Published in final edited form as:
Neurogastroenterol Motil. 2011 March ; 23(3): 193–200. doi:10.1111/j.1365-2982.2010.01643.x.

LX-1031, a Tryptophan 5-hydroxylase Inhibitor, and Its Potential in Chronic Diarrhea Associated with Increased Serotonin

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Abstract

Background—LX-1031 is an oral, small-molecule tryptophan 5-hydroxylase (TPH) inhibitor that reduces serotonin (5-HT) synthesis peripherally. It has potential for illnesses characterized by excess 5-HT, such as diarrhea-predominant irritable bowel syndrome (IBS-D) and carcinoid diarrhea. In vitro, inhibition of TPH1 occurred in 10^{-8} – 10^{-7} M range. In vivo in rodents, LX-1031 has no effect on brain 5-HT while dose-dependently reducing 5-HT, particularly in the small bowel.

Pharmacokinetics—After oral LX1031 in humans, systemic exposure is very low, plasma concentrations are linear in dose range 250 mg QD to 750 mg QID; the median $T_{1/2}$ for elimination is ~20 hrs, and repeat administration for 14 days doubles C_{max}.

Pharmacodynamics—In ascending-*single-dose* and *multiple dose* (14 day) trials in healthy volunteers, LX-1031 2g-4g/day significantly reduced urinary 5-hydroxyindoleacetic acid (5-HIAA) starting by day 5, and persisting over the 14 day exposure.

Clinical safety and efficacy—There are no dose limiting toxicities in healthy subjects or remarkable adverse effects in clinical trials to date. Over a 28-day treatment period, LX-1031 was associated with improved weekly global scores (2/4 weeks) and improved stool consistency with lower urinary 5-HIAA excretion.

Conclusion—LX-1031 appears promising for chronic diarrhea associated with increased 5-HT expression including IBS-D. Optimal doses, efficacy and safety in IBS clinical trials need to be fully elucidated; low systemic exposure, selectivity for TPH1 over TPH2, and lack of effect on brain 5-HT in several species suggest that LX-1031 is unlikely to cause affective disorders.

Keywords

irritable bowel; carcinoid

LX-1031 is a heterocyclic substituted phenylalanine analog, an oral small-molecule (molecular weight 538) tryptophan hydroxylase (TPH) inhibitor that reduces synthesis of serotonin (5-HT) peripherally and is being developed for conditions characterized by excess 5-HT expression such as diarrhea-predominant irritable bowel syndrome (IBS-D) and, possibly, carcinoid diarrhea. The goal of blocking the effects of excessive 5-HT is certainly not new (1). However, prior approaches aimed at the inhibition of the synthesis of 5-HT, as

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Author's Contributions: Dr. Camilleri conceived, researched, and wrote this paper.

Disclosures: Dr. Camilleri has no disclosures relevant to this subject.

with para-chlorophenylalanine, have been impeded by the central adverse effects of inhibition of brain 5-HT synthesis with consequent affective disorders (2,3).

Carcinoid diarrhea is the principal condition resulting from the excessive production of 5-HT usually by metastatic tumor in the liver; it responds to inhibition of 5-HT's effects as with octreotide treatment (4,5), or to blocking the effects of 5-HT on the motor (6) and secretory (7,8) mechanisms that result in diarrhea as with alosetron (9). Tryptophan hydroxylase is expressed in carcinoid tumors (10) and may potentially be a target for pharmacological inhibition of 5-HT synthesis in this class by an agent that has sufficient systemic exposure; this might constitute an effective treatment for carcinoid diarrhea. However, carcinoid diarrhea is a relatively rare disorder compared to the chronic diarrhea associated with IBS.

The objective of this review is to appraise the pharmacology of LX-1031 and to assess its potential relative to medications in development for the treatment of IBS. IBS is considered to be a disease of the brain-gut axis. It may involve a broad range of physiological and psychological alterations affecting brain-gut regulation, gut function, visceral perception, and mucosal integrity and function (11). Published evidence supports a role of psychosocial (e.g. life event stress) and physical (e.g., enteric infections) stressors as central and peripheral triggers, respectively (12), and a putative role of low-grade chronic inflammation in the pathogenesis of IBS (12).

