Pharmacological and Pharmacokinetic Aspects of Functional Gastrointestinal Disorders

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Medications are commonly used for the treatment of patients with functional gastrointestinal disorders. The general goal of this report is to review the pharmacokinetics and pharmacology of medications used in functional gastrointestinal disorders. Methods included literature review, consensus evaluation of the evidence for each topic assigned originally to 1 or 2 authors, and broader review at a harmonization session as part of the Rome III process. This report reviews the animal models that have been validated for the study of effects of pharmacologic agents on sensation and motility; the preclinical pharmacology, pharmacokinetics, and toxicology usually required for introduction of novel therapeutic agents; the biomarkers validated for studies of sensation and motility end points with experimental medications in humans; the pharmacogenomics applied to these medications and disorders; and the pharmacology of agents that are applied or have potential for treatment of functional gastrointestinal disorders, including psychopharmacologic agents. Clinician and basic investigators involved in the treatment or investigation of functional gastrointestinal disorders or disease models need to have a comprehensive understanding of a vast range of medications. It is anticipated that the interaction between investigators of basic science, basic and applied pharmacology, and clinical trials will lead to better treatment of these disorders.

In relation to functional gastrointestinal disorders (FGIDs), this report reviews animal models that have been validated for the study of effects of pharmacologic agents on sensation and motility; the preclinical pharmacology, pharmacokinetics, and toxicology usually required for introduction of novel therapeutic agents; the biomarkers validated for studies of sensation and motility end points with experimental medications in humans; the pharmacogenomics applied to these medications and disorders; and the pharmacology of agents that are applied or have potential for treatment, including psychopharmacologic agents.

Animal Pharmacology: Models Validated for the Study of Sensation and Motility

The development of new drugs for the treatment of patients with FGIDs is facilitated by preclinical animal models that must reproduce the pathophysiology of FGIDs as closely as possible. This section reviews the most commonly used animal models of visceral pain and disturbed gastrointestinal motility.

Visceral Pain

There are several forms of stimulation and end points to measure visceral pain.

Mechanical stimuli. Experiments are performed in awake or anesthetized rats, and the most frequently used stimulus of pain in animals is distention of a gut segment with a balloon connected to a barostat to measure simultaneously compliance and the response to the painful stimulus. Such a balloon can be chronically implanted in the gut[1]; variability in balloon construction and unfolding influences the reproducibility of experiments. Arterial embolectomy probes[2] have a very reproducible diameter but do not permit accurate measurement of pressure-volume relationships (or compliance).

Chemical stimuli. In rats, infusion of glycerol into the colon through a chronically implanted catheter induces abdominal cramps.[3]

Other stimuli. Other stimuli have been used to investigate visceral pain modulation in animal models, including other chemical irritants (such as trinitrobenzene sulfuric acid, dioctyl sodium sulfosuccinate, zymogen) and parasite infestations (such as *Nippostrongylus*

Abbreviations used in this paper: FGID, functional gastrointestinal disorder; 5-HT, serotonin/5-hydroxytryptamine; IBS, irritable bowel syndrome; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

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brasiliensis or *Trichinella spiralis*). The "writhing test," consisting of an intraperitoneal injection of an irritant compound such as acetic acid, is used for pharmacologic studies of analgesic compounds, but it reflects peritoneal irritation (and activates somatic pain) rather than visceral pain. At present, there is no consensus as to the best model to study visceral pain.

End points. Nociceptive responses to stimuli, called "pseudoaffective" responses, are brainstem or spinal reflexes that cease when the noxious stimulus is terminated. The most commonly used end point is the contraction of abdominal muscles induced by rectal or colorectal distention in the rat; the contractions are typically recorded by electromyography.[2,4] The number of spike bursts or integrated signals correspond to abdominal contractions over the period of distention, and they correlate with the intensity of the stimulus applied.[2] In mice, colorectal distention triggers only one sustained contraction at the onset of the distention.[5] Gastric distention in rats does not induce abdominal contractions, but stretching of the body or raising of the head and electromyography of neck muscles has been used as a biomarker of the nociceptive response to gastric distention.[6] It is, however, also possible that the electromyographic recording may reflect contractions associated with a distention-induced defecation reflex rather than being a measure of pain.

Visceral distention also induces viscerovisceral reflexes, such as relaxation of anal sphincters during rectal distention or rectocolonic inhibition of gastric emptying.[7]

Change in blood pressure is a pseudoaffective response widely used to assess visceral pain. Cardiovascular and muscular responses are mediated via brainstem reflexes; both are vigorous in decerebrated but not spinalized rats.

Electrophysiologic recordings from sensory neurons or second-order neurons in the spinal cord may provide the most direct evidence that a pharmacologic agent alters afferent function.[8,9] Measurements of the effect of the medication on viscus compliance are essential to differentiate effects on volume thresholds to activate sensory fibers from drug-induced contraction or relaxation.[10]

Several behavioral end points have been used and involve brain centers higher than the brainstem. They do not cease when the noxious stimulus is terminated and therefore are not pseudoaffective responses. Referred somatic hyperalgesia is evaluated in mice by application of von Frey hairs with forces from 1 to 32 mN on the abdomen; the subsequent behavioral response is a measure of sensation.

