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REVIEWS IN BASIC AND CLINICAL GASTROENTEROLOGY

Challenges to the Therapeutic Pipeline for Irritable Bowel Syndrome: End Points and Regulatory Hurdles

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Recent advances in our understanding of basic neuroenteric mechanisms and the role of effectors and transmitters in the brain-gut axis have provided opportunities to develop new therapeutic agents for irritable bowel syndrome (IBS). Furthermore, human pharmacodynamic studies utilizing transit, colonic, or rectal sensitivity and brain imaging have been useful in determining therapeutic efficacy (particularly for drugs that act on motor function). This review provides an overview of medications that have not yet been approved for treatment of patients with IBS yet have shown promise in phase IIB trials. These include drugs that act on the serotonin receptor and transporter system: antidepressants, norepinephrine reuptake inhibitors, opioids, cholecystokinin antagonists, neurokinin-antagonists, chloride channel activators, guanylate cyclase C agonists, atypical benzodiazepines, probiotics, and antibiotics. The changing landscape in the regulatory approval process has impacted the development of IBS drugs. Guidance documents from regulatory agencies in Europe and the United States have focused on patients' reported outcomes and associated quality of life. After a decade of experience with different end points that have generated some data on psychometric validation and unprecedented information about responsiveness of the binary or global end points to drug therapy, it is necessary to pursue further validation studies before or during pivotal phase IIB or III trials. The hope of providing relief to patients should galvanize all parties to achieve these goals.

Irritable bowel syndrome (IBS) involves a broad range of physiologic and psychologic alterations that affect brain-gut dysregulation, gut function, visceral perception, and mucosal integrity and function. In the absence of a reliable biologic marker of IBS, it has been challeng-

our understanding of basic neuroenteric mechanisms and the role of effectors and transmitters in the brain-gut axis, the pipeline of drugs for IBS and lower functional gastrointestinal (GI) disorders (Table 1), and relevant pharmacodynamics end points to predict proof of efficacy, the changing landscape in the regulatory approval process, particularly the expectations of IBS trial end points, have impacted the development of IBS drugs. This review addresses 3 main topics: the pipeline for IBS and lower functional GI disorders, approaches to the development of medications for IBS, and IBS trial end points and insights into regulatory affairs.

What Therapeutic Agents Are in the Pipeline for IBS?

There are a number of novel agents with different mechanisms of action that are in various stages of development. Several of the drugs in development that are in ongoing or planned clinical trials for IBS are presented in Table 1. The rationale, putative action, pharmacodynamics, and results in clinical trials[1–90] are summarized in Table 2.

Appraisal of Drugs That Affect GI Motility, Sensation, Secretion, or Central Actions

Although there is a greater understanding of the basic neuroenteric mechanisms and the role of effectors and transmitters within the brain-gut axis, which provide opportunities for development of new therapeutic agents in IBS, there are still significant conceptual and practical barriers. IBS is a complex multifactorial disorder with distinct but often interrelated pathophysiologies. These

Abbreviations used in this paper: 5-HT, serotonin; IBS, irritable bowel syndrome; IBS-C, irritable bowel syndrome with predominant constipation; IBS-D, irritable bowel syndrome with predominant diarrhea.

Table 1. Drugs in Development for IBS in Open or Planned and Classified by Phase I to III Clinical Trials

