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

Michael Camilleri, M.D. and Lin Chang, M.D.*

Clinical Enteric Neuroscience Translational and Epidemiological Research (CENTER), Mayo Clinic, Rochester, MN 55905

* *Center for Neurobiology of Stress, David Geffen School of Medicine at UCLA, VAGLAHS Los Angeles, CA 90073*

Abstract

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 endpoints that have generated some data on psychometric validation and unprecedented information about responsiveness of the binary or global endpoints 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.

Keywords

irritable bowel syndrome; patient reported outcomes; treatment

Corresponding author: Michael Camilleri, M.D., Mayo Clinic, Charlton 8-110, 200 First Street S.W., Rochester, MN 55905, Email: E-mail: camilleri.michael@mayo.edu.

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INTRODUCTION

Irritable bowel syndrome (IBS) involves a broad range of physiological and psychological 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 challenging to develop well-targeted, effective IBS drugs and optimal endpoints for clinical trials. Despite advances in 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 disorders (Table I), and relevant pharmacodynamics endpoints to predict proof of efficacy, the changing landscape in the regulatory approval process, particularly the expectations of IBS trial endpoints, have impacted the development of IBS drugs. This review addresses three main topics: the pipeline for IBS and lower functional gastrointestinal disorders; approaches to the development of medications for IBS; and IBS trial endpoints 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 I. The rationale, putative action, pharmacodynamics and results in clinical trials (1–90) are summarized in Table II.

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

While there is a greater understanding of 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 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. Yet, 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 alleviate bowel dysfunction or induction of intestinal secretion might alleviate constipation, but the component of bloating and pain might be left unattended. Anti-inflammatory approaches that have been investigated in small trials, even in those that include many patients with post-infectious 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 disturbance in brain-gut axis. However, their efficacy has generally been disappointing 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 pharmacological assessment of candidate drugs or other therapies using validated biomarkers and relevant clinical endpoints. It is also important to recognize that multiple, complex, and dynamic pathophysiologic processes that underlie IBS might be best 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 II), rigorous phase III trials are still awaited.

APPROACHES TO PROOF OF CONCEPT FOR NOVEL IBS DRUGS

There are at least three 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 test article has been shown to be effective in pre-clinical 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 gastrointestinal (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 (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs).

An alternative approach to drug discovery and development is pharmacological 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 three 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 it 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. To date, few studies have collected biological samples (or other measurements) for ancillary evaluations of efficacy in IBS. This is a vestige of the belief that IBS is a disorder of function with no valid biological marker. However, evidence with physiological (e.g., transit), biochemical (e.g., 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 to placebo. The study protocol specifies all endpoints 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 endpoint 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 endpoints in clinical trials support or explain the results of the primary outcome analysis (particularly if a global endpoint or composite score is used). Improvements in secondary endpoints can help to characterize the response to a global endpoint since they represent the multiple manifestations of the global or multidomain measure (94). Primary endpoints 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 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 (i.e., 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 multi-dimensional conceptual framework. It is recommended that this framework guide the development and measurement of valid, reliable, and reproducible patient reported endpoints 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 (e.g., visual analog scale, Likert scale, numeric rating scale, checklist of binary endpoints), assessment that patients understand the instrument, development of format, instructions and training of those collecting the instrument data, identification of scoring of items and domains, and assessment of respondent and administrator burden.

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 (e.g., rectal or colonic pain thresholds and perceptual ratings) and intestinal transit (e.g., 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 endpoints such as adequate or satisfactory relief of IBS pain and discomfort in patients with constipation or diarrhea-predominant IBS (96,97).

Gastrointestinal (GI) and colonic transit—Transit is a clinically relevant and noninvasive measure of GI function, primarily 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-D, compared to healthy individuals, and those with IBS-C range from normal to slow transit times (102). About 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), the guanylate cyclase-C agonist, linaclotide (73), and the probiotic combination, VSL#3 (80). Correlations between effects of medications on regional or total colonic transit and stool number or stool form have been shown for a number of drugs, including 5-HT₄ agonists such as prucalopride (6) and tegaserod (108), the combined 5HT₄ agonist-5HT₃ antagonist, renzapride (109), the guanylate cyclase-C agonist, linaclotide (73), and the chloride channel activator, lubiprostone (63).