Allodynia and hyperalgesia. These models permit evaluation of allodynia (decrease in the threshold of sensitivity to distention) and hyperalgesia (enhanced response to painful stimulus). Gastric hypersensitivity to distention has been induced by inflammation[6] and intestinal hypersensitivity by helminth infection.[11] Colonic and rectal hypersensitivity are induced with stress (eg, maternal deprivation, water avoidance models),[12] inflammation,[2] and lipopolysaccharide injection.[13] Long-term colonic hyperalgesia may be induced by neonatal maternal deprivation[14] or colonic inflammation.[15]

Motility

The techniques used to record motility or measure transit in animals may differ from techniques used in humans, but the end points are identical.

Delayed gastric emptying. Stress inhibits gastric emptying in animals and humans. Numerous stressors have been proposed to inhibit gastric emptying in rats, including restraint, acoustic stress, cold stress, combined acoustic and cold stress, and passive avoidance. Prolonged colonic distention[16] inhibits gastric emptying, and this is considered relevant because, in humans, voluntary suppression of defecation for 4 days inhibits gastric emptying.[17] Another experimental method to inhibit gastric emptying is the duodenal infusion of lipids in humans or animals.

Altered duodenojejunal migrating motor complex pattern. Acute stress affects migrating motor complex patterns[18]; however, there are no models of chronic disruption of the migrating motor complex in animals.

Altered colonic motility and transit. Colonic motility can be inhibited by several pharmacologic compounds, such as α_2-adrenergic and μ-opioid receptor agonists. Stress has been used to stimulate colonic motility, colonic transit, and fecal excretion in rats.[19]

In summary, because the present knowledge of the pathophysiology of FGIDs is limited, selection of one or more definitive animal models of visceral hyperalgesia is not possible. It is also difficult, based on results in a single animal model, to predict efficacy of a compound in clinical trials. Using results from more than one animal model may enhance the probability of selecting effective drugs for further development. To date, only 2 medications (tegaserod and cilansetron) have had a track record of proven efficacy in animal models (for both transit and sensation) and proven clinical efficacy. In addition, it is worth emphasizing that pain is not the only symptom of FGIDs affecting quality of life, and animal models providing information on motility effects may be relevant to the assessment of new compounds.

Preclinical Pharmacology, Pharmacokinetics, and Toxicology Required for Novel Therapeutic Agents

This section outlines some general pharmacodynamic, pharmacokinetic, and safety aspects that are important for the development of new drugs for FGIDs.

The Pharmacodynamic Target

Drug selectivity. Selectivity refers to the ability of a compound to interact with only one receptor subtype, leaving other receptors unaffected at concentrations achieved at clinically used doses and avoiding side effects. Although this definition was considered key to finding effective new or experimental medications, there are several important pitfalls in this approach.

First, drug selectivity is a relative concept, and the tendency to label a drug as a "selective" ligand for a given receptor subtype ignores the fact that a single molecule, at therapeutic doses, may have several, sometimes different, biological targets. For instance, cisapride was found to be a partial 5-HT_4 receptor agonist,[20] a 5-HT_3 receptor antagonist, and a fairly potent HERG K^+ channel blocker.[21]

The second pitfall is that, because of the multifactorial pathophysiology of FGIDs, single-receptor modulating drugs may be less likely to achieve a substantial therapeutic gain. In several fields,[22] evidence suggests that balanced modulation of multiple targets may provide a superior therapeutic effect and side effect profile compared with the action of a selective ligand. Rational approaches in which structural features from selective ligands are combined have produced designed multiple ligands that span a large variety of targets.[22] A key challenge in the design of a ligand with multiple actions is to achieve a balanced potency and activity at each target of interest and a suitable pharmacokinetic profile. The less selective a ligand is, the harder it is to predict toxicity; once toxicity occurs, it becomes even more difficult to provide a mechanistic explanation for it. This may jeopardize the development and regulatory approval of such a less selective ligand.

Third, it is likely that the mechanisms responsible for symptoms in FGIDs may differ from one patient to another and a single target may not achieve adequate efficacy in a patient population. With the selective approach to relieving symptoms or groups of symptoms (eg, pain and constipation or diarrhea), experience shows that primary clinical end points were achieved in $<70\%$ of patients with agents such as tegaserod or alosetron.[23–25] The lack of efficacy is unlikely to reflect an inadequate dose because phase 2 studies did not suggest a higher dose was more effective; hence, there is the need to consider using multiple therapies or "designed" multiple ligands to enhance the benefit/risk ratio. For instance, a 5-HT_3 receptor antagonist with partial agonist action at 5-HT_4 receptors may be less constipating than a pure 5-HT_3 receptor antagonist. Another example is provided by tachykinin receptor antagonists; it has been suggested that the analgesic efficacy and motility inhibition of multi-tachykinin or pan-tachykinin receptor antagonists are superior to that of monoreceptor antagonists.[26,27]

Pharmacodynamic versus pathophysiologic target. When drugs target a single receptor mechanism, heterogeneity in pathophysiology (eg, dysmotility vs hypersensitivity) has a negative impact on the therapeutic gain if patients are not selected on the basis of the specific disorder. Indeed, some of the disappointing results of the past decade can be attributed to the heterogeneity of functional disorders, lack of understanding of pathophysiology, and lack of short-term mechanistic studies that can predict clinical outcome. New drugs should target the entire pathophysiologic mechanism(s) contributing to the functional disorder rather than only an individual part or a specific receptor. Thus, nonselective agents designed to modulate multiple targets of the whole pathophysiologic process (eg, dysmotility, sensory disorder, inflammation) would be advantageous over highly selective medications addressing a single mechanism. Appropriate patient subgroups should be recruited to show the therapeutic properties of a medication, although this may reduce the generalizability of the results of the trial.

