Behavioural and new pharmacological treatments for constipation: getting the balance right

Michael Camilleri, Adil E Bharucha

ABSTRACT
Chronic constipation affects almost one in six adults and is even more frequent in the elderly. In the vast majority of patients, there is no obstructive mucosal or structural cause for constipation and, after excluding relatively rare systemic diseases (commonest of which is hypothyroidism), the differential diagnosis is quickly narrowed down to three processes: evacuation disorder of the spastic (pelvic floor dysynergia, anismus) or flaccid (descending perineum syndrome) varieties, and normal or slow transit constipation. Treatment of chronic constipation based on identifying the underlying pathophysiology is generally successful with targeted therapy. The aims of this review are to discuss targeted therapy for chronic constipation: behavioural treatment for outlet dysfunction and pharmacological treatment for constipation not associated with outlet dysfunction. In particular, we shall review the evidence that behavioural treatment works for evacuation disorders, describe the new treatment options for constipation not associated with evacuation disorder, and demonstrate how ‘targeting therapy’ to the underlying diagnosis results in a balanced approach to patients with these common disorders.

INTRODUCTION
Chronic constipation affects almost one in six adults and is even more frequent in the elderly. In the vast majority of patients, there is no obstructive mucosal or structural cause for constipation and, after excluding relatively rare systemic diseases (commonest of which is hypothyroidism), the differential diagnosis is quickly narrowed down to three processes: evacuation disorder of the spastic (pelvic floor dysynergia, anismus) or flaccid (descending perineum syndrome) varieties, and normal or slow transit constipation. Figure 1 illustrates the function of the pelvic floor and anal sphincters during the process of defecation. The coordinated relaxation of the pelvic floor and anal sphincters, together with propulsion of content in the distal colon and raised intra-abdominal pressure during straining, allow the straightening of the rectoanal angle and comfortable, unimpeded evacuation of stool.

Treatment of chronic constipation based on identifying the underlying pathophysiology is generally successful with targeted therapy. The aims of this review are to discuss targeted therapy for chronic constipation: behavioural treatment for outlet dysfunction and pharmacological treatment for constipation not associated with outlet dysfunction. In particular, we shall review the evidence that behavioural treatment works for evacuation disorders, describe the new treatment options for constipation not associated with evacuation disorder, and demonstrate how ‘targeting therapy’ to the underlying diagnosis results in a balanced approach to patients with these common disorders.

ALGORITHM FOR THE MANAGEMENT OF CHRONIC CONSTIPATION
Figure 2 illustrates the algorithm used in our practice for the management of patients with chronic constipation. After excluding underlying diseases such as cancer, strictures, hypothyroidism and the adverse effects of medications and ensuring the patient has received an adequate trial of fibre supplementation (at least 12 g per day), there are assessments that are essential to guiding management: a test of evacuation function, typically ano-rectal manometry with balloon expulsion test, and a test of colonic transit, typically a radio-opaque marker transit test (figure 3). Alternatively, transit can be measured by radio-isotopic scanning or a wireless motility capsule. While the performance characteristics of the latter two transit methods have been extensively documented, they are not generally available or approved for use in some countries, and the most widely used transit method is based on radio-opaque markers. In our practice, almost half the patients referred with constipation not responding to first-line therapies have a disorder of rectal evacuation. It is important to note that delayed colonic transit may be the result of an evacuation disorder. Hence, colonic transit measurements have to be interpreted within the context of the evacuation dynamics. While it may not be essential to assess colonic transit initially in patients with defaecatory disorders, this test has been positioned at an early stage in the algorithm because many practitioners are more likely to have access to colonic transit than ano-rectal testing in their practice.

In selected patients, other tests may be required, as second-line approaches, such as magnetic resonance defaecography to evaluate evacuation dynamics. Barium or magnetic resonance defaecation videography may reveal anatomical disorders (eg, internal prolapse, intussusception, persistent rectoceles that
does not empty) that are amenable to surgical intervention. Similarly, colonic manometry and/or barostat testing may be needed to assess colonic motor activity in patients with severe slow transit constipation that is unresponsive to medical therapy, if the patient is being considered for colectomy.