Drug/agent in development	Mechanism	IBS patients	Phase
SSR241586	NK2/NK3 antagonist	IBS	I
SAR102779	NK2/NK3 antagonist	IBS	I
Octreotide	Somatostatin analog	Women only	I
Guanilib (SP304)	Guanylate cyclase-C agonist	IBS-C	I
RR210	5-HT_3 partial agonist	IBS	I
BMS 562086	CRF-1 antagonist	IBS	I
GW876008	CRF-1 antagonist	Women only	I/II
LX1031	Tryptophan hydroxylase inhibitor	IBS	I/II*
Dextofisopam	2,3-Benzodiazepine agonist	IBS	II
Citalopram	Selective serotonin reuptake inhibitor	IBS	II
AST 120 (kremezin)	Adsorbs bile acids and bacterial toxins	Non-IBS-C	II
Traditional Chinese medicine	Herbal medicine	IBS	II
AGN 203818	Alpha 2B agonist	Pain predominant IBS	II
VSL#3	Probiotic combination	IBS-D	II
Flora-Q	Probiotic	IBS-D	II
Lactobacillus farciminis	Probiotic	IBS-D	II
Tianeptine	Enhances serotonin reuptake	IBS	II
DDP733	Partial 5-HT_3 agonist	IBS	II
DDP225	Serotonin and noradrenaline reuptake inhibitor	IBS-D	II
Mesalamine	5-Aminosalicylate	PI-IBS	II
Ibaconda (olsalazine/colchicine)	5-aminosalicylate/intestinal secretion	IBS-C	II
Gastrafate IB (sucralfate)	Sucrose sulfate-aluminum salt: cytoprotection	All subtypes	II/III
Arverapamil	Enantiomer of verapamil; calcium channel blocker; 5-HT_2b and melatonin (MT1) binding	IBS-D	III
Linaclotide	Guanylate cyclase-C agonist	IBS-C	III
Rifaximin	Antibiotic	IBS-D	III
Saccharomyces boulardii	Probiotic	IBS-D	III

CRF, corticotropin releasing factor; NK, neurokinin.

pathophysiologic processes and associated symptom phenotypes can change within an individual over time. Furthermore, several putative mechanisms may control the pathophysiologic processes that might underlie the generation of symptoms. Although a significant number of IBS patients report meal-related symptoms, the interaction of food and intraluminal content with secretory, motor, and sensory mechanisms in IBS is poorly understood. The approach to development of medications for IBS has been based on specificity of targets, analogous to that of, for example, hypertension. The difference is that, whereas hypertension is dominated by the biology of vascular tone, IBS does not have a dominant mechanistic pathway to symptom generation. Moreover, there are single targets that appear to regulate multiple functions, including gut motor function and sensitivity in animal models, such as specific serotonergic (5-HT) receptor subtypes. However, despite the apparent relevance of such targets, efficacy and safety are not always clearly demonstrable in the IBS patient population. As a result of the approach based on targeting specific receptors in a disease that does not have a malfunction of a single receptor or transmitter deficiency, approaches that target one receptor or pathophysiologic mechanism cannot be expected to affect the broad spectrum of patients. Thus, approaches directed at changing motor function could

nent of bloating and pain might be left unattended. Antiinflammatory approaches that have been investigated in small trials, even in those that include many patients with postinfectious IBS, have been disappointing. Therefore, multitargeted approaches are often used in clinical management, particularly in patients with moderate to severe IBS. Centrally acting agents appear to be promising because they might correct disturbances in the brain-gut axis. However, their efficacy has generally been limited in clinical trials, and many patients prefer to avoid taking "mind-altering" medications for symptoms that disturb their quality of life but are not life-threatening. The risk-benefit ratio of any new medication for IBS is clearly a determining factor in the approval and marketing of such compounds. It is understandable, therefore, that approaches with probiotics and antibiotics have reached a level of acceptance in practice that exceeds the available evidence of efficacy in support of their use.