Pharmacokinetics

Pharmacokinetics may help to achieve gut selectivity. This approach is particularly relevant when there are potential actions outside the gut. For example, peripherally restricted opioid receptor antagonists such as methylnaltrexone and alvimopan do not cross the blood-brain barrier and, in addition, have very low oral bioavailability.[28,29] This offers the potential to modulate intestinal motility without systemic effects. Moreover, targeted drug delivery to the colon with pH- or time-dependent release[30,31] or bacterial activation of a prodrug offer potential new approaches for FGIDs.

Another important pharmacokinetic property is the lack of interactions with food or other drugs. CYP2D6 (10% slow metabolizers in the community), CYP3A4, and CYP2C19 are important isoenzymes because of their involvement in the metabolism of many drugs and drug-drug interactions. Significant interactions with these en-

zymes should be ruled out in early drug discovery and may be achieved by computational prediction. Specifically, it is important to distinguish between pharmacokinetic modification resulting from drug metabolism by one of the enzymes versus drug interactions at one of the enzymes, which may be inhibition or induction. In both situations, drug-drug interactions may occur if inhibition or induction occurs at clinically relevant doses.

Safety Aspects

Apart from the standard safety evaluations of every new medicinal product, 2 examples deserve special attention because of recent experience: cisapride resulted in tachyarrhythmia associated with prolongation of the QT interval of the electrocardiogram due to blockade of the HERG K^+ channels[32] and alosetron or cilansetron were associated with ischemic colitis.[33] Although these are very rare events, even a low risk is not acceptable for drugs that target pathophysiologic mechanisms and provide relief of nonfatal diseases such as FGIDs, and the drug development process should identify such undesired effects as early as possible.[34] Overall, low risk of these adverse effects or minor adverse events may be acceptable in patients with severe FGIDs that affect daily living. A third issue of particular relevance in FGIDs is the potential for drug interactions, given the problem of polypharmacy and the frequent use of psychotropic agents (which often depend on CYP2D6 metabolism).

Human Pharmacology: Nonpsychotropic Agents

Gastrointestinal motor and sensory function can be altered through several pharmacologic approaches; the most important are summarized in Table 1 and are discussed in this section. However, it is also important to recognize 2 other classes of agents that are commonly used in FGIDs, that is, laxatives in the treatment of constipation (alone or in association with IBS)[35] and probiotics.[36]

Several meta-analyses of pharmacologic treatments for IBS have been published in recent years.[37] The pharmacology of agents directed to amine receptors or peptides is summarized (Table 1).

Serotonergic Agents

Serotonin, or 5-hydroxytryptamine (5-HT), plays a key role in the control of gastrointestinal motility, sensitivity, and secretion. Actions of 5-HT are terminated by a reuptake system, which is inhibited by antidepressants.[38] Selective serotonin reuptake inhibitors (SSRIs) alter motility in the stomach, small bowel, and colon,[39] but to date no convincing beneficial therapeutic effects have been reported in FGIDs. Several 5-HT receptor types are present on both nerves and smooth muscle and mediate a number of different actions.[40]

5-HT_3 receptor antagonists, such as alosetron, delay orocecal and colonic transit times and reduce colonic compliance but not sensitivity to isobaric distention.[41–43] Several clinical studies confirmed the efficacy of alosetron in diarrhea-predominant irritable bowel syndrome (IBS).[25] Shortly after its introduction, alosetron was withdrawn due to suspected side effects of ischemic colitis/colonic ischemia[33] and is now available for restricted use in the United States only. Preliminary data suggest a therapeutic potential for cilansetron,[44] although there is also potential for ischemic colitis.[45]

5-HT_4 receptor agonists, such as tegaserod or prucalopride, act on intrinsic neurons to stimulate gastric, small bowel, and colonic transit in health, in constipation, and in constipation-predominant IBS.[46–48] In the stomach, 5-HT_4 receptor agonists enhance (postprandial) proximal gastric volumes in health but have no effects on sensation.[49] In healthy subjects, tegaserod does not alter sensory thresholds or sensory ratings during rectal distention but reduces the inhibition of the RIII reflex caused by slow-ramp colorectal distention, which was proposed as a surrogate marker of visceral pain.[50,51] Tegaserod improves constipation, provides relief of pain/discomfort and bloating, and is approved for women with constipation-predominant IBS and for men and women younger than 65 years with chronic constipation.[24,52,53] Prucalopride and tegaserod were shown to be effective in the treatment of constipation.[54,55]

Activation of 5-HT_{1A} receptors on enteric neurons inhibits the release of acetylcholine.[56] In humans, 5-HT_{1A} receptor agonists such as buspirone inhibit motility and decrease gastric tone, but therapeutic usefulness has not been established.[57]

Motilides

Activation of motilin receptors on smooth muscle and on cholinergic nerves enhances gastric contractility.[58] Motilin receptor agonists, such as erythromycin or the macrolide prokinetic ABT-229, enhance antral contractility, fundic tone, and gastric emptying in health and in gastroparesis (Cuomo et al, manuscript in submission).[59–62] The symptomatic impact of enhanced emptying by erythromycin in gastroparesis has been questioned,[63] and no symptomatic benefit (but rather some symptom aggravation) was found in studies with ABT-229.[64] The occurrence of tachyphylaxis with motilides may be an important factor.[65]