Importantly, the results from phase IB or IIA studies using scintigraphic colonic transit have correctly predicted efficacy of treatments in phase IIB or phase III studies in IBS with the following medications: alosetron, tegaserod, prucalopride, renzapride, linaclotide, and lubiprostone. For example, the efficacy of lubiprostone (63) in improving colonic transit and stool form in pharmacodynamic studies in healthy volunteers accurately predicted clinical efficacy in patients with IBS-C (66). At present, the only discrepancy between results of scintigraphic transit (111) and phase IIB clinical trial data pertains to the drug, solabegron (preliminary data, in press); results of larger phase II trials are eagerly awaited. Nonetheless, GI transit assessment can be a useful biomarker for predicting the effects of a test article on bowel habits and overall response in patients with IBS.

Visceral hypersensitivity—Twenty to 94% of IBS patients are more sensitive than healthy individuals to balloon distension of the colon or rectum via barostat, a computerized distension device used to measure viscus compliance, tone and perception (91). Variability in the prevalence of visceral hypersensitivity across IBS patients (reviewed in reference 102) suggests that level of rectal sensitivity is not a biological marker of IBS, as was previously claimed (112). A number of factors affect visceral perception: gender (113), predominance of bowel dysfunction (114,115), psychological factors (116,117), and specifics of the experimental study protocol, such as inclusion of data on stress (118,119) or food ingestion (120,121). Whereas levels of pain and bloating have high correlation values with measures of visceral hypersensitivity (122), perceptual thresholds and ratings have only moderate correlation values with IBS symptom severity or response to treatment (91). It is possible that, with more effective visceral analgesics, testing of visceral sensitivity would have utility similar to that of transit measurement in predicting efficacy of drugs affecting intestinal transit.

Barostat testing has been used in patients with IBS to measure the changes in visceral sensitivity to opiates, serotonergic agents and antidepressants. Small crossover studies support the validity of the barostat test as a valid human experimental model for visceral pain, especially with the μ -opioid agonist, fentanyl, and to a lesser extent the κ -opioid agonist, fedotozine (29,32). However, visceral barostat testing might not predict the effect of a candidate drug on IBS symptoms (17,91). The barostat studies that correctly identified clinical efficacy of candidate drugs with alosetron utilized brain imaging (123).

Brain imaging—Neuroimaging techniques such as positron emission tomography (PET) or functional magnetic resonance imaging (fMRI) show that brain activation patterns elicited in anticipation of a noxious distension and/or actual intestinal distension are different in IBS patients than controls (112,124–126). The mechanisms proposed to explain an altered brain response in patients with IBS are unclear, but may include increased signaling from the gut or

amplification of a normal signal during transmission from the gut or in the brain (127). Brain activation patterns can be influenced by gender (128,129), bowel function (130), psychological symptoms (131), and adaptation to experimental conditions over time (132).

There are limited data evaluating brain activation responses to efficacious IBS treatments. In a $H_2^{15}O$ PET study performed in nonconstipated IBS patients, 3 weeks of treatment with the 5-HT₃ antagonist, alosetron, improved IBS symptoms and was associated with reduced regional cerebral blood flow (rCBF) in limbic, paralimbic regions and central autonomic circuits (which contain 5-HT₃ receptors), particularly during anticipation of distension (123). In the alosetron-treated patients, lower activity in bilateral orbitofrontal cortex and medial temporal gyrus during pretreatment scans suggested changes in rCBF and psychological symptoms predicted treatment response (123,133).

