage time of loose/watery stool IBS-C IBS-M IBS-D IBS-U Percentage time of hard/lumpy stool 75 100 Fig. 15.13.4 The different subtypes of IBS are classified according to the predominant bowel habit. IBS with constipation (IBS-C), IBS with diarrhoea (IBS-D), IBS with mixed bowel habit (IBS-M), and IBS unclassified (IBS-U).

15.13 Irritable bowel syndrome 2955 commonest subtype, accounting for approximately 40% of cases, with mixed IBS (with alternating constipation and diarrhoea; IBS-M) being the least common. IBS with constipation (IBS-C) is significantly more common in women, and IBS-D has been dem- onstrated to be more common in men. IBS is associated with a re- duction in health-related quality life, increased absenteeism from work, as well as a diminution in productivity. By definition, the physical examination in IBS is normal, although it should be undertaken to reassure the patient as well as to help exclude other organic diseases. For instance, a rectal examination is often helpful to identify patients with disordered defecation syn- dromes such as dyssynergic defecation. Differential diagnosis and investigations Patients displaying the typical features of IBS, in the absence of alarm or red flag symptoms (Box 15.13.2), can be confidently diagnosed with IBS. Given the relative lack of specificity of symp- toms in IBS, the differential diagnosis is broad and includes lac- tose intolerance, small intestinal bacterial overgrowth, coeliac disease, inflammatory bowel disease, bile acid malabsorption, and food allergies. Screening investigations typically include a full blood count, inflammatory markers (such as ESR and/or C-reactive protein), serum ferritin and vitamin B12, thyroid function tests, serological testing for coeliac disease (antitissue transglutaminase antibodies), and consideration of testing CA125 in women. Recent evidence has shown that a faecal calprotectin concentration of less than 40 μg/g and a C-reactive protein concentration of less than 0.5 mg/dl can confidently exclude inflammatory bowel disease in patients with IBS symptoms. Stool microscopy may be helpful in diagnosing chronic enteric in- fections such as giardiasis, although these are uncommon in western IBS patients. In elderly patients, endoscopic imaging of the colon is required in order to exclude microscopic colitis, which is common and can account for up to 20% of unexplained diarrhoea in patients aged over 70 years. Bile acid malabsorption is also an important differential diag- nosis of IBS with diarrhoea, since the clinical response to bile acid sequestrants, such as cholestyramine, is good. A recent meta- analysis reported that 28.7% of those meeting the criteria for IBS with diarrhoea had bile acid malabsorption, which can be diagnosed using 75SeHCAT testing. In patients with watery diarrhoea, the diag- noses of small intestinal bacterial overgrowth and lactose intoler- ance should also be considered. Further testing is not required in most cases of IBS, although if alarm symptoms are present, or if there is diagnostic uncertainty regarding an inflammatory disorder, then colonoscopy can be con- sidered. In patients presenting with diarrhoea, colonic biopsies should be taken at colonoscopy to exclude microscopic colitis, espe- cially in females over 50 years old. In patients with severe constipa- tion, further investigation directed at assessing colonic motility may be performed, for instance, a transit study, or evaluating anorectal anatomy and physiology, such as a colonic marker study, anorectal manometry or proctography. In patients presenting with severe pain and other red flag symptoms, further investigations such as cross- sectional imaging should be considered. Figure 15.13.5 shows a sug- gested diagnostic algorithm for the patient presenting

with IBS-like symptoms. Box 15.13.2 Alarm symptoms that should prompt further investigation • Abnormalities on clinical examination • Weight loss • Rectal bleeding or masses • Nocturnal symptoms • History of recent antibiotic use • Raised inflammatory markers • Family history of colorectal carcinoma or ovarian cancer Fig. 15.13.5 Suggested diagnostic algorithm for IBS. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FBC, full blood count; TFTs, thyroid functions tests; tTG, tissue transglutaminase.