Current Treatment of IBS

Meta-analyses suggest (13) that several treatments such as peppermint oil, antidepressants, and probiotics based on *Bifidobacteria* are efficacious in treatment of IBS. The pipeline of medical treatments in IBS is replete with inconsistent or unclear results and failed drug development programs (14). Some targets for therapy are new such as the chloride channels; others are new approaches with promise to safely restore normal bowel function by stimulating motility and secretion. On the other hand, there are still no definite targets or proven therapies for visceral pain.

The predominant mechanism targeted for IBS-D is the 5-HT_3 receptor with antagonists like ramosetron. This class of drugs is associated with ischemic colitis and complications of constipation, and, over a 6.5 year period, only ~28,000 patients received the approved drug, alosetron, in the United States after the implementation of a risk management plan (15). A recently proposed use of the agent, colesevelam, is based on sequestration of bile acids and appears mostly applicable in patients with high rates of bile acid synthesis and presumably bile acid malabsorption (16). Rifaximin, a non-absorbable antibiotic, appears efficacious in non-constipated IBS. Current status of the efficacy and safety of new 5-HT_4 agonists, 5-HT_3 antagonists, intestinal secretagogues (chloride channel activators, guanylate cyclase C agonists), bile acid modulation, anti-inflammatory approaches, κ-opioid agonist, pregabalin and gabapentin is reviewed elsewhere in detail (17), and a summary is provided in Table I. Thus, there is a continued unmet need for new, safe, effective treatment of diarrhea and global symptoms in IBS-D.

Serotonin Synthesis, Actions in GI Tract and Putative Role in IBS Pathogenesis

It is estimated that 95% of the 5-HT in the human body is located in the GI tract, with 90% being in enterochromaffin (EC) cells in the epithelial layer and 5% in the neural structures intrinsic to the bowel wall. 5-HT is also present in blood platelets. 5-HT is synthesized from tryptophan sequentially by tryptophan hydroxylase (TPH) and aromatic amino acid

decarboxylase (AADC). TPH exists as two isoforms: TPH1 and TPH2. These share ~70% identity and they are ~50% identical to phenylalanine and tyrosine hydroxylases. In enterochromaffin (EC) cells of the gut, TPH1 is primarily expressed; in contrast, TPH2 is expressed exclusively in neuronal cells, including the myenteric plexus. 5-HT is involved in motility, sensation and secretion in the gastrointestinal tract (18).

There are seven main classes of 5-HT receptors, with several subclasses that can be differentiated on the basis of their molecular structure, transduction pathways and functions (19). To date, the serotonergic receptors of greatest relevance in the GI tract are the 5-HT_3 receptors which are ion channels, and the 5-HT_4 receptors which have 7 transmembrane domains. 5-HT reuptake is a mechanism for inactivation of released 5-HT in the digestive tract as well as in the central nervous system (CNS) and platelets. 5-HT reuptake is controlled by a serotonin transporter protein (SERT) which is one of the solute carrier family of proteins (SLC6A4).

The principles linking 5-HT as a critical transmitter involved in the pathophysiology of IBS are summarized here and have been discussed in detail elsewhere (18).

The most consistent findings are the increase in plasma 5-HT in diarrheal diseases such as carcinoid diarrhea and IBS-D, including in children with IBS-D, and reduced levels in IBS-C (20–24). In addition, some reports document alterations in tissue levels of 5-HT and of the reuptake protein SERT in IBS. Thus, for example, post-infectious IBS is associated with increased 5-HT content in rectal biopsies (25,26); on the other hand, tissue expression of SERT in rectal or colonic biopsies is inconsistent in different reports in the literature (27–29). Reduced platelet SERT has been reported with increased plasma 5-HT in IBS-D, and platelet SERT influences the response to the 5-HT_3 receptor antagonist, alosetron (30). Several groups investigated whether genetic control of SERT was associated with IBS, in view of the potential role of SERT in determining plasma and tissue 5-HT levels. Meta-analysis shows that *5-HTTLPR* genotype (the gene controlling the promoter for SERT protein synthesis) is not significantly associated with IBS in Caucasians or Asians (31). Conversely, Niesler et al. have demonstrated association of a functional variant in the 5-HT_{3e} gene and IBS-D (32).