In a fMRI study (134) conducted in 19 women with painful IBS, amitriptyline was associated with decreased activation in the rostral anterior cingulate cortex (ACC) and the left posterior parietal cortex during the combined rectal distension and psychological stress but not during the relaxation condition. There was no reported association of brain responses with symptom ratings in this small study. Lackner et al. (135) measured brain responses using $H_2^{15}O$ PET in 6 women with IBS before and after treatment with cognitive behavioral therapy and found a reduction in rCBF in the parahippocampal gyrus and the ventral portion of the ACC. These reductions correlated with improvement in GI symptoms and psychological functioning. Thus, IBS treatments exert beneficial effects via brain regions concerned with pain modulation and autonomic responses; neuroimaging is a promising modality for proof-of-concept studies.

An average of 50% of patients with IBS experience abnormal visceral hypersensitivity or abnormal transit, and approximately 20% have evidence of both pathophysiologies (102). Further research in central processing and its modulation with therapy is necessary to provide alternative therapies for IBS.

IBS TRIAL ENDPOINTS AND REGULATORY INSIGHTS

Almost a decade ago, the path to successful development of therapeutics for IBS seemed fairly clear: appropriate trial design, clear pharmacological efficacy, safety, and use of binary endpoints that assessed the global effects of medications or a global improvement scale (54). Academics, clinical trial designers, biostatisticians, and the FDA had agreed on this path; there was a significant pipeline of medications with potential for treating patients with IBS and other bowel dysfunction.

With the withdrawal of cisapride, alosetron and tegaserod, and lack of approval of cilansetron for alleged safety concerns, the risk-benefit ratio of new drugs for IBS was reexamined, and the psychometric validation of endpoints used in previous clinical trials was questioned. The need for psychometric validation of patient response outcomes has been increasingly emphasized by regulatory agencies to be consistent with standards set for other disorders characterized predominantly by patient responses rather than objective biomarkers. It is assumed that application of principles and validation of endpoints used in chronic pain, fibromyalgia, or cancer pain will prove effective in IBS. The clinical trial experience and responsiveness observed in almost 20,000 IBS patients with at least five different medications (alosetron, cilansetron, tegaserod, lubiprostone, dextofisopam) tested with binary or global improvement endpoints have been devalued on the grounds that some aspects of psychometric validation are not available.

What Endpoints Were Used in Clinical Trials in the Past Decade?

Table III (28,35,38,66,67,136–158,160) summarizes endpoints used in clinical trials involving at least 100 patients with IBS. There is compelling evidence in favor of the binary or global endpoints used in the past 10 years and involving 20,000 people studied with five different drugs. First, these trials showed that the endpoints are responsive: a meta-analysis of 6000 patients in clinical trials of 5-HT₃ antagonists with several different outcomes/endpoints showed that global endpoints can document responsiveness to this class of medication (97). Second, participants in trials were able to relate the level of relief to the level of their symptoms, determined at baseline, and provided consistent responses. In the trial of alosetron, 80% of patients reported consistent responses in subsequent weeks. Third, the performance measures (validity and reliability) were independently assessed and found to be acceptable; binary or global response endpoints (159) and global improvement scale (160), and responses were typically driven by the patients' most bothersome symptoms (159).

A review of the validation of the diverse endpoints (Table IV) on the basis of 12 prespecified criteria concluded that the weight of evidence is in favor of adequate relief (161), confirmed by an independent group (162). The 7-point Likert global improvement scale (GIS) has also been validated for clinical, satisfaction, and productivity significance (160), and responsiveness of GIS in several trials with alosetron and cilansetron has been reviewed (97). Fourth, drugs that are effective, based on the binary or global response endpoints, were also found to improve general or disease-specific quality of life (163).

The Rome III guidance on clinical trials (93) has endorsed use of a global measure that integrates the symptom data into a single numerical index, "alternative outcome measures such as integrative symptom questionnaires" and an IBS Symptom Severity Scale [IBS-SSS (164)]. This scale was described as the only IBS symptom severity scale "shown to be responsive to treatment effects", even though the last claim pertained to non-pharmacological trials (e.g., hypnotherapy). The IBS-SSS measures pain, distension, an overall gestalt of interference with life, and bowel "dissatisfaction"; the latter has been shown by focus groups to be an unclear term.