WHAT IS THE EVIDENCE THAT BEHAVIOURAL TREATMENT WORKS FOR EVACUATION DISORDERS?

The predominant behavioural treatment is biofeedback. Through biofeedback therapy, patients are taught to appropriately use their abdominal and pelvic floor muscles during defaecation; patients receive feedback of anal and pelvic floor muscle activity recorded by surface electromyographic (EMG), anal pressure sensors, or digital examination by a therapist. Generally, patients are taught how to use their abdominal muscles to increase intra-abdominal pressure and keep the pelvic floor muscles relaxed during evacuation, and then employ these techniques to evacuate an air-filled rectal balloon while a therapist assists by providing external traction. Sensory retraining, in which patients learn to recognise weaker rectal filling sensation, can also be provided.

After several uncontrolled trials, there have been controlled trials assessing the role of behavioural therapy in the form of retraining with biofeedback. These studies started in the paediatric population, but recent data also included adults and the elderly. While childhood constipation is different from constipation in adults, we have included information from paediatric practice to provide a more comprehensive assessment, and because there were lessons learned from the paediatric experience. The trials are summarised in table 1. Recent advances in clinical practice group.bmj.com on March 12, 2011 - Published by gut.bmj.com
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ano-rectal functions in adults with defaecatory disorders. This improvement is sustained for up to 2 years. Moreover, in contrast to earlier studies from the St. Mark’s group, more recent data demonstrate that biofeedback therapy benefits patients with defaecatory disorders but not isolated slow transit constipation. Thus, biofeedback therapy is the treatment of choice for functional defaecatory disorders. The evidence in children and the elderly is somewhat weaker. In contrast, differences between EMG versus other forms of biofeedback therapy were not significantly different (OR 1.436, CI 0.692 to 3.089). Enck et al recommended caution in the interpretation of the meta-analysis, since the included trials showed a substantial lack of quality and harmonisation; for example, use of variable endpoints and missing psychological assessment across studies. Further studies are required to compare different types of instrumented therapy and also to compare instrumented versus non-instrumented feedback (ie, teaching pelvic floor exercises by digital examination with verbal feedback) are necessary.

Three issues unique to biofeedback training deserve emphasis. First, it requires concentration and cognitive processing that may be beyond the abilities of younger children. Second, it requires skilled and experienced therapists and an optimal therapist—patient relationship; the required skill level and experience is not widely available. Third, the efficacy of biofeedback retraining in flaccid disorders of evacuation (such as descending perineum syndrome) has not been evaluated in controlled studies, and the data from observational studies suggest it may be efficacious in only ~50% of patients. In addition, while the St. Mark’s group had suggested it is equally effective for patients with slow transit as for those with evacuation disorder, this was not confirmed by Chiarioni et al and most centres reserve this treatment for patients with evacuation disorders. Approximately 50% of patients with a defaecatory disorder have delayed colonic transit. Some patients with evacuation disorders continue to experience constipation after retraining; they usually have a combination of evacuation disorder and slow transit constipation and, typically, the constipation resolves with standard treatment with fibre and osmotic or stimulant laxatives, as long as the pelvic floor dysfunction has been rehabilitated.

What are the new treatment options for constipation not associated with evacuation disorder?

The efficacy of dietary fibre supplementation, osmotic laxatives, particularly polyethylene glycol, and stimulant laxatives (eg, bisacodyl) for chronic constipation is supported by rigorously conducted controlled trials. In addition to improving symptoms, these agents also accelerate colonic transit. For example, bisacodyl and sorbitol accelerate ascending colon emptying and colonic transit respectively in healthy subjects. A placebo-controlled study observed that bisacodyl, 10 mg/day for three consecutive days, was an effective rescue agent for chronic constipation. In another study, bisacodyl also improved stool frequency and consistency and straining at 14 and 28 days. These inexpensive approaches should be tried initially, particularly for patients who do not have an underlying evacuation disorder and in primary care.