Serotonergic agents are used in therapy of lower functional gastrointestinal disorders. In IBS-D, alosetron (which blocked the effects at 5-HT_3 receptors that are relevant to stimulation of motility and secretion and transmission of pain in the gut) shows considerable efficacy in the relief of urgency, diarrhea and abdominal pain. These agents did not reduce the 5-HT content, production or release from the gut. The early generation 5-HT_4 receptor agonists, such as cisapride and tegaserod, reversed slow motility and relieved constipation, but they have been withdrawn because of cardiac or vascular adverse effects. These agents activate receptors on intrinsic cholinergic neurons to stimulate motility without increasing the levels of 5-HT which appears to be deficient in patients with IBS-C or diseases associated with constipation (33). Newer 5-HT_3 receptor antagonists (34–36) and 5-HT_4 receptor agonists (37–39) are efficacious, appear to be safer than earlier generation agents in these classes, and promise to provide relief for IBS symptoms in patients (40).

A novel class of compounds (of which the prototype is LX-1031) is being developed that directly inhibits 5-HT synthesis in enterochromaffin cells, potentially reversing the underlying pathogenetic factor in conditions like IBS-D. This could be an alternative to the application of 5-HT_3 receptor antagonists in IBS-D.

Serotonin Synthesis Inhibition

Direct blockade of 5-HT synthesis can be achieved through inhibition of TPH with para-chlorophenylalanine (pCPA); however, this results in depletion of brain 5-HT, and it is linked to depression and other alterations in CNS-mediated functions such as weight loss ataxia and debilitation (41), thus precluding therapeutic use.

LX-1031 is an oral, small-molecule TPH inhibitor that reduces synthesis of 5-HT peripherally. LX-1031 is one of a series of substituted 3-(4-(1,3,5-triazin-2-yl)-phenyl)-2-aminopropanoic acids that were optimized through extensive structure-activity relationship studies (42,43) to act locally in the intestine with minimal systemic exposure after oral administration. The class of drugs does not penetrate the blood-brain barrier, in part, as a result of its molecular size.

Preclinical Development

Preclinical pharmacology

The series of aminopropanoic acid compounds (that include LP-533401 and its ethyl ester prodrug LP-615819) inhibit TPH1 at low concentrations: the *in vitro* IC50 value of LP-533401 was 0.7μM against purified human TPH1 in enzyme and cell-based assays, and IC50 value was 0.4 μM in inhibition of 5-HT synthesis in the rat mastocytoma cell line RBL-2H3 (44). This class of compounds, exemplified by effects in vitro in enzyme and cell-based assays (44), inhibits both TPH1 and TPH2. The selectivity for inhibition of TPH1 in the gastrointestinal tract rather than the brain is, therefore, based on distribution of the compound and failure to cross the blood-brain barrier. Thus, Shi et al. reported that the concentration of LP533401 in the brain is approximately 1% of that in the plasma after dosing at 10mg/kg by oral gavage (42,44).

In mice, administered doses of 0, 30 and 90 mg/kg *in vivo* LP-533401 had no effect on 5-HT levels in the brain, but it dose-dependently reduced 5-HT levels in the duodenum, jejunum and ileum. At equal doses, LP-615819 was more potent than para-chlorophenylalanine in reducing 5-HT in the jejunum. However, unlike para-chlorophenylalanine, LP-615819 did not reduce brain 5-HT (44).

Dose-dependent 5-HT reduction in the gastrointestinal tract by LP-615819 was also demonstrated in the mouse in studies that compared vehicle, 20, 45 and 90 mg/kg. Effects in duodenum, jejunum and ileum were consistent (44); effects in the antrum and colon were less dramatic (about 25 and 50% relative reductions compared to vehicle); in contrast, there were no effects on brain 5-HT expression. The effects on intestinal 5-HT expression were confirmed by immunohistochemistry (Figure 1).