Some of the challenges are, in our current state of knowledge, not easily resolved. Given the high prevalence and disease burden associated with IBS, there needs to be continued and vigorous basic and translational research in the field, rigorous pharmacologic assessment of candidate drugs, or other therapies using validated biomarkers and relevant clinical end points. It is also important

Table 2. Summary of Rationale, Mechanisms, and Efficacy of Medications in Pipeline for IBS

Drug class	Examples	Rationale or putative action	Pharmacodynamic (intestine or colon)	Clinical efficacy: phase IIB or III primary end points	Safety issues/comments	Reference No.
5-HT_3-agonist	DDP-733	Stimulate intrinsic cholinergic neurons to enhance motility	4-mg dose delayed fasting migrating motor complexes, accelerated small intestinal transit, and induced softer stools or diarrhea in 15% of subjects	IIB, dose-ranging study in 91 IBS-C patients: 1.4-mg dose associated with significantly greater proportion of responders (subject global assessment of relief)	No known vascular effects	1, 2
5-HT_4-agonists	Prucalopride	Stimulate intrinsic cholinergic neurons to enhance motility	Increases SB, colon motility and transit in healthy controls and patients with chronic constipation	IIB and III in CC (thousands of patients): BM frequency and satisfaction with bowel function both improved	Greater selectivity for 5-HT_4 than 5-HT_{1B} or hERG channel	3–10
	ATI-7505	Stimulate intrinsic cholinergic neurons to enhance motility	Increases colon transit in healthy controls	None reported	Greater selectivity for 5-HT_4; not metabolized by CTP 3A4	11
	TD-5108	Stimulate intrinsic cholinergic neurons to enhance motility	Dose-related increase in SB and colon transit in healthy controls	IIB, dose-ranging study in 401 CC patients increased BM frequency and proportion with adequate relief	Greater selectivity for 5-HT_4	12–14
NARI and 5-HT_3-antagonist	DDP-225	May increase synaptic levels of norepinephrine to reduce visceral pain; inhibit intrinsic cholinergic neurons	Uninterpretable	IIB, dose-ranging study in 87 IBS patients increased proportion with adequate relief	No constipation reports suggest low expectation for 5-HT_3 antagonist activity	15
Antidepressants		May reduce visceral sensation and relieve depression associated with IBS	SSRIs, fluoxetine and paroxetine, and TCA, amitryptiline, do not reduce visceral sensitivity, in contrast to the SNRI, venlafaxine; SSRI accelerates and TCA slows SB transit	Small studies with SSRI or TCA equivocal; large study had no significant benefit of desipramine over placebo in ITT analysis, but did in per-protocol analysis (completed treatment)	Side effects common with TCA. Post hoc analysis for desipramine showed benefit in those with moderate symptoms, abuse, no depression, and IBS-D	16–28
κ-opioid agonist	Asimadoline	κ-opioid receptors in visceral perception	Reduce sensation in response to colon distentions in the nonnoxious range; relax colon tone in healthy controls; increase sensory thresholds in patients with IBS	On-demand dosing not effective in reducing severity of abdominal pain in 100 IBS patients; IIB, dose-ranging study, 596 IBS patients: at least average moderate pain benefit in IBS-D and IBS-A		33–36
2,3-Benzodiazepine modulator	Dextofisopam	Potential to reduce stimulation-induced colonic motility and visceral sensitivity	None reported	IIB study in 140 IBS patients: increased number of months of adequate overall relief of IBS symptoms; efficacy lower over time	Possibly more events of worsening abdominal pain; headaches were more frequent with placebo	37, 38
CCK_1 antagonist	Dexloxiglumide	Competitive antagonist of the CCK_1-receptor	Slower ascending colon emptying with no significant effect on overall colonic transit	Two initial IIB or III trials: not efficacious in IBS-C; a randomized withdrawal design trial showed longer time to loss of therapeutic response, longer for dexloxiglumide		45–50
NK antagonists	NK_1 antagonist, ezlozipant	NK_1-receptors' role in nociception	Reduce the emotional response of IBS patients to rectosigmoid distention	None		51–53
	NK_2-antagonist, nepadutant	NK_2-receptors' influence on smooth muscle contractility	Reduce contraction frequency and amplitude on MMC in SB in healthy males	None		51, 52, 54, 57
	NK_3-antagonist, talnetant	NK_3-receptors' role in nociception	No effect on rectal compliance, sensory thresholds, or intensity ratings in healthy controls	Two IIB trials in 1350 IBS patients: no benefit		58, 59
Cl-C2 channel activator	Lubiprostone	Increases intestinal water and electrolyte secretion	Accelerates SB and colonic transit in healthy controls	Two phase III in several hundred CC and IBS-C patients: efficacious	Nausea that is usually mild; FDA approved	62–67
Guanylate cyclase-C agonist	Linaclotide	Increases intestinal water and electrolyte secretion	Accelerated ascending colonic transit and altered bowel function in 36 women with IBS-C	IIA and IIB studies in CC or IBS: increased BM frequency		73–75
Probiotics	Several, eg, *Bifidobacteria*, *Lactobacillus*, *Saccharomyces* species, or combinations	Potential mechanisms: immune, barrier, fermentation	Slow colonic transit in IBS-D	Several IIB studies: efficacy in overall IBS and single symptoms, eg, flatulence, pain		76–84
Antibiotics	Neomycin, metronidazole, rifaximin	Changes in gut microflora may be present in IBS	No consistent reduction in breath hydrogen excretion after lactulose load in those with symptom relief	IIB trials of various sizes: efficacy for global symptoms in some, gas and bloating in others		85–90