Another severity scale, the Functional Bowel Disorder Severity Index [FBDSI (165)], includes only current and chronic pain and the number of doctor visits during the past 6 months; however, data on the number of doctor visits are not relevant in a structured clinical trial, and the 6-month period of appraisal does not allow for changes or measurement of treatment response during short periods of time (166).

In contrast, one observational study of usual care in an HMO setting that compared satisfactory relief with the IBS-SSS found that the performance of a satisfactory relief endpoint was significantly influenced by baseline symptom severity (167). The generalizability of these observations has therefore been questioned because clinical trials assess specific interventions rather than usual care, the clinical-trial population can differ from a managed-care population, and patients with mild symptoms are less likely to meet screening criteria and be included in a clinical trial. The concern (167) that baseline severity compromises the performance of a dichotomous endpoint, such as satisfactory relief, does not appear to affect the current design of clinical trials. For example, trials with alosetron and dextofisopam (38,168) and one involving behavioral treatment (169) have not confirmed the impact of baseline severity on the performance of adequate relief as a trial endpoint.

Regulatory Guidance on Endpoints in IBS Clinical Trials: Should the Focus Be on Pain?

A regulatory agency in Europe has specifically addressed the issue of endpoints for IBS trials (170); a more general guidance document from the FDA (the PRO) describes development of

endpoints that involve patient response outcomes (92). However, academic clinicians from Europe responded to the publication of the European guidance document with a scholarly critique (171) and endorsed global assessments as endpoints, rather than focusing on pain.

Appropriate psychometric validation of all PROs is essential but not necessarily sufficient for utility as an endpoint in IBS. All endpoints must also be “conceptually sound, reliable and valid measures, incorporated into well-designed clinical trials with interpretable findings, and include the “right concepts” (172). It is unclear whether psychometrically validated PROs borrowed from other fields, such as pain syndromes or cancer, are pertinent to IBS or what the minimally important difference (MID) is for any endpoint in IBS, based on PRO guidance.

After extensive research on the visceral pain component in IBS, some researchers consider IBS to be a pain syndrome, and regulatory agencies have advised development of clinical trials that use pain level as an endpoint, measured with instruments that have validated psychometric properties. For example, the Brief Pain Inventory (BPI) could be used to measure pain level; this instrument was originally developed to measure cancer-related chronic pain (173) and was subsequently validated for nonmalignant chronic pain (174). However, no information has been published regarding the performance, validation or MID data obtained using the BPI in patients with IBS. Clinicians recognize that the pain of IBS is linked to bowel dysfunction or motor pathophysiology (39,102,175). Typical pain in IBS-D is described as colicky, propagates around the periphery of the abdomen over the colon, precedes the bowel movement (BM), and is relieved after the passage of the BM. Alternatively, patients with IBS-C report a sense of chronic distension, discomfort and bloating, and absence of the colicky propagated pain described above. IBS pain is linked with bowel function or dysfunction, whereas chronic pain syndromes are typically unrelated to bodily functions. IBS is not chronic functional abdominal pain (FAP), which is unrelated to bowel function, and might be conceptually closer to chronic pain syndromes like fibromyalgia or chronic back or temporomandibular joint pain. For chronic FAP, it is reasonable to consider a recent consensus statement on interpreting the clinical importance of treatment outcomes in chronic pain clinical trials [IMMPACT (176)] with specific outcome measures for four core chronic pain outcome domains: pain intensity, physical functioning, emotional functioning, and participant ratings of overall improvement.

Given the regulatory agencies’ focus on pain, it is also worth noting the Rome definition of discomfort in IBS: “Discomfort means an uncomfortable sensation not described as pain” (177), suggesting a continuum between discomfort and pain (178). Symptoms of “pain” and “discomfort” were interpreted to be two distinct symptoms by 14 of 16 participants with IBS-C in a focus group (159); this finding raises questions about the combined assessment of these symptoms in patients with IBS (177).