With oral administration of LX-1031 in mice, the average 5-HT reductions in the jejunum relative to control were ~33, 51, and 66% with the 15, 45 and 135 mg/kg/day doses respectively (Figure 2); the effect of 5 mg/kg/day on GI 5-HT content was not significantly different from control. In separate studies, 15, 50 and 150 mg/kg p.o. daily did not alter brain 5-HT content [(45) Figure 2]. In a preliminary report (in abstract form), the effects of LX-1031, 100mg/kg daily, on 5-HT levels in jejunal mucosa were reversible within 2 days of discontinuation in mice (45).

Animal pharmacology

In a dose-response study of 10, 30 and 90 mg/kg, LP-615819 reduced by 50% (relative to the active comparator, ondansetron) the cisplatin-induced, centrally-mediated emesis associated with release of gut 5-HT in ferrets. The anti-emetic effects of LP-615819 were

associated with the reduced duodenal and jejunal 5-HT content and no effect on brain 5-HT content.

Pharmacokinetics

Pharmacokinetics

After oral administration of LX-1031, systemic exposure is very low; the mean $t_{1/2}$ of elimination is ~20 hours across all dose groups tested. C_{max} ranged from 84.4 to 384 ng/mL under fed conditions. LX-1031 was detected in plasma ~30 minutes after a single oral dose on Day 1. Plasma concentrations and exposures increased over the range 250 mg q.d. to 750 mg q.i.d., but plasma concentrations were similar between 750 mg q.i.d. and 1000 mg q.i.d. (Figure 3). A preliminary report indicates the mean $AUC_{(0–6h)}$ was approximately 3-fold higher and the C_{max} was 2-fold higher on Day 14 than Day 1 for all dose groups, and the elimination pattern of LX-1031 from plasma was multiphasic (45). A full report is awaited to assess the potential for accumulation of medication, as well as the relationship of trough and peak levels to pharmacodynamic effects.

In view of the low systemic exposure of LX-1031, treatment of carcinoid diarrhea may require development of an analog [LX-1032 (46)] with greater systemic exposure to target synthesis of 5-HT in metastatic carcinoid tumor cells. Review of LX-1032 is outside the scope of the current review of LX-1031.

Pharmacodynamics in healthy volunteers

In double-blind, serial, multiple-ascending dose tolerance studies (doses of LX-1031 ranging from 250 mg q.d. to 1000 mg q.i.d.), mean 5HIAA reductions of 33% were noted (47). In phase I multiple-dose studies, 54 healthy volunteers received the drug for up to 14 days while the diet was strictly controlled to avoid 5-HT-rich foods. Urine 24-hour collections were obtained at baseline and on days 5, 10 and 14. Significant reductions in urinary 5-HIAA, observed by day 5, persisted over the duration of exposure [(47) Figure 4].

Safety

In studies conducted in healthy normal participants receiving 250 mg up to 2000 mg, single daily doses in 39 volunteers (30 male, 9 female), and multiple doses in 72 volunteers (54 males and 18 females) over 2 weeks were well tolerated with no dose limiting toxicities reported. LX-1031 was well tolerated at doses up to 4g/day over 14 days (47).

Clinical Development: Phase II Study

LX-1031 was tested in a multicenter, double-blind, placebo-controlled, randomized clinical trial (NCT00813098) of 250 or 1000 mg q.i.d. vs. placebo for 28 days in 155 patients with non-constipated IBS (48). The results appear in an abstract (48): Urine and blood samples were collected pre-dose, on Day 28, and 2 weeks after last dose in a subset of patients (n=80) to evaluate blood 5-HT and urinary 5-HIAA. A dose-dependent reduction in 24-hour urinary 5-HIAA was observed (49), indicating pharmacologic inhibition of peripheral 5-HT production. A reduction in whole-blood 5-HT was also observed. These reductions in 5-HIAA correlated with improvements in global assessment of adequate relief and stool consistency in patients with non-constipating IBS. The study endpoint was global assessment of relief of pain/discomfort weekly, and responders were defined based on weekly global relief in 2/4 weeks: 61% of 1000 mg q.i.d. LX-1031-treated and 45% of placebo-treated patients achieved this primary study endpoint. It is unclear how the drug performed using the more stringent definition of weekly responders based on 75% of weeks

of the trial. LX-1031, 1000 mg dose, improved stool consistency. This effect occurred from week 1 and there was significant correlation with urine 5-HIAA reduction (49).