section 15 Gastroenterological disorders 2956 Management: general approaches Given the incomplete understanding of the pathophysiology of IBS, treatment is directed towards the predominant or most bothersome symptom(s). Central to a successful outcome is the doctor–patient relationship. In particular, validation of a patient's symptoms in a supportive environment is an absolute corner- stone of management. It is not uncommon to encounter patients who have experienced negative attitudes towards their symptoms from healthcare professionals, a situation compounded by the current lack of an objective diagnostic biomarker. Such negative attitudes result in a breakdown of the therapeutic relationship and thus patients are often disenfranchised. Reassurance and education are required, and the underlying rationale of treat- ment should be discussed in detail with the patient when this is initiated. The clinician and the patient should also agree upon, and set, reasonable treatment goals in the context of regular outpatient re- views. In this context, it is important not to underestimate the role of the wider multidisciplinary team, such as colleagues in psych- iatry, psychology, and dietetics. The frequency and regularity of such reviews may be limited by local service provision, but they do permit definition of response or nonresponse, facilitate earlier es- calation of intervention as appropriate, and importantly also leave patients with a sense of confidence that their symptoms are being taken seriously. Although such an approach is resource intensive, over the long term it is likely to be cost-effective, and most IBS pa- tients will not need such an intensive approach. In addition to these general approaches, various interventions have been suggested as being beneficial, including lifestyle measures and pharmacological and psychological treatments. The National Institute for Health and Care Excellence has recently published up- dated clinical guidelines on the management of IBS. A central aspect of pharmacological management is the stratification of patients into the predominant subtype of IBS, which aids in directing therapeutics towards the most problematic symptoms. A management algorithm is shown in Fig. 15.13.6. Lifestyle and dietary interventions There are numerous lifestyle aspects that can be modified, and which frequently result in symptomatic improvement. For example, patients should be given written information emphasizing the im- portance of self-help measures such as taking exercise and creating time to relax. General advice includes taking regular meals, drinking at least eight cups of fluid per day, and limiting caffeinated drinks. Patients often report that certain dietary components can both precipitate and exacerbate symptoms, hence their diet and nutrition should be assessed. The role of avoidance of certain dietary com- ponents has generated considerable interest in the role of ferment- able oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) in the symptomology of IBS. FODMAPs are ferment- able carbohydrates, which provide substrate to the GI microbiota, resulting in enhanced colonic fermentation and the production of intraluminal gaseous distension in addition to exerting a direct os- motic effect. The net result is colonic distension, which may mani- fest as bloating, distension, and abdominal pain. Foods high in Establish therapeutic relationship, reassurance, and education Establish IBS subtype/predominant bowel habit All management undertaken in the context of regular review IBS-constipation IBS-diarrhoea First-line pharmacology Antispasmodics Simple laxatives First-line pharmacology Antispasmodics

Loperamide Second-line pharmacology Linaclotide Low-dose SSRI* Second-line pharmacology Low-dose TCA* Consider ondansetron* For patients unresponsive to standard therapies consider: Referral to psychiatrist with expertise in managing IBS Psychological interventions such as hypnotherapy or cognitive behavioural therapy Antibiotics, probiotics Exercise Increase fluid intake Dietary advice Consider dietician referral for low-FODMAP diet Fig. 15.13.6 A suggested management approach for IBS.

15.13 Irritable bowel syndrome 2957 FODMAPs include fruits such as apples, peaches, and nectarines, lactose-containing substances, legumes, and artificial sweeteners such as those containing sorbitol (Fig. 15.13.7). A randomized con- trolled crossover trial reported that patients with IBS had a reduc- tion in bloating, abdominal pain, and flatus, with greater satisfaction with stool consistency, with a diet low in FODMAPs. Furthermore, a recent study has reported that dietitian-led FODMAP group educa- tion is clinically effective and may represent significant cost savings over individually administered advice. Pharmacotherapy Elucidation of optimum pharmacotherapy has proved difficult in IBS, not least due to a particularly high placebo response rate, which is approximately 40%. This means that to demonstrate the ef- ficacy of a novel compound, over and above the placebo response rate, the recruitment of large numbers of participants is necessary. Nevertheless, there are a variety of pharmacological options, which are included in most recent United Kingdom clinical guidelines, al- though the absolute evidence base for many of these is limited. Antispasmodic drugs Antispasmodic drugs largely compete with acetylcholine at post- ganglionic vagal nerve endings and therefore reduce the strength of smooth muscle contraction, reducing abdominal pain. A recent Cochrane database system review has highlighted cimetropium/ dicyclomine, peppermint oil, pinaverium, and trimebutine to be beneficial in reducing IBS symptoms (Table 15.13.1). Low-dose antidepressants Low-dose tricyclic antidepressants are recommended as second-line treatment for those patients in whom laxatives, loperamide, or anti- spasmodics have not reduced symptoms. The exact mechanisms by which they exert their analgesic effects within the viscera are yet to be completely understood, although they modulate both ascending Lactose Fructans/frutose FODMAPs Gas distension Osmotic effect Increased abdominal pain and distension Polyols Fig. 15.13.7 A schematic detailing the mechanism of action of foods that are high in FODMAPs on symptom production in IBS. Lactose (e.g. milk, yoghurt, custard, ice cream), fructans/fructose (e.g. apples, garlic, onions, wheat) and polyol (e.g. plums, peach, pear, watermelons) components of food are high in FODMAPs and cause a gaseous and osmotic distension effect. In patients with IBS, this can lead to increased abdominal pain and distension. Table 15.13.1 The relative risk of improvement in abdominal pain, global assessment, and symptom score using antispasmodics in patients with IBS IBS symptom Relative risk 95% confidence interval Numbers needed to treat Improvement in abdominal pain 1.32 1.12–1.55 7 Improvement in global assessment 1.49 1.25–1.77 5 Improvement in symptom score 1.86 1.26–2.76 3