A preliminary report (179) of an ongoing study conducted in a longitudinal IBS registry from eight geographically diverse U.S. centers developed a single item numeric rating scale for *overall severity* during the *past week*: from 0 (no symptoms) to 20 (the most intense symptoms imaginable). Data from 170 patients (79% female) collected at baseline and from 64 patients 3 months later showed correlations between this single numeric rating scale and bowel symptoms, severity indices, quality of life and worker productivity, absenteeism and presenteeism, with R-values ranging from 0.18 to 0.47. The correlation coefficient of the single numeric rating scale and IBS-SSS was 0.65. The MID was identified to be 4 ± 5 points. In a study of 755 patients with IBS, performed at a single center, predictors of severity included pain, the belief that something was seriously wrong with the body, straining with defecation, urgency with defecation, myalgias and bloating (180). Therefore, the domain of bowel dysfunction is integral and relevant to symptoms of IBS patients. Further clinical studies are required to determine responsiveness and the level of correlation between specific symptoms

and secondary endpoints, to ensure that this single numeric rating scale (179) accurately predicts the severity of IBS and the efficacy of potential therapeutics.

The development of new drugs that affect visceral sensations might improve prospects for reducing abdominal pain. On the other hand, the benefits of a drug designed to improve motility, transit, intraluminal fermentation, secretion, absorption, or inflammation (all relevant concepts in IBS) might not affect a chronic pain endpoint. Such a drug might still affect the important components of IBS, relieve bothersome symptoms, and could be regarded as effective by many patients with IBS. By the same token, a drug that relieves chronic pain with little clinical impact on other IBS symptoms, such as the bowel dysfunction or pain during bowel function, could be regarded as ineffective by many patients with IBS. Thus, it is important to select trial endpoints that can identify reagents that relieve important symptoms based on their effect on pathophysiological mechanisms in patients with IBS.

Do Committee for Proprietary Medicinal Products (CPMP) and PRO Guidance Provide a Path to IBS Drug Approval or Impact Current Clinical Practice?

Experts in psychometric validation and PRO have cautioned that, “Using the PRO in a clinical trial may be risky, because clinically meaningful effects may go undetected” (181). Identifying a clinically meaningful difference has value; however, demonstrating the minimal clinically important difference for a PRO measure presents challenges beyond responsiveness (181). These challenges suggest it is essential that the right concepts of IBS are selected into a PRO rather than simply borrowing validated endpoints from other fields of clinical research.

Given the lack of approval of alosetron, cilansetron and tegaserod for treatment of IBS in the European Union and the restricted access to alosetron in the U.S., this is a challenging time for clinicians. Despite the best quality evidence on the pharmacodynamic actions and clinical benefit in well-constructed clinical trials for IBS, medications such as tegaserod have been withdrawn because of equivocal safety reasons. In an effort to help their patients, clinicians revert to prescription of medications approved for other indications, despite limited, anecdotal or unproven efficacy in IBS. For example, gastroenterologists frequently prescribe off-label use of antidepressant medications, which have been shown to be of limited benefit in large clinical trials for IBS (22) and in meta-analyses (182) and have significant side effects.

The lack of clear, realistic and consistent guidelines for the approval of IBS therapeutics has caused drug companies to leave this field of research. Ultimately, we all bear responsibility, because treatment delayed is treatment denied.

CONCLUSION

The pipeline of drugs for IBS is fairly healthy; pharmacodynamic studies provide reasonable prediction on proof of efficacy; clinical trial methodology and mechanics have improved considerably in the last decade. The main challenges that should galvanize the efforts of all parties lie in regulatory affairs.

It is essential that academic-clinical leaders be invited to work with regulatory agency clinicians and psychometricians to facilitate a greater understanding of the pathophysiology, mechanisms and symptom complex of IBS. This approach will identify the right concepts for the PROs and improve measurement of severity in IBS. There is a need for a high-level NIH consensus conference on clinical trial endpoints for functional gastrointestinal disorders, followed by a deliverable consensus paper.