The preliminary report provided no data on the effects of the 250 mg q.i.d. dose in the phase II trial.

No Phase III trials have been reported to date.

Adverse Effects

Data available in an abstract (47) suggest that, in two small clinical trials (LX.1031.102, n=30 and LX.1031.103, n=24), LX-1031 was well tolerated, with no imbalance in adverse effects other than incidental injury (4/30 vs. 0/18 for placebo), skin or subcutaneous disorders (4/30 vs. 0/18 for placebo) and vascular disorders (2/30 vs. 0/18 for placebo) in one of the two clinical trials. In the other clinical trial with 24 participants, none of these adverse effects were recorded.

In the phase II clinical trial (48), LX-1031 was well tolerated at both dose levels (250 and 1000 mg q.i.d.) over the 28-day treatment period with no evidence of dose-limiting toxicity.

Summary and a Look to the Future

LX-1031 represents a novel class of drugs that has the potential to reverse one of the mechanisms that mediates symptoms of IBS, including diarrhea and, potentially, also pain. Efficacy studies have demonstrated that an increased proportion of LX-1031-treated patients with IBS experienced global relief and improved bowel function (e.g. stool consistency) compared with patients who received placebo. The multiple studies in animal species suggest the inhibition is selective to the periphery and the central effects attributed to the drug, para-chlorophenylalanine, are avoided.

The proof of concept studies to data have focused on the use of a biochemical marker, that is, urinary 5-HIAA excretion, which reflects metabolism of 5-HT. Dose selection to date appears based on the urinary 5-HIAA excretion and plasma 5-HT. There are no reports of dose-response studies using pharmacodynamic measurements that more closely reflect the manifestations of IBS, such as colonic transit or sensation. The drug development program has fairly extensively tested in humans the 250 mg and 1000 mg q.i.d. doses. However, in the phase IIB clinical trial, the preliminary report did not provide data on efficacy of the lower dose. Hence, the lowest and highest effective doses are as yet unclear. Further studies are needed using the endpoints proposed for regulatory approval (50); in particular, the potential benefit of TPH1 inhibition for the pain component of IBS requires further study. Whereas, the 5-HT_3 receptor antagonist, alosetron, significantly impacted the pain of IBS by targeting visceral afferents that have 5-HT_3 receptors (51) or central mechanisms in IBS patients (52), it is uncertain whether global inhibition of 5-HT synthesis by LX-1031 will have direct effects on pain pathways.

While we await the results of phase III clinical trials, the potential adverse effects and safety from inhibition of peripheral 5-HT synthesis in large numbers of patients are similarly important. Will TPH inhibitors induce severe constipation? Will the imbalance of 5-HT alter platelet function or function of vascular smooth muscle? Will this class of drugs induce ischemic colitis, which remains a disincentive to prescription of 5-HT_3 receptor antagonists in IBS patients? On the other hand, there appears to be a potential advantage for women with IBS-D receiving TPH1 inhibitors. Thus, this class of compounds appears to have an effect on osteoporosis, based on the observation that LP533401, another small molecule inhibitor of TPH1, administered orally daily for up to six weeks acts prophylactically or

therapeutically, in a dose-dependent manner, to treat osteoporosis in ovariectomized rodents by increase in bone formation (53).

In conclusion, small molecule TPH1 inhibitors, of which the prototype is LX-1031, constitute an intriguing class of novel compounds which has the potential to improve bowel dysfunction in conditions associated with increased production of 5-HT. This class of compounds has potential in IBS-D and carcinoid diarrhea. Optimal dose, efficacy and safety require further elucidation.

Acknowledgments

Dr. Camilleri's work in IBS is supported by NIH grants DK79866 and DK86182.

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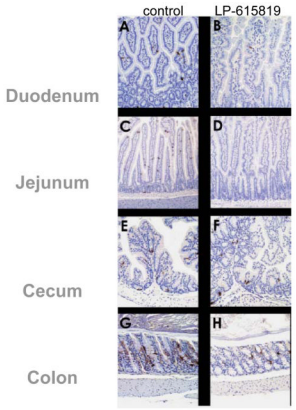

Figure 1.
Effect of LP-651819 on expression of 5-HT in mice, based on immunohistochemistry. Reproduced with permission from ref. [44], Liu et al. JPET 2008;325:47–55.