Patients who do not respond to or tolerate these therapies may have a more complicated disorder such as an evacuation disorder, slow transit constipation or iatrogenic (usually drug-induced) constipation, as shown previously. The next section briefly reviews drugs in the pipeline for treatment of chronic constipation based on either recent regulatory approved in some countries or published data including at least phase II trials, based on a PubMed Search. There are two general categories of medications that are being developed for the treatment of chronic constipation: colonic prokinetics in the serotonin receptor subtype 4 (5-HT4) agonist class and intestinal secretagogues.

5-HT4 agonists

Of the 5-HT receptor subtypes in the gut, 5-HT3 and 5-HT4 receptors have been most extensively studied as potential targets of prokinetic drugs in humans. They have the potential to enhance laxation through the induction of fast excitatory postsynaptic potentials in intrinsic neurons, release neurotransmitters such as the excitatory acetylcholine, and...
induce mucosal secretion by activating submucosal neurons. With the withdrawal of cisapride and tegaserod because of cardiac or potential vascular adverse events and the appreciation that serotonin receptors modify vascular function (eg, 5-HT1B, 5-HT1D, 5-HT3B, 5-HT4 and 5-HT7 receptors induce contraction of arterioles and venules, and 5-HT1D, 5-HT3B, 5-HT4 and 5-HT7 receptors induce relaxation of venules), all new drugs in this class have to be devoid of cardiac effects (eg, arrhythmogenic effects and prolongation of QTc interval) and selective for 5-HT4 receptors over other receptors (eg, 5-HT3B, 5-HT7) and channels (eg, delayed rectifier potassium channel) and safety through studies of arrhythmogenic potential and effects on QTc interval. For example, it has been demonstrated that tegaserod has significant effects on receptors other than 5-HT4 that could conceivably influence vascular function.48 Table 2 is a summary of the three main candidate 5-HT4 agonists in development: prucalopride, velusetrag and ATI-7505. The properties of these newer agents, and in particular, their specificity and cardiovascular safety, differ from those of older 5-HT4 agonists.39 40 The largest body of evidence 41–47 on pharmacodynamic and clinical efficacy in disease (chronic constipation) is available for prucalopride, with several thousand patients exposed for assessing safety (at least 2000 in phase III clinical trials and 1000 patient-years cumulative follow-up). The European Agency for Evaluation of Medicinal Products (EMEA) approved the medication for chronic constipation at a dose of 2 mg per day in adults and 1 mg per day in the elderly.

Velusetrag, which shows specificity and safety in vitro and in vivo,48 49 has also been tested in pharmacodynamic studies in humans50 and in a large (400 patient) phase IIb study.51 While a single dose of velusetrag also accelerated colonic transit in a dose-dependent manner, there was tachyphylaxis with repeat dosing, particularly at the highest doses tested (eg, 50 mg daily).50 However, there was no evidence of tachyphylaxis during the 4-week clinical trial. Velusetrag has one metabolite which is almost as potent as the parent drug.

ATI-7505 has only recently entered into clinical trials, but the pharmacodynamic efficacy appears promising.52 53 The lack of CYP3A4 metabolism of prucalopride and ATI-7505 is also potentially advantageous to avoid drug interactions.

In conclusion, the new generation of 5-HT4 agonists appears effective and safe. Prucalopride has been approved for marketing at a standard dose of 2 mg per day for adults and a starting dose of 1 mg per day for elderly patients. The velusetrag development programme includes one completed phase IIb study51 that confirms efficacy. There is reason for optimism in medical treatment of chronic constipation that is unresponsive to current therapy, as shown for prucalopride in the phase III programme44–46 in which patients had an average of less than one spontaneous bowel movement per week and ~80% reported insufficient response to current treatment with laxatives.