section 15 Gastroenterological disorders 2958 visceral sensory afferents and central transmission, slow GI transit, and treat comorbid anxiety and depression. Tricyclic antidepres- sants reduce persisting IBS symptoms by an odds ratio of 0.68. It is important to present the rationale for using tricyclic antidepres- sants in patients with IBS and to communicate potential side effects including tiredness, dry mouth, and constipation. Considering that constipation is a side effect, it is recommended that amitriptyline be avoided in patients with IBS-C. Selective serotonin reuptake inhibitors are thought to select- ively block the presynaptic serotonin reuptake transporter, thereby

increasing the quantity of serotonin within the synaptic space. Citalopram has been shown to reduce abdominal pain in com- parison to placebo in IBS patients, an effect that was independent of drug-induced changes in anxiety and depression. Selective sero- tonin reuptake inhibitors can cause diarrhoea and are therefore gen- erally best avoided in patients with IBS-D. Psychological and psychiatric therapies In IBS, psychological treatments as a class of interventions per se are effective in reducing symptom burden and treating coexistent psychiatric pathology. Behavioural therapies, including cognitive behavioural therapy, dynamic psychotherapy, and hypnotherapy, all alleviate symptoms associated with IBS. For example, gut-focused hypnotherapy, whereby the aim is to reassure the patient regarding their symptoms with the aid of hypnosis, improves GI symptoms through cognitive changes and has been demonstrated to signifi- cantly improve abdominal pain and quality of life in a cohort of pa- tients with drug-refractory IBS. The role of the psychiatrist with an interest in functional GI disorders is a critical facet of management of IBS patients, and in particular those in whom symptoms are recalcitrant to standard therapies. In such patients, there may be coexistent psychiatric diag- noses that warrant expert evaluation and treatment. Manipulation of the microbiota Considering that the microbiota is a burgeoning area of research in the field, a considerable effort has been afforded to studying both probiotics and antibiotics. Although the quality of evidence for probiotics is limited, a large placebo-controlled trial of rifaximin, a nonabsorbable antibiotic, observed symptomatic improvement, al- though the numbers needed to treat were relatively high. Given con- cerns around antimicrobial resistance, further work is needed to stratify patients who may preferentially benefit from this intervention.

Management: specific types of irritable bowel syndrome Constipation predominant IBS In those with IBS-C, simple laxatives such as senna and docusate are often effective in managing symptoms, in addition to lifestyle measures. Lactulose is often poorly tolerated, due to worsening of bloating, and is therefore not advocated. Linaclotide is a minimally absorbed peptide guanylate cyclase-C agonist and recommended as second-line therapy in patients who have symptoms for longer than 12 months. Its mechanism of action is shown in Fig. 15.13.8a. Notably, linaclotide has an important ef- fect on colonic nociceptors, which is a central feature of IBS-C, and two randomized controlled trials have shown it to be effective in re- ducing abdominal pain, bloating, and constipation symptoms. The 5-hydroxytryptamine (serotonin) type 4 (5-HT4) agonists such as tegaserod have been demonstrated to be effective, although this particular compound was withdrawn due to an excess of cardio-vascular side effects in comparison to placebo. The results from trials of newer agents, such as prucalopride and naronapride, with a more favourable side-effect profile, are awaited. The mechanism of action of 5-HT4 agonists is shown in Fig. 15.13.8b. Linaclotide (a) (b) Lumen Increased 5-HT Enterochromaffin cells Mucosa Lumen 5-HT4 agonist Submucosal plexus Circular muscle Myenteric plexus Increased contractions and prokinetic effect Serosa Afferent pain fibres Enterocyte CFTR P GC-C + GTP cGMP PKGII + Fig. 15.13.8 Mechanism of action of guanylate cyclase-C (GC-C) agonists and 5-HT4 agonists. (a) Intraluminal linaclotide binds to the GC-C receptor stimulating the production of cyclic GMP (cGMP) leading to activation of protein kinase II (PKGII) and phosphorylation (P) of the cystic fibrosis transmembrane conductance regulator (CFTR) and secretion of chloride (Cl^-) and bicarbonate (HCO_3^-) into the lumen which is followed by sodium (Na^+) and water (H_2O). The overall effect is to increase/accelerate intestinal transit. cGMP also inhibits the afferent pain fibres leading to analgesia. (b) Circulatory 5-HT4 agonists activate 5-HT4 receptors on enterochromaffin cells within the GI tract causing direct activation of the enteric nervous system leading to increased frequency and strength of contractions within the circular muscle in the GI tract leading to a prokinetic effect.