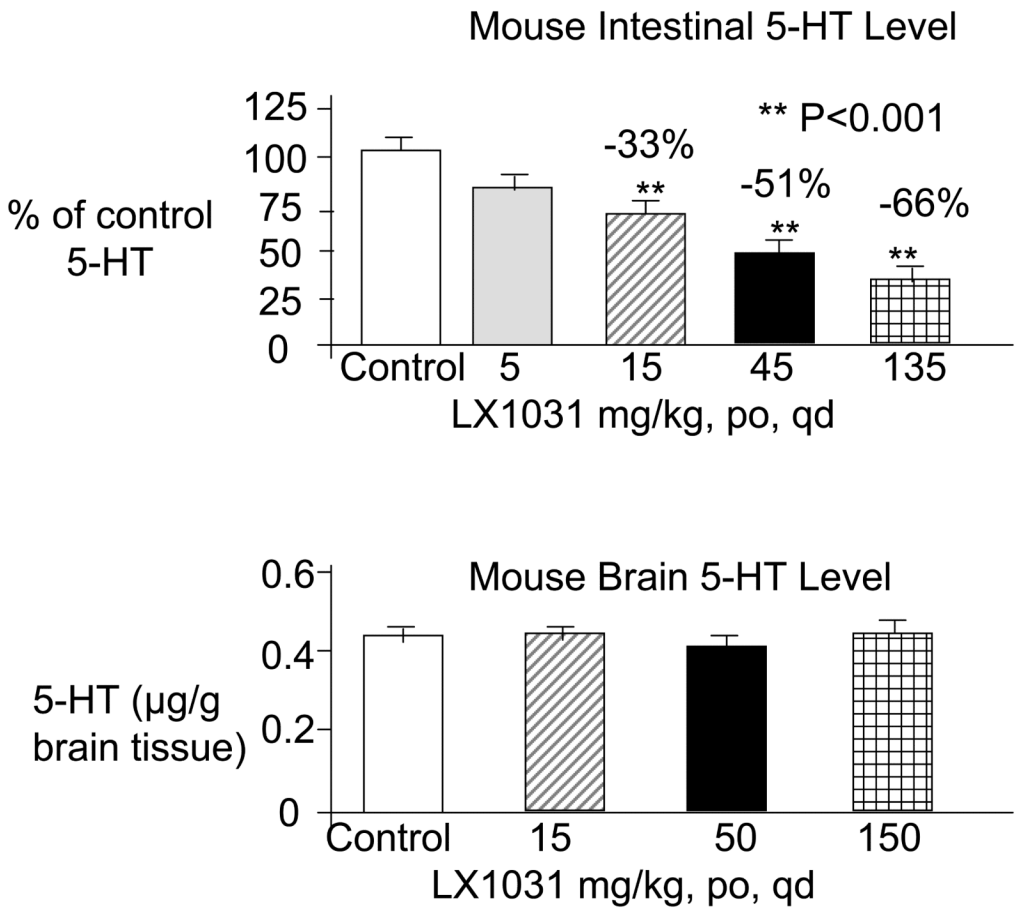

Figure 2.
Administration of LX-1031 reduces 5-HT in the GI tract but not in the brain. Reproduced from ref. [45], Brown PM et al. Am J Gastroenterology 2007;102:S961 (abstract).

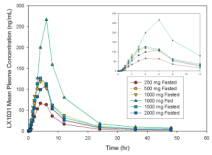

Figure 3.
LX-1031 mean plasma concentration over time.
Inset: The plasma concentrations are plotted over the first 12 hours after oral administration.
Reproduced from ref. [45], Brown PM et al. Am J Gastroenterology 2007;102:S961 (abstract).