BM, bowel movements; CC, chronic constipation; Cl-C2, chloride channel type 2; IBS, irritable bowel syndrome; ITT, intention to treat; MMC, migrating motor complexes; NARI, norepinephrine reuptake inhibitor; NK, neurokinin; SB, small bowel; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin and norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant.

addressed with a multicomponent approach. This has to be coupled with awareness of safety signals in drug development programs in IBS. For almost all of the drug classes described here (Table 2), rigorous phase III trials are still awaited.

Approaches to Proof of Concept for Novel IBS Drugs

There are at least 3 different approaches to determining the efficacy of new treatments of IBS. The traditional path is based on *identifying the molecular targets* in animal models that are thought to mediate the human phenotype, such as visceral hyperalgesia and rapid gut transit.[91] If a candidate drug has been shown to be effective in preclinical studies, and it is safe in phase I trials in humans, it is moved into trials in healthy human subjects and subsequently in patients with IBS during different phases of clinical trials.

Other approaches occur at later stages of drug development. For example, a drug in development or one that is already *approved for another condition that has an associated effect on GI function or symptoms* can be tested in patients with IBS. For example, if a drug has been found to be effective in treating patients with constipation, it could be further investigated as a treatment for patients with IBS with constipation. It is also possible to assess the efficacy of a drug that is used to treat *a condition* that commonly *coexists with IBS* and/or is thought to have shared pathophysiology, such as fibromyalgia, anxiety, or depression. Examples of these agents include selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors.

An alternative approach to drug discovery and development is pharmacologic brain imaging in animal models and humans.[91] Brain responses can reflect global IBS symptoms; this approach to drug development is the subject of ongoing study.

The Drug Development Path

Before regulatory approval, candidate drugs move through a long and complex development path that includes toxicology, toxicokinetics, pharmacokinetics, and in vivo efficacy testing in animals as well as 3 phases of clinical trials. Phase I trials are dose-ranging studies designed to measure the safety, tolerability, pharmacokinetics, and pharmacodynamics of a test drug. If the drug is found to be safe and tolerable in phase I trials, phase II studies are then conducted in relatively larger numbers of subjects. Phase IIA trials are designed to assess the dosing in patients and serve as proof-of-concept studies. In phase IIB trials, the efficacy of the drug is determined at specific prescribed doses. Definitive evaluation of efficacy is determined in phase III studies, which are multicenter, randomized, controlled trials in large numbers of patients

efficacy in IBS. This is a vestige of the belief that IBS is a disorder of function with no valid biologic marker. However, evidence with physiologic (eg, transit), biochemical (eg, serum or other markers of immune activation), and even pharmacogenetic modulation suggests that there is a need to reassess the optimal drug development path.