PRO endpoints should be enhanced with clinically applicable biomarkers. Thus, while endoscopic, blood and rectal sensitivity tests do not currently provide sufficiently sensitive

biomarkers in IBS, data regarding colonic transit from two centers (100,102) independently suggest that transit responses are significant factors in defining the IBS phenotype, determining the severity of the pathophysiology, and predicting response to therapy with a wide range of pharmacological agents that target different mechanisms [transit, motility, and mucosal secretion (63,73,80,107–109,183)]. A paradigm shift has been proposed for the approval and surveillance standards for new drugs [see Table V (184)]. Given the current position of the FDA (185), future attempts to develop or modify an existing PRO instrument are inevitable.

At this stage, all aspects of validation, including prior performance in clinical trials and responsiveness, should be used to select IBS endpoints for drug development programs. Until new endpoints are validated, it is imperative that, for the sake of the patients, regulators approve binary or global improvement endpoints that have been previously shown to have responsiveness, longitudinal construct validity, and interpretability, and also insist on validation of additional endpoints and definition of MID for future studies.

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Abbreviations used

CI	confidence interval
CRF	corticotropin releasing factor
FAP	functional abdominal pain
5-HT	serotonin
HMO	health maintenance organization
IBS	irritable bowel syndrome
IBS-C	irritable bowel syndrome with predominant constipation
IBS-D	irritable bowel syndrome with predominant diarrhea
NK	Neurokinin
OR	odds ratio
non-IBS-C	non-constipated IBS

SNRI

Serotonin-norepinephrine reuptake inhibitor

SSRI

selective serotonin-norepinephrine reuptake

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Figure 1.

The Process Recommended by the PRO Guidance Document for Developing of New or for Modifying Existing Instruments for Clinical Trials (reproduced from ref. 92)

Table I

Drugs in Development for IBS in Open or Planned, Classified by Phase I–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
<i>Lactobacillus farciminis</i>	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
GastrafateIB (sucralfate)	Sucrose sulfate-aluminum salt: cytoprotection	All subtypes	II/III
Arverapamil	Enantiomer of verapamil; calcium channel blocker; 5-HT _{2b} and melatonin (MT ₁) binding	IBS-D	III
Linacotide	Guanylate cyclase-C agonist	IBS-C	III
Rifaximin	Antibiotic	IBS-D	III
<i>Saccharomyces boulardii</i>	Probiotic	IBS-D	III

Table II
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 Endpoints	Safety Issues/Comments	Ref.
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 pts): BM frequency and satisfaction with bowel function both improved	Greater selectivity for 5-HT ₄ than 5-HT _{1B} or hERG channel	3-10
	ATL-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 CYP 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	12-1
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 suggests low expectation for 5-HT ₃ antagonist activity	15
Antidepressants		May reduce visceral	SSRIs, fluoxetine and paroxetine, and	Small studies with SSRI or	Side effects common with TCA. Post-hoc analysis	16-2

Drug Class	Examples	Rationale or Putative Action	Pharmacodynamic (intestine or colon)	Clinical Efficacy: Phase IIB or III Primary Endpoints	Safety Issues/Comments	Ref.
		sensation and relieve depression associated with IBS	TCA, amitriptyline, do not reduce visceral sensitivity, in contrast to the SNRI, venlafaxine; SSRI accelerates and TCA slows SB transit	TCA equivocal; large study had no significant benefit of desipramine over placebo in ITT analysis, but did in per-protocol analysis (completed treatment)	for desipramine showed benefit in those with moderate symptoms, abuse, no depression and IBS-D	
κ -opioid agonist	asimadoline	κ -opioid receptors in visceral perception	Reduce sensation in response to colon distensions in the non-noxious 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		33-3
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	? more events of worsening abdominal pain; headaches were more frequent with placebo	37,3
CCK ₁ antagonist	dexloxiplumide	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 dexloxiplumide		45-5