Table 1. Agents Directed to Amines/Receptors and Peptides

Target receptor	Type of ligand	Distribution of receptors	Pharmacologic action in animals	Pharmacologic action in humans
Amines/receptors				
5-HT	5-HT_3 receptor antagonists (eg, alosetron, cilansetron)	Intrinsic and extrinsic neurons	Inhibits visceral sensitivity, absorption/secretion, motility	Slows transit, increases colonic compliance
	5-HT_4 receptor agonists (eg, tegaserod, renzapride, prucalopride)	Enteric neurons, smooth muscle cells	Enhances secretion and motility, reduces visceral sensitivity	Accelerates transit, increases colonic high-amplitude propagated contractions and gastric accommodation, reduces inhibition of R1II reflex during rectal distention
	5-HT_{1A} receptor agonists (eg, buspirone)	Enteric neurons, extrinsic afferent neurons	Inhibits motility and enhances compliance	Increases accommodation
Ach (muscarinic)	M_3 receptor antagonists	Smooth muscle	Increases smooth muscle relaxation, compliance	No published data
	M_1 and M_2 receptor antagonists	Enteric neurons and smooth muscle	Increases gastric emptying	May enhance accommodation
Adrenoceptors	β_3-adrenoceptor agonists	Smooth muscle	Inhibits motility	No published data
	α_2-adrenoceptor agonists	Enteric neurons and enterocytes	Reduces secretion, enhances compliance, and reduces motility and tone	Reduces secretion, enhances compliance, and reduces motility and tone and sensation
Dopamine	D_2 receptor antagonists (eg, domperidone, levosulpiride, metoclopramide)	Area postrema, smooth muscle, enteric neurons	Contracts muscle	Antiemetic, prokinetic, reduced sensation?
Peptides				
Motilin	Motilides	Smooth muscle, enteric neurons	Motility stimulation	Motility and transit stimulation
Opioid	μ-receptor agonists (eg, loperamide)	Enterocyte, enteric neurons, afferent neurons, and inflammation	Reduces intestinal secretion and transit	Slows colonic transit, antidiarrheal, increases resting anal tone
	μ-receptor antagonists (eg, naloxone, methyl-naltrexone, and alvimopan)	Enteric neurons, afferent neurons, and inflammation	Reverses opioid effects on motility	Accelerates colonic transit; reverses effect of opiates on bowel dysfunction; reduces duration of postoperative ileus
	κ-receptor agonists (eg, fedotozine asimadoline)	Enteric neurons and afferent neurons	Reduces sensation, variable effect on motility	Reduces sensation
Somatostatin	SSR-2 receptor agonists (eg, octreotide, lanreotide)	Enterocyte, submucosal neurons, myenteric neurons	Retards transit, reduces afferent firing and sensation	Retards transit, reduces sensitivity, enhances absorption
Tachykinin	NK_1 receptor antagonists (eg, aprepitant)	Enteric neurons, interstitial cells of Cajal, smooth muscle, immune cells	Inhibits motility, fluid secretion, vagal afferent sensation, and inflammation	Antiemetic
	NK_2 receptor antagonists (eg, nepadutant)	Enteric neurons, smooth muscle, extrinsic afferents	Inhibits motility, fluid secretion, sensation, and inflammation	Inhibits NKA-induced motility
	NK_3 receptor antagonists (eg, talnetant)	Enteric neurons, extrinsic afferents	Inhibits motility and sensation	No published data
Cholecystokinin	Cholecystokinin-1 receptor antagonists (eg, dexloxiglumide)	Afferent vagal nerves and enteric neurons	Accelerates gastric emptying, inhibits TLESR	Inhibits lipid-induced gastric motor effects, inhibits TLESR

NK, neurokinin; TLESR, transient lower esophageal sphincter relaxation.

Tachykinin Receptor Antagonists

Three distinct receptors, neurokinin 1, neurokinin 2, and neurokinin 3, mediate the biological effects of endogenous tachykinins substance P, neurokinin A, and neurokinin B in the gastrointestinal tract. Through the locations of neurokinin receptors on intrinsic nerves,

extrinsic nerves, inflammatory cells, and smooth muscle, inhibition of tachykinin receptors has the potential to inhibit motility, sensitivity, secretion, and inflammation in the gastrointestinal tract.[27,66] Neurokinin 1 receptor antagonists also have antiemetic properties.[27] Several tachykinin receptor antagonists are currently under evaluation for treatment of FGIDs.

Adrenoceptor Agonists

The α_2-adrenoceptor agonist clonidine was shown to reduce colonic tone and pain sensation in response to distention.[67–69] A preliminary study of clonidine in diarrhea-predominant IBS suggested therapeutic potential for clonidine, but clinical application is hampered by dose-limiting side effects such as somnolence or hypotension.

Opioid Receptor Ligands

Three types of opioid receptors, μ, δ, and κ receptors, located in the enteric nervous system and on nociceptive pathways, have effects on human gastrointestinal function. Opioid receptor activation reduces visceral pain through peripheral (spinal afferents) and central mechanisms and inhibits motility through decreased acetylcholine release. κ-opioid receptor agonists have been proposed as a pharmacologic approach to the treatment of hypersensitivity in FGIDs. Acute studies with fedotozine and asimadoline showed decreased sensitivity to gastric or colonic distention.[70–73] However, therapeutic studies in IBS and functional dyspepsia with fedotozine have been disappointing.[74,75] The μ-opioid receptor agonist loperamide, used in the treatment of diarrhea, inhibits secretion, reduces colonic transit, and increases resting anal sphincter tone.[76] Peripherally restricted μ-opioid receptor antagonists, such as *N*-methylnaltrexone and alvimopan, normalize bowel function in opiate-treated patients without compromising central opioid analgesia.[29] The use of these agents in constipation and in constipation-predominant IBS is under investigation.