15.13 Irritable bowel syndrome 2959 Diarrhoea-predominant IBS Loperamide exerts an antidiarrhoeal effect through the inhibition of peristalsis, leading to prolongation of gut transit time through its action as a mu (μ)-opioid receptor agonist. It does not cross the blood–brain barrier and is frequently used as a first-line agent in IBS-D. Although loperamide has no benefit on overall symptoms in IBS, it does reduce stool frequency and defecatory urgency and im- proves stool consistency. 5-HT3 receptor antagonists may be effective in the management of treatment IBS-D symptoms, given serotonin is a major mediator of afferent nerve signalling and prokinetic activity within the GI tract. Previously, the 5-HT3 receptor antagonist aldosterone was ap- proved for use as a second-line agent in IBS-D, although it has been withdrawn due to the rare complication of ischaemic colitis. Since this withdrawal other 5-HT3 receptor antagonists have been studied. A recent placebo-controlled crossover trial of ondansetron in 120 IBS-D patients has shown significant improvement in IBS symp- toms, including reduced urgency within 7 days of treatment. Given that ondansetron has a well-established safety profile from its use as an antiemetic agent for many years, these initial findings warrant further investigation. Conclusions and future directions IBS remains a prevalent, multifactorial, and enigmatic disorder. Its diagnosis relies on the identification of a characteristic symptom pattern coupled with the exclusion of other organic disorders. In reality, however, it is likely that IBS represents a number of distinct pathophysiological processes that culminate in identical clinical phenotypes. While the diverse management options available offer the potential to improve symptoms, further work is warranted on the individualization of therapeutic interventions. Nevertheless, despite the clinical burden of IBS, it remains a fruitful area of gastro- enterological practice and clinical research. The pharmacotherapeutic pipeline for IBS is a fruitful area of development with a number of novel compounds in active phase II and III development. In IBS-C, plecanatide, another guanylate cyclase-C agonist, and A3309, an ileal bile acid transporter inhibitor, are demonstrating promise in early-phase clinical trials. Phase III studies of eluxadoline, a locally active, mixed μ-opioid receptor agonist/delta (δ)-opioid receptor antagonist, have shown moderate efficacy in the treatment of IBS-D. FURTHER READING Canavan C, West J, Card T (2014). Review article: the economic im- pact of the irritable bowel syndrome. Aliment Pharmacol Ther, 40, 1023–34. Chang L, Lembo A, Sultan S (2014). American gastroenterological association institute technical review on the pharmacological management of irritable bowel syndrome. Gastroenterology, 147, 1149–72.e2. Chey WD, et al. (2012). Linaclotide for irritable bowel syndrome with constipation: a 26-week, randomized, double-blind, placebo- controlled trial to evaluate efficacy and safety. Am J Gastroenterol, 107, 1702–12. Ford AC, et al. (2009). Efficacy of antidepressants and psychological therapies in irritable bowel syndrome: systematic review and meta-analysis. Gut, 58, 367–78. Jeffery IB, et al. (2012). An irritable bowel syndrome subtype de- fined by species-specific alterations in faecal microbiota. Gut, 61, 997–1006. Mearin F, et al. (2016). Bowel Disorders. Gastroenterology, pii: S0016-5085(16)00222-5. doi: 10.1053/j.gastro.2016.02.031. Simren M, et al. (2013). Intestinal microbiota in functional bowel disorders: a Rome foundation report. Gut, 62, 159–76.

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