Drug Class	Examples	Rationale or Putative Action	Pharmacodynamic (intestine or colon)	Clinical Efficacy: Phase IIB or III Primary Endpoints	Safety Issues/Comments	Ref.
NK antagonists	NK ₁ antagonist, ezlozipant	NK ₁ -receptors' role in nociception	Reduce the emotional response of IBS patients to rectosigmoid distension	None		51-5
	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		51,5 54,5
	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		58,5
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	62-6
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		73-7
Probiotics	Several, e.g., <i>Bifidobacteria</i> , <i>Lactobacillus</i> , <i>Saccharomyces</i> species or combinations	Potential mechanisms: immune, barrier, fermentation	Slow colonic transit in IBS-D	Several IIB studies: efficacy in overall IBS and single symptoms, e.g., flatulence, pain		76-8
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		85-9

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; Ref=reference; SB=small bowel; SSRI=selective serotonin reuptake inhibitor; SNRI=serotonin and norepinephrine reuptake inhibitor; TCA=tricyclic antidepressant

Table III
Spectrum of Endpoints Used in Trials Involving Drug Treatment in IBS

Endpoint	Description of Endpoint	Response	Medication	Ref. #
Adequate Relief	<p>“In the past 7 days, have you had adequate relief of your IBS pain and discomfort?”</p> <p>“In the past 7 days, have you had adequate relief of your IBS symptoms?”</p> <p>“Would you rate your overall relief of irritable bowel symptoms during the past week as adequate?”</p>	binary endpoint (Yes/No)	Alosetron Cilansetron Dextofisopam, Imipamine and Citalopram	136–141 142–144 38 28
Satisfactory Relief	<p>“Over the past week, do you consider that you have had satisfactory relief from your symptoms of IBS?”</p> <p>“Did you have satisfactory relief of your overall IBS symptoms during the last week?”</p> <p>“Did you have satisfactory relief of your abdominal discomfort or pain during the last week?”</p>	binary endpoint (Yes/No)	Tegaserod	145–148
Subject Global Assessment of Relief (SGA)	<p>“Please consider how you felt during the past treatment period in regard to your IBS, in particular your overall well-being, and symptoms of abdominal pain/discomfort and altered bowel habit”</p> <p>AS ABOVE, +</p> <p>“Compared to the way you usually felt before entering the study, how would you rate your relief of symptoms during the past week?”</p>	5-point Likert scale (worse, not at all relieved, somewhat relieved, considerably relieved, completely relieved). 5-point Likert Scale (completely relieved, considerably relieved, somewhat relieved, unchanged, worse)	Tegaserod	149–152
Modified version of the SGA (secondary endpoint)	Responder defined by 4/4 weeks of at least a little bit effective, or $\geq 2/4$ weeks of at least quite a bit effective	5-point Likert scale (0=not at all effective, 1=a little bit effective, 2=somewhat effective, 3=quite a bit effective, 4=extremely effective)	Lubiprostone	66
Modified version of the SGA	“How would you rate your relief of IBS symptoms (abdominal discomfort/pain, bowel habits, and other IBS symptoms) over the past week compared to how you felt before you entered the study?”	7-point Likert scale: substantially worse, moderately worse, slightly worse, no change, slightly improved, moderately improved, or substantially improved	Lubiprostone	67
Global Improvement Scale	“Compared to the way you felt during the 3 months before you entered the study, are your IBS symptoms over the past 4 weeks....?”	7-point Likert scale: substantially worse, moderately worse, slightly worse, no change, slightly improved, moderately improved, or substantially improved	Alosetron (phase IV)	153–155,160
IBS Severity Scoring System (IBS-SSS)	5-item instrument that includes abdominal pain (severity), abdominal	Responses to five items measured on a 0–100 VAS summed to derive	Non-pharmacological treatment	156–158