Miscellaneous Agents

Cholecystokinin has a large number of effects on gastrointestinal contractility and secretion.[77] Cholecystokinin-1 receptor antagonists such as loxiglumide and dexloxiglumide enhance gastric emptying in health and in constipation-predominant IBS, although effects on colonic motility are unclear.[78,79] So far, clinical usefulness has not been established.

The transient receptor potential ion channel of the vanilloid type 1 (TRPV1), expressed by primary afferent neurons, is viewed as a trigger for chemonociception and may be up-regulated in some FGIDs.[80] Long-term administration of capsaicin, which is believed to desensitize TRPV1, was more effective than placebo in decreasing symptoms in functional dyspepsia.[81]

Dopamine$_2$ receptor antagonists have gastroprokinetic effects and central antiemetic properties resulting in suppression of nausea and vomiting. Although clinically used in the treatment of FGIDs and gastroparesis,[82] efficacy has not been established by high-quality studies.[83,84]

Muscarinic receptor antagonists and smooth muscle relaxants are used in some countries for the treatment of IBS. Meta-analysis suggests they are superior to placebo in IBS-related pain,[85] although the quality of trials has been questioned.

Somatostatin and its stable analogues such as octreotide inhibit rapid gastric and small bowel transit as well as sensitivity to rectal or colonic distention in humans.[86–88] The need for multiple subcutaneous injections, high cost, and potential side effects limit its present use in FGIDs.

Cannabinoid CB_1 receptors are expressed on nociceptive afferents and enteric nervous system neurons, whereas CB_2 receptors are expressed on immune cells. Activation of CB_1 receptors slows gastrointestinal transit in animals through inhibition of acetylcholine release. The nonspecific agonist δ-9-tetrahydrocannabinol has strong antiemetic properties and delays gastric emptying in humans.[89,90] It is unclear whether the potential for abuse of CB_1 agonists would preclude their regulatory approval. Inverse CB_1 agonists (which function as antagonists at constitutively active CB_1 receptors)[91] are being developed for treatment of obesity, because they may induce nausea and vomiting. The effects on stomach function are unclear. On the other hand, agonists at the nonneuronal CB_2 receptors have no abuse potential and exert antinociceptive effects in pain associated with inflammation.[92]

Pharmacodynamics: Biomarkers for Sensation and Motility End Points in Experimental Medicine

This section reviews the application of physiologic tests as potential biomarkers to understand mode of action and to predict efficacy of an experimental medicine in FGIDs.

Measurements of Colonic Transit

The radiopaque marker test for colonic transit is commonly performed and widely available to assess whole gut transit time. Studies with fiber or loperamide

suggest that overall effects of these therapies can be predicted by the marker transit test, although there was considerable overlap.[93,94] Examples from the literature support the use of detailed scintigraphic colonic transit measurement in the development of medications for IBS-associated changes in bowel function. Alosetron, a 5-HT_3 receptor antagonist that slows colonic transit, was shown to be effective in diarrhea-predominant IBS,[25] and tegaserod, a 5-HT_4 receptor agonist that accelerates colonic transit, was shown to be effective in constipation-predominant IBS.[24,52,53]

Intraluminal Measurements of Rectal or Colonic Motility and Sensitivity

Intracolonic measurements of postprandial tone showed the potential of 5-HT_3 receptor antagonists to prevent diarrhea and other postprandial symptoms in diseases including IBS and carcinoid diarrhea.[95] Measurements of rectal or colonic sensation have not been consistent in predicting therapeutic efficacy. Changes in rectal sensitivity have been associated with responsiveness to octreotide[86–88,96] and opiates,[97] but rectal sensory thresholds do not seem to be significantly altered by tegaserod when using rapid distention.[51]

Gastric Biomarkers in Functional Dyspepsia

Scintigraphic gastric emptying has been a classical investigation for drug development for gastroparesis[98]; however, the prediction of clinical efficacy is not consistent.[63,98] This analysis is also complicated by the occurrence of tachyphylaxis to some medications and by changes in gastric emptying rate with placebo.[62,64,99,100]

A second approach is to use the gastric barostat to measure compliance, tone, and sensitivity. Studies with the κ-opioid agonist fedotozine and with the 5-HT_{1A} receptor agonist R-137696 showed acute effects on barostat measurements of sensitivity or tone that did not translate into significant clinical benefit during placebo-controlled studies of oral administration of these medications for several weeks in patients with functional dyspepsia.[57,74]

A recent approach in evaluating symptoms in dyspepsia has used the symptoms induced by a standardized provocative meal, which is either water or a liquid nutrient drink or a solid meal.[101,102] Although these tests separated healthy controls from patients with functional dyspepsia, it is unclear whether changes in symptom severity after meal provocative tests will prove effective predictors of the clinical efficacy of medications.