Current Considerations in Study Design

IBS has no "gold standard" of treatment, so candidate drugs are usually compared with placebo. The study protocol specifies all end points that will be measured, including each domain score that is targeted to support a specific claim.[92] Drug approval by regulatory agencies is based on achieving the primary end point in phase III trials.

The Rome III guideline on design of trials for functional GI disorders recommended the use of validated instruments as primary outcome assessment tools in IBS clinical trials.[93] Secondary end points in clinical trials support or explain the results of the primary outcome analysis (particularly if a global end point or composite score is used). Improvements in secondary end points can help to characterize the response to a global end point because they represent the multiple manifestations of the global or multidomain measure.[94] Primary end points have been described as what is of interest to patients, whereas secondary variables are generally of interest to clinical researchers.[95]

In the Patient-Reported Outcome (PRO) Guidance Document, released in 2006, the US Food and Drug Administration (FDA) mandated that outcome measures for clinical studies be validated.[92] The process for developing a new PRO instrument or modifying an existing instrument is shown in Figure 1. The starting point in developing a valid and meaningful outcome measure is to establish a conceptual framework (ie, a path diagram) for IBS. This framework can be developed using patient-reported information to characterize the full disease experience, factors related to severity, impact on daily activities, and treatment response. In addition, published studies in well-characterized IBS patients that have addressed disease mechanisms or treatment response can help establish a multidimensional conceptual framework. It is recommended that this framework guide the development and measurement of valid, reliable, and reproducible patient reported end points and objective biomarkers. This is followed by creation or modification of the instrument including the generation of items; choice of the data collection method; choice of the recall period; choice of response options (eg, visual analog scale, Likert scale, numeric rating scale, checklist of binary end points); assessment that patients understand the instrument; development of format, instructions, and training of those collecting the instrument data; identi-