**Intestinal secretagogues**

In addition to being troublesome per se, hard stools are also more difficult to evacuate, providing the rationale for intestinal secretagogues to relieve constipation. Both secretagogues for chronic constipation increase intestinal chloride secretion which is followed by secretion of water into the lumen. There are several different classes of chloride channels (CIC) including CIC-2 and CIC-3 which are expressed in most cells. Epithelial chloride transport induces fluid secretion: chloride enters into the enterocyte or colonocyte through the basolateral Na+-K+2Cl− co-transporter (with the cations being exported through the Na+ pump (Na+, K+, ATPase) and KCNQ1/KCNE3 heteromeric K+ channels which are needed for K+ recycling) (figure 4). Secretory pathways in the apical membrane of the enterocyte include cystic fibrosis transmembrane regulator (CFTR) and CIC-2 chloride channels, which allow chloride secretion.54–56

**Lubiprostone**

Lubiprostone is a bicyclic fatty acid that is derived from prostaglandin E1. It selectively activates apical membrane CIC-2 channels to increase intestinal and colonic secretion of chloride-rich fluid into the intestinal lumen. Lubiprostone increased electrogenic chloride transport with a 50% effective concentration (EC50) of ~18 mmol/l in vitro54 and dose dependently increased water and chloride secretion in rats in vivo.57 Though initial studies suggested it does not activate CFTR channels, more recent data suggest that CFTR is necessary58 and prostaglandin E1 receptors may be activated, too.59 Lubiprostone accelerated intestinal and colonic transit in healthy subjects,59 but had no significant effect on colonic motility or sensation60 in humans or smooth muscle in vitro.61 Lubiprostone may enhance mucosal barrier function.62 Clinical trials demonstrate its efficacy and safety in chronic constipation, and it is FDA approved at a dose of 24 µg twice daily for this indication.63–65 Lubiprostone is reported to cause nausea in about 20% of patients.

**Guanylylcy clase C**

Guanylylcy clase C (GC-C) is the principal receptor for heat-stable enterotoxins (STa), a major causative factor in *Escherichia coli*–induced secretory diarrhea. GC-C is enriched in intestinal epithelium, though it is detected in other epithelia.66 It consists of an extracellular receptor domain, a single transmembrane domain, a kinase homology domain, and a catalytic domain. It is modified by N-linked glycosylation and, at least in the small intestine, by proteolysis, resulting in an STα receptor that is coupled non-covalently to the intracellular domain. The enteric bacterial peptides in the heat-stable enterotoxin family (ST peptides) (19 AAs) induce secretion by activating this surface receptor. There are two endogenous ligands of GC-C: the small cysteine-rich peptides, guanylin (15AA) and uroguanylin (16AA), which are released in an autocrine or paracrine fashion into the intestinal lumen,
<table>
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<tr>
<th>Reference</th>
<th>Patients</th>
<th>Behavioural treatment</th>
<th>Design and comparator</th>
<th>Main results</th>
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<tr>
<td><strong>Children</strong></td>
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<td>Wald 1987</td>
<td>50 encopretic children; 18 FFR</td>
<td>BF</td>
<td>Single blind, versus mineral oil</td>
<td>At 12 months, FFR remission or markedly improved: 6/9 (BF) vs 3/9 on mineral oil</td>
</tr>
<tr>
<td>Loening-Baucke 1990</td>
<td>43 children: impaction, encopresis</td>
<td>BF + laxatives</td>
<td>DB, RCT, versus laxatives</td>
<td>At 12 months, 50% (BF) vs 16% (laxatives) symptom resolution; 55% (BF) vs 5% defecation dynamic response</td>
</tr>
<tr>
<td>Van der Plas 1996</td>
<td>192 children constipation, not all FFR</td>
<td>EMG BF + laxatives</td>
<td>DB, RCT, versus laxatives</td>
<td>No symptomatic benefit from BF but improved defecation dynamics</td>
</tr>
<tr>
<td>Nolan 1998</td>
<td>29 children with anismus</td>
<td>EMG BF + CMT</td>
<td>RCT versus CMT</td>
<td>No symptomatic benefit from BF but improved defecation dynamics</td>
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<td><strong>ADULTS</strong></td>
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<tr>
<td>Bleijen-berg 1994</td>
<td>20 adults with constipation+PD</td>
<td>Intra-anal EMG BF</td>
<td>RCT versus balloon training</td>
<td>73% (EMG BF) vs 22% (balloon BF) symptom response rate</td>
</tr>
<tr>
<td>Koulso-manis 1995</td>
<td>60 adults constipation; 47/60 PD</td>
<td>EMG and rectal balloon BF</td>
<td>RCT versus muscular coordination training + balloon</td>
<td>Relative to baseline, both arms (EMG and pressure) of BF effective, but no difference between the 2 Rx arms</td>
</tr>
<tr>
<td>Heymen 1999</td>
<td>36 adults with constipation</td>
<td>4 anal EMG BF arms</td>
<td>RCT</td>
<td>Relative to baseline, EMG BF alone as effective as EMG+balloon training, home training, or both.</td>
</tr>
<tr>
<td>Gla 1997</td>
<td>20 adults with constipation+PD</td>
<td>Peri-anal EMG BF</td>
<td>RCT versus pressure BF+balloon training</td>
<td>Relative to baseline, both arms (EMG and pressure) of BF effective, but no difference between the 2 Rx arms</td>
</tr>
<tr>
<td>Chiarioni 2006</td>
<td>99 adults with PD</td>
<td>BF</td>
<td>RCT versus PEG (14.6-29.2 g/d) + counselling</td>
<td>At 6 months, major clinical improvement 80% (BF) group versus 20% PEG group; results sustained 2 years</td>
</tr>
<tr>
<td>Rao 2007</td>
<td>77 adults with constipation+PD</td>
<td>BF</td>
<td>RCT versus Sham (relaxation Rx)</td>
<td>88% (BF) satisfactory response vs 48% on control; improved defecation dynamics</td>
</tr>
<tr>
<td>Heymen 2007</td>
<td>84 adults with constipation and PD</td>
<td>EMG BF + pelvic floor exercises</td>
<td>3-arm RCT versus diazepam or placebo 1–2 h before attempt to defaecate</td>
<td>Adequate relief of constipation: 70% (BF) vs 23% (diazepam) vs 38% (placebo); more unassisted BMs and reduced strain</td>
</tr>
<tr>
<td>Farid 2009</td>
<td>48 adults with anismus</td>
<td>balloon pressure BF</td>
<td>RCT; Botulinum toxin (BTX) -A to EAS</td>
<td>1 month improvement: 6% versus BTX-A 71% (p = 0.008); 1 year improvement 25% vs 33%</td>
</tr>
<tr>
<td>Simon 2009</td>
<td>30 elderly constipated with PD</td>
<td>EMG BF</td>
<td>Counselling on behavioural mechanisms in defaecation</td>
<td>Improved symptoms and EMG results in biofeedback group at 4 weeks and 2 months</td>
</tr>
</tbody>
</table>