As a further development along this line, the combined use of the nutrient drink test with assessment of symptoms and measurement of gastric volume and emptying as with single photon emission computed tomography, ultrasonography, or magnetic resonance imaging may be useful because it simultaneously measures several of the previously mentioned potential biomarkers.[103,104]

Principles of Pharmacogenomics in FGIDs

Pharmacogenetics refers to the study of individual variations in DNA sequence related to drug response. Pharmacogenomics is the study of the variability of the expression of individual genes relevant to disease susceptibility and drug response at cellular, tissue, individual, or population levels.

Polymorphisms may be markers associated with predisposition to FGIDs. Examples in the literature include patients with IBS having significantly reduced frequencies of the high producer genotype for interleukin-10 than controls, suggesting that at least some patients with IBS may be genetically predisposed to produce lower amounts of this anti-inflammatory cytokine. This lends some support to the hypothesis that there may be an inflammatory or genetic component in some cases of IBS.[105] There are contradictory data in the literature suggesting an association of IBS subgroups with polymorphisms of the serotonin transporter (SERT).[106] A polymorphism (C825T) in the gene controlling G-protein synthesis has been described in functional dyspepsia and IBS.[107] Clearly, more studies are needed to confirm or refute the genotype associations for interleukin-10 and GNβ3.

A second aspect is genetic variations influencing response to medications. There may be genetic polymorphism in drug metabolism. For instance, the number of functional CYP2D6 genes determines the pharmacokinetics and plasma levels of the commonly used tricyclic agent nortriptyline[108] or the action of codeine (which has to be converted to morphine by the CYP2D6 isoenzyme to be effective). Note also that several antidepressants are metabolized by these enzymes, and this may affect their clinical efficacy and safety.

Genetic polymorphism may also involve transporters[109] that may influence drug response. Two examples of pharmacodynamic variation are provided from the field of FGIDs. 5-HT undergoes reuptake by SERT. Polymorphisms in the promoter for synthesis of SERT (SERT-P) influence response to serotonergic medications in depressed individuals. SERT polymorphisms were associated with a greater colonic transit response in those with long homozygous than those with heterozygous or short homozygous polymorphisms in diarrhea-predominant IBS.[110]

Table 2. Pharmacologic Actions of Psychotropic Drugs on Monoamine Reuptake and Receptors

	Neurotransmitter reuptake blockade						Receptor blockade		
	5-HT	Norepinephrine	Dopamine	α_1	α_2	H_1	Ach	5-HT_{1A}	5-HT_2
Tricyclic antidepressants									
Amitriptyline	+++++	+++	−	+++	+	++++	+++	+	+++
Imipramine	++++	+++++	−	++	+	++++	++	++	++
Desipramine	+++	+++++	−	++	+	++	++	−	−
Clomipramine	+++++	+++	−	++		+++	++	−	−
SSRIs									
Fluoxetine	+++++	++	−	−	−	−	−	−	−
Paroxetine	+++++	+++	+−		−	0	++	−	−
Sertraline	+++++	+	+++	++	+	0	+	−	−
Citalopram	+++++	−	0	+	+	+	0	−	−
SNRIs									
Venlafaxine	++++	+	−	0	0	0	0	0	0
Duloxetine	+++++	++++	+	−	−	−	−	−	−
Atypical agents									
Bupropion	0	+	+	−	−	−	0	−	−
Nefazodone	++	++	++	+++	−	++	−		+++
Mirtazapine[a]	−	0	0	+		++++	+		+++
Azapirones									
Buspirone	0	0	0	0	0	0	0	++	0

α, α-adrenergic; H, histamine; Ach, muscarinic cholinoceptors; + to +++++, increasing levels of potency; −, weak; 0, no effect.
[a]Mirtazapine also blocks 5-HT_3 receptors (+++), which reduces nausea and has acute anxiolytic effects in humans.

A second observation is that drug response in patients with functional dyspepsia may be influenced by genetic variation in GNβ3 translation. Holtmann et al found that G-protein polymorphisms were predictors of symptom outcome in functional dyspepsia, based on the rationale that G proteins act as second messengers and may influence multiple receptor-mediated mechanisms.[107]

These results require confirmation, but they suggest that pharmacogenetics may affect drug response and need to be considered in drug development programs and in clinical therapeutics. Pharmacogenetics may also provide new insights on the mechanism or pathophysiology of FGIDs.

Psychopharmacology of FGIDs

The acute effects of various psychotropic drugs are shown in Table 2. 5-HT_{1A} receptors and α_2 adrenoceptors are both presynaptic and postsynaptic receptors and heteroreceptors (ie, they modulate norepinephrine and 5-HT neurotransmission, respectively, via presynaptic somatodendritic receptors). When administered long-term, all antidepressants also enhance glucocorticoid signaling and inhibit overactivity of corticotrophin-releasing factor in the brain and presumably in the periphery. Each class affects several transmitters via reciprocal actions between amine and neuropeptide systems and reduces excessive cytokine release associated with various conditions in which inflammatory cytokines play a role.[111]

Long-term treatment with any antidepressant alters receptor sensitivity, which in all cases is believed to result in enhanced 5-HT neurotransmission. Tricyclic antidepressants, but not SSRIs or serotonin-norepinephrine reuptake inhibitors (SNRIs), increase the sensitivity of postsynaptic 5-HT receptors and down-regulate α_2 presynaptic receptors and heteroreceptors. The analgesic effect of tricyclic antidepressants is also mediated by blockage of a class of voltage-dependent sodium channels in extrinsic sensory neurons. SSRIs and SNRIs reduce the sensitivity of 5-HT_{1A} autoreceptors and heteroreceptors. Buspirone (which is an anxiolytic, not an antidepressant) down-regulates 5-HT_{1A} somatodendritic autoreceptors to produce anxiolysis. Down-regulation of 5-HT_{1A} receptors is believed to play the most important role in antidepressant, anxiolytic, and analgesic effects of antidepressants.