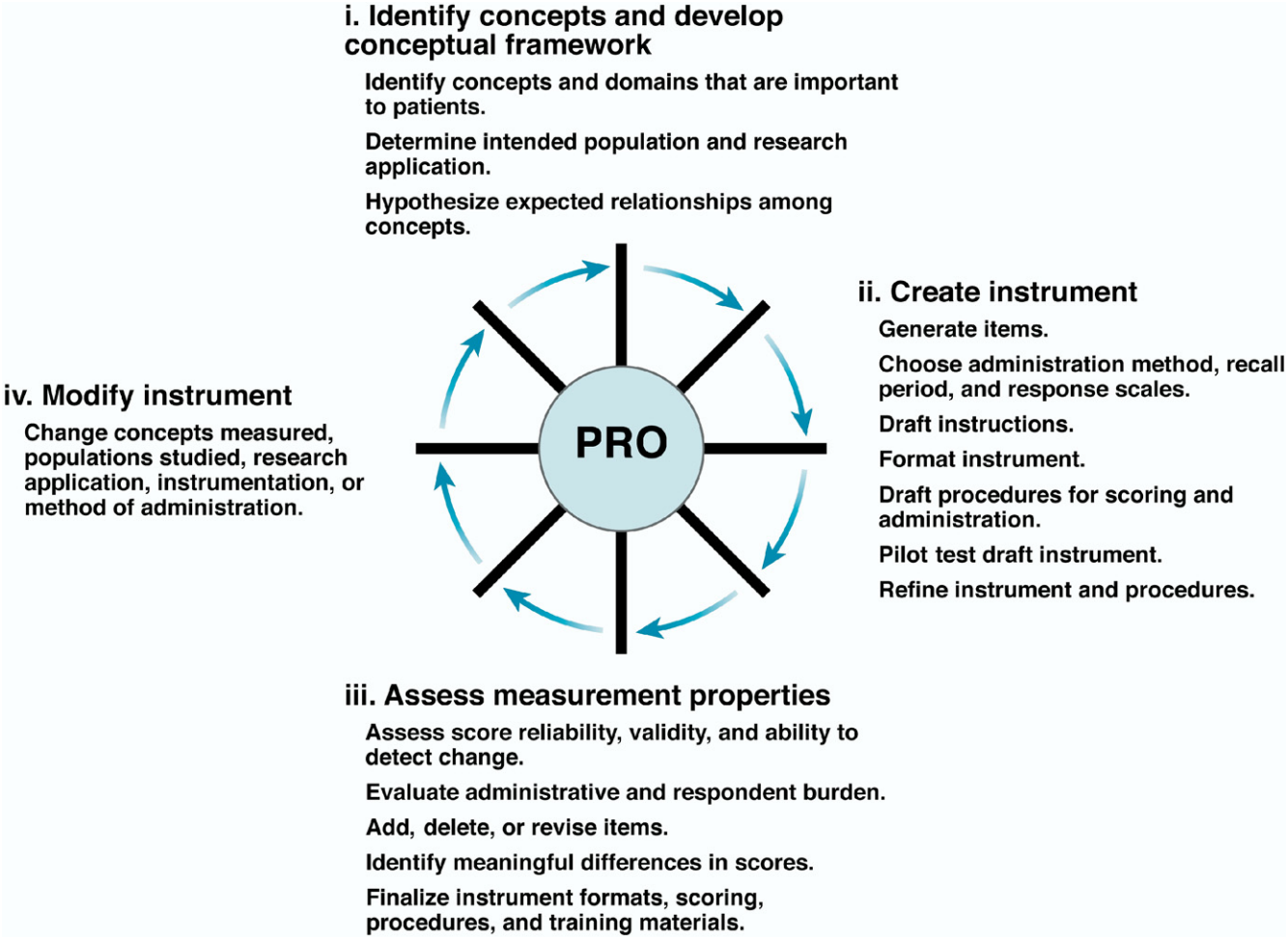

Figure 1. The process recommended by the PRO guidance document for developing of new or for modifying existing instruments for clinical trials (reproduced from US Department of Health and Human Services FDA Center for Drug Evaluation and Research; US Department of Health and Human Services FDA Center for Biologics Evaluation and Research; US Department of Health and Human Services FDA Center for Devices and Radiological Health[92]).

Biomarkers Used in IBS Treatment Studies and Their Validity

A number of physiologic outcome measures to assess treatment responses have been studied in IBS. These include measures of visceral perception (eg, rectal or colonic pain thresholds and perceptual ratings) and intestinal transit (eg, orocecal and colonic transit times). A recent review of the literature determined that the correlations between biomarkers obtained in preclinical and clinical models and respective symptoms are relatively small, and the ability to predict drug effectiveness for specific as well as for global IBS symptoms is limited.[91] On the other hand, colonic transit measurements correctly predict the effects of agents on bowel function and are generally associated with global, binary end points such as adequate or satisfactory relief of IBS pain and discomfort in patients with constipation- or diarrhea-predominant IBS.[96,97]

related to motility and secretion. Colonic transit time has been shown to correlate with stool form, as measured by the Bristol Stool Form Scale.[98] It can be measured by different techniques including radiopaque markers[99,100] and breath hydrogen tests.[101]

However, the most robust and consistent results for detailed GI transit measurements have been reported with scintigraphy, which allows for regional transit assessments. Colonic transit is accelerated in IBS-diarrhea (IBS-D) predominant patients, compared with healthy individuals, and those with IBS-constipation (IBS-C) predominant range from normal to slow transit times.[102] Approximately 35% of patients with IBS have abnormal overall colonic transit, including 48% of those with IBS-D.

The effect of medications that affect GI transit time has been studied in patients with IBS. These include bulking agents,[103,104] cimetropium bromide,[105] imipramine,[101] alosetron,[106,107] tegaserod,[108] renzapride,[109,110]

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