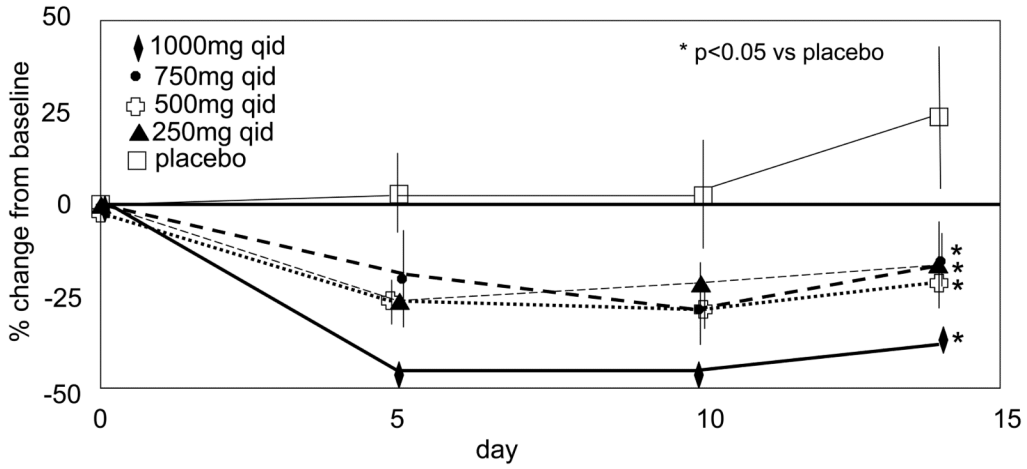

Figure 4.
Inhibition of 5-HT synthesis shown by reduced urinary 5-HIAA. Reproduced from reference [47], Brown P et al. Gastroenterology 2009;136(Suppl 1):A237 (abstract).

Table 1

Summary of Current and Most Promising Novel Therapies for IBS

Drug	Drug Class	Pharmacodynamic	Clinical Efficacy	Adverse effects
Antispasmodics, peppermint oil	Antispasmodics, peppermint oil	Muscle relaxant	Episodic pain; older, relatively small trials	-
Prucalopride	5-HT_4 receptor agonist	Accelerate colon transit	Extensive clinical trial efficacy for CC, not for IBS	Concerns about 5-HT_4 cardiac effects appear unfounded based on dose difference to stimulate IKr
Velusetrag	5-HT_4 receptor agonist		Single phase II CC study shows efficacy	
Naronapride	5-HT_4 receptor agonist		Single phase II CC study shows efficacy	
Alosetron	5-HT_3 receptor antagonist	Delay colon transit, reduce visceral sensation	Extensive clinical trial efficacy for IBS-D	Significant constipation, class-related ischemic colitis
Ramosetron	5-HT_3 receptor antagonist		2 trials clinical efficacy for IBS-D	
Dexloxiglumide	CCK_1 receptor antagonist	Delay asc. colon transit	Inconsistent efficacy in trials	-
Lubiprostone	Cl-channel opener	Accelerate SB and colon transit	Extensive clinical trial efficacy for CC, IBS-C	Nausea in ~25%
Linaclotide	Guanylate cyclase C receptor agonist	Accelerate colon transit	Extensive clinical trial efficacy for CC, IBS-C	Diarrhea
Colesevelam	Bile acid binder	Slows colon transit based on BA synthesis rate	No clinical trials	-
Na cromoglycate	Mast cell stabilizer	Reduced mast cells	Weak clinical trial efficacy	-
Ketotifen	Mast cell stabilizer, histamine H_1 receptor antagonist	Unclear, ? reduced sensation	Weak clinical trial efficacy	Central effects e.g. fatigue
Mesalazine	5-ASA agent	Reduced inflammation	Weak clinical trial efficacy	-
Pregabalin	GABA; α2δ ligand	Reduced pain in animal and human models of IBS	No completed clinical trials	Central effects
Tricyclics	Tricyclics		Few small positive trials; Meta-analysis unconvincing	Central effects; constipation; anti-cholinergic effects
SSRI/SNRI	SSRI/SNRI			Central effects; diarrhea
Dextofisopam	Benzodiazepine	Unclear	Weak clinical trial efficacy	Central effects?
Asimadoline	K opioid receptor agonist	Reduced pain in models	Weak clinical trial efficacy	-
Probiotics		Unclear	*Bifidobacteria*, combined probiotics beneficial	-
Rifaximin	Unabsorbed antibiotic	Adequate relief of IBS and bloating	Extensive clinical trial efficacy for IBS-non-C	Efficacy persists for 10 weeks after stopping Rx