Benzodiazepines enhance the inhibitory effects of γ-aminobutyric acid via potentiation at the $GABA_A$ receptors, indirectly enhance 5-HT, and diminish norepinephrine neurotransmission and antagonize the effects of cholecystokinin in brain and gut. This results in immediate anxiolytic activity.

Evidence for Efficacy of Psychotropic Treatments in FGIDs

Psychotropic agents are commonly used to treat patients with FGIDs.[112] Two groups examined the accrued evidence for efficacy of antidepressants for IBS and

reached remarkably different conclusions. Jackson et al[113] conducted a meta-analysis of randomized controlled trials published between 1966 and 1988, focused on the effectiveness of antidepressants for FGIDs, and suggested that antidepressants were as effective for IBS as other commonly prescribed treatments, such as antispasmodics and antidiarrheals. However, there is justifiable debate over the conclusions drawn due to the inclusion of one study showing an unusually large treatment effect, without which the findings would have been less conclusive. Brandt et al[114] assessed randomized controlled trials for all studies published between 1980 and 2001 that examined the efficacy of different IBS treatments, including tricyclic antidepressants. They concluded that none of the tricyclic antidepressant studies was sufficiently long or used sufficiently large sample sizes to assure efficacy. These studies were considered to have a high probability of type I or II errors; tricyclic antidepressants are not superior to placebo for global IBS symptoms, but there was "limited evidence that tricyclic antidepressants may decrease abdominal pain."

Table 3. Dosing Guidelines for Antidepressants and Anxiolytics for FGIDs

Antidepressants	Treatment (6–8 wk) (*mg*)	Starting dose (*mg*)
Tricyclic antidepressants		
Imipramine	100	10
Desipramine	100	10
Clomipramine	75	2.5–10
SSRIs/SNRIs		
Sertraline	50	12.5–25
Paroxetine	20	5–10
Fluoxetine	20	2–5
Escitalopram	10	5
Citalopram	20	10
Fluvoxamine	50	25
Venlafaxine	75	18.75
High-potency benzodiazepines[a]		
Alprazolam	2	0.25–0.5 3 times daily
Clonazepam	1	0.25–0.5 twice daily

NOTE. Some patients may still benefit from dosages lower than indicated. For treatment of major depression or anxiety disorders, dosages are at least double what is indicated.
[a]Not useful as antidepressants.

Newer Studies of Psychotropic Agents in FGIDs

Tricyclic antidepressants. Drossman et al[115] compared the efficacy of the tricyclic antidepressant desipramine (on average 100 mg/day) with placebo in women with moderate to severe IBS. In the intention-to-treat analysis, treatment with desipramine failed to reach statistical superiority over placebo in the overall sample. Post hoc analysis of subjects completing therapy and a separate analysis that excluded subjects with undetectable desipramine levels (assumed to be noncompliant with therapy) favored desipramine over placebo on the main outcome measure and on quality of life and pain ($P = .09$ each) and on patient-rated "satisfaction with treatment" (desipramine > placebo; $P = .011$). It was concluded that because most of the patients who dropped out did so due to side effects and a significant portion had nondetectable desipramine levels, tolerability of desipramine treatment ultimately limited the statistical power of this study.

SSRIs. Clinically, SSRIs appear to be useful for some patients with FGIDs. Kuiken et al[116] reported that 6 weeks of treatment with fluoxetine 20 mg daily was not superior to placebo overall but did reduce abdominal pain in the subgroup with rectal hypersensitivity. These findings need confirmation. In a pediatric population with recurrent abdominal pain, a response was reported in 21 of 24 subjects (ages 7–18 years) after 12 weeks of treatment with flexible-dose citalopram.[117]

In the only placebo-controlled, randomized, controlled trial of the SSRI paroxetine to date, Tabas et al[118] compared 12 weeks of flexible-dose treatment with paroxetine (10–40 mg/day) with placebo in 81 patients with IBS. Treatment with paroxetine was associated with significantly higher improvement of overall well-being and patient preference compared with placebo. Abdominal pain and bloating were not significantly better after treatment with paroxetine.

Two open-label treatment studies with paroxetine in IBS have been recently reported. Creed et al[119] reported significant improvement of abdominal pain severity in 86 patients with severe IBS during 12 weeks of treatment with paroxetine 20 mg/day. Masand et al[120] reported improvement in overall pain, pain severity, and frequency in 20 patients with IBS treated for 12 weeks with paroxetine (mean dose, 31 mg), with a trend toward greater improvement in pain in patients with anxiety disorder. These results should be interpreted cautiously due to the open-label design.

Indication and Choice of Psychotropic Agents in FGIDs

Psychotropic agents are indicated in the presence of significant psychiatric symptoms. The goal of therapy is to achieve relief of gastrointestinal and psychosocial distress. Patients with prior mania, prominent suicidal ideation, or a history of worrisome or unstable behavior should be referred promptly for assessment by a mental health specialist.