Endpoint	Description of Endpoint	Response	Medication	Ref. #
	pain (number of days with pain), abdominal distention (severity only), satisfaction with bowel habit, and interference with life in general.	total score between 0-500: <75 normal, 75–175 mild, 175–300 moderate, >300 severe.		
Abdominal discomfort/pain score	Abdominal pain/discomfort responses <ul style="list-style-type: none"> - coded on a scale of 0 (absent) to 4 (very severe) - recorded as responses to specific queries in patients' daily electronic diaries. 	Change from baseline in mean abdominal discomfort/pain score during the first 28 days of treatment calculated by subtracting the average of all scores during the baseline period from the average of all scores during the first month of treatment	Lubiprostone	66
Abdominal Pain Severity Score	Abdominal pain severity on 100 mm VAS in the diary Change from baseline in mean abdominal discomfort/pain score during the first 28 days of treatment; abdominal discomfort/pain recorded as responses to specific queries in daily electronic diaries	Whenever pain of at least moderate intensity felt the first time during a day and two hours after the intake of the medication 5-point Likert 0=absent; 1=mild; 2=moderate; 3=severe; 4=very severe	Asimadoline on demand Lubiprostone	35 66

Comparison of Psychometric and Methodological Properties of Standardized IBS Outcome Measures: Symptoms Questionnaires (reproduced from ref. 161)

eliability	Assessment Criteria										Use in Primary care
	Sensitive to change	Face validity	Content validity	Construct validity	Interpretable	Practical utility	Appro priate for use	Variables clearly defined	Eligibility Criteria Reported	Patients defined	
–	+	+	±	+	+	+	+	+	+	+	–
–	+	+	+	+	+	±	+	+	±	+	–
+	±	+	+	+	±	±	+	±	–	–	–
–	–	±	+	+	±	+	+	+	±	+	–
+	+	±	±	±	–	–	±	±	+	±	–

Twelve Criteria Used for Assessment of Symptom Questionnaires and Health-Related Quality of Life Instruments

- 1 Does the measure have satisfactory reliability (internal consistency)?
- 2 Is the measure sensitive to change (responsiveness)?
- 3 Does the measure what it is supposed to measure (face validity)
- 4 Does the measure sample the domain of interest comprehensively content validity?
- 5 Is the measure compared with other measures and is the relation between measure and patient characteristics defined (construct validity)?
- 6 Is the outcome interpretable; are changes in score related to clinical indicators that are familiar and meaningful to clinicians?
- 7 Is the measure easy to administer, showing practical utility?
- 8 Are the measure appropriate for use?
- 9 Are the variables clearly and unambiguously defined?
- 10 Are criteria for in- and exclusion reported?
- 11 Is the population in the validation report described?
- 12 Has the measure been used in a primary care population?

); FBDSI = functional bowel disorder severity index; GSRS = GI symptom rating scale; Criteria for Assessment of Symptom Questionnaires and Health-Related Quality of Life IBS-Q = IBS symptom questionnaire; IBS-SSS = IBS severity

reviewers agree that the measure satisfies the assessment criterion;

reviewers agree that the measure partly satisfies the criterion or less than five agree that it fully meets the criterion, or less than five agree that it does not meet the criterion;

reviewers agree that the measure does not satisfy the assessment criterion or that the

Table V
A Paradigm Shift in the Approval and Surveillance Standards for New Drugs
(adapted from ref. 184)

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1	Careful mechanistic studies in small numbers of patients and volunteers
2	Expanded and more integrated approach to the use of preclinical information to inform human pharmacology.
3	Detailed human investigations, including phenotypic manipulations in a controlled environment, to elucidate the mechanism of drug action and refine dose selection in humans.
4	More complex analysis of the factors that contribute to inter- and intra-individual differences in drug response.
5	Greatly expanded Phase II to yield a range of indices — pharmacokinetic and dynamic, biochemical and genetic — of drug efficacy and safety.
6	Need of investigators capable of developing and projecting hypotheses on the basis of quantitative biomarkers of mechanism, drug efficacy and safety from model systems into studies of drug response in humans.
7	Harness unbiased technologies to select candidates from among multiple compounds directed at a single molecular target.
8	Focus on individualized medicine and thereby transform and expand Phase II trials, while potentially shrinking, shortening and reducing the costs of Phase III studies.
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