All the antidepressant classes and the anxiolytics shown in Table 3 have efficacy in placebo-controlled,

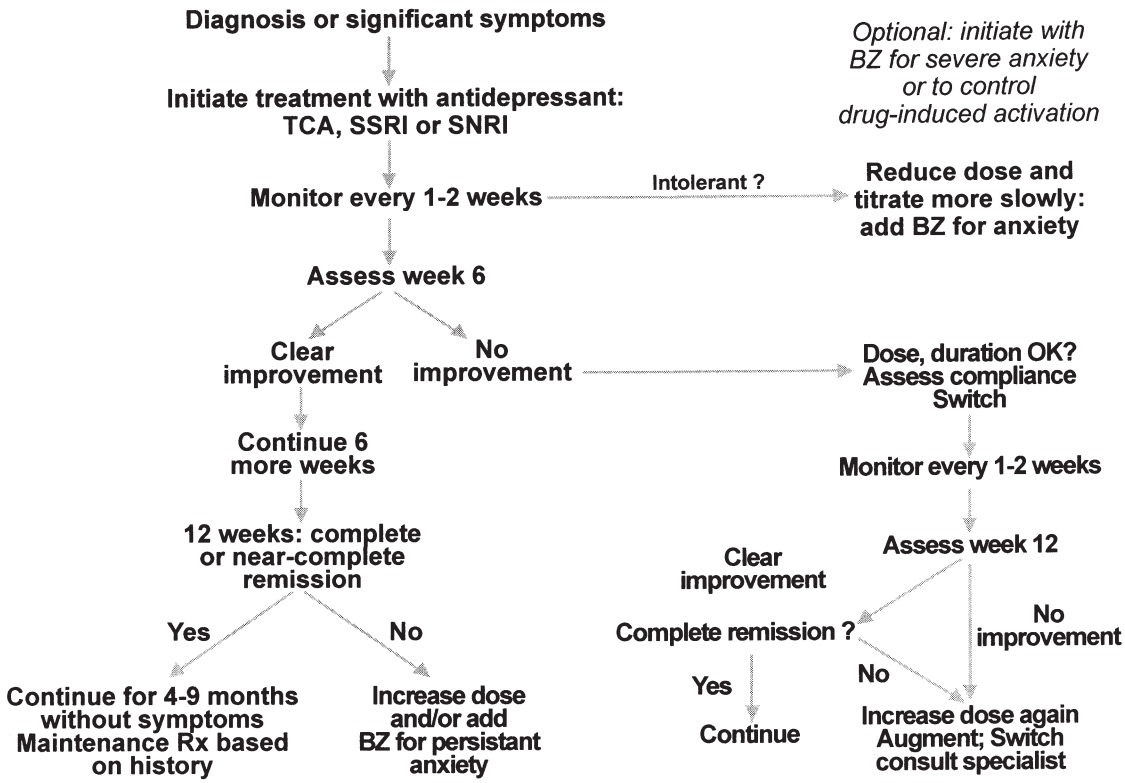

Figure 1. Algorithm for use of treatment with psychotropics for psychiatric symptoms in FGIDs in clinical practice. BZ, benzodiazepines; SNRI, serotonin-norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant.

randomized, controlled trials for the disorders shown. However, not all antidepressants are broadly effective anxiolytics. The SNRIs and SSRIs are generally considered to be equivalent in efficacy and tolerability, and either class is a reasonable first-line approach. They are broadly efficacious as antidepressants and anxiolytics and are safer and more tolerable than the traditional antidepressants. The relative advantages and disadvantages of each of the available treatments should be anticipated for the individual patient, and participation in the initial treatment choice should be negotiated with the patient as an active partner in the process in the interest of maximizing compliance. For some patients, finding a tolerable and effective choice may require using more than one medication. Obtaining tricyclic agent plasma levels (8–12 hours after the last dose) after initiating therapy can assure continued patient safety.

If patients are intolerant of antidepressants and have prominent anxiety, they can be treated with benzodiazepine monotherapy.[121] However, long-term use in patients with FGIDs is discouraged due to a number of factors. Treatment with benzodiazepines may be associated with the development of tolerance, physical dependence, abuse, sedation, cognitive impairment, and, in particular, inability to discontinue benzodiazepines when their use is no longer clinically indicated.

Buspirone is a partial 5-HT_{1A} receptor agonist that is efficacious in general anxiety disorder, but efficacy in FGIDs needs to be studied.

Starting psychotropic drugs for FGIDs at a low dosage may help reduce exacerbation of preexisting gastrointestinal and other symptoms. An algorithm for the use of psychotropic agents is outlined in Figure 1. Achieving full remission is not a reasonable goal for the initial 6- to 8-week treatment and may require 4–6 months or even longer. For some patients, the use of concomitant benzodiazepines for anxiety control may help with compliance and allow more optimal control of symptoms.

In summary, the presence of clinically significant psychiatric symptoms in patients with FGIDs is an indication for psychotropic agents, especially when stress reactivity is observed. Enthusiasm for newer antidepressants for FGIDs is based on their broad efficacy in the psychiatric conditions and potential efficacy on core IBS symptoms. Confirmation of existing practice with randomized controlled trials is still needed.

Conclusions

Clinician and basic investigators involved in the treatment or investigation of FGIDs or disease models need to have a comprehensive understanding of a vast

range of medications. It is anticipated that the interaction between investigators of basic science, basic and applied pharmacology, and clinical trials will lead to better treatment of patients with these disorders.

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