BF, biofeedback; BM, bowel movements; CMT, conventional medical therapy; DB, double-blind; EAS, external anal sphincter; EMG, electromyography; FFR, functional faecal retention; PD, puborectalis dyssynergia; RCT, randomised controlled trial.
Table 2  Comparison of novel 5-HT\textsubscript{4} agonists

<table>
<thead>
<tr>
<th></th>
<th>Prucalopride</th>
<th>Velusetrag</th>
<th>ATI-7505</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemistry</strong></td>
<td>Benzofuran carboxamide</td>
<td>Quinolinone carboxamide</td>
<td>Benzoamide</td>
</tr>
<tr>
<td><strong>Selectivity and affinity for 5-HT\textsubscript{4} receptor</strong></td>
<td>Highly selective, high-affinity; weak affinity for human D\textsubscript{2} and (\alpha\textsubscript{1}), and mouse 5-HT\textsubscript{1A} receptors at concentrations exceeding the Ki for 5-HT\textsubscript{4} receptors by 290-fold</td>
<td>High affinity and selectivity for h5-HT\textsubscript{4} over other biogenic amine receptors; &gt;500-fold selective over other 5-HT receptors (including h5-HT\textsubscript{2B}, h5-HT\textsubscript{3A})</td>
<td>Specific 5-HT\textsubscript{4} full agonist activity in the GI tract, but a partial agonist activity in the heart</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Limited hepatic, not CYP 3A4</td>
<td>CYP 3A4</td>
<td>Hydrolytic esterase, not CYP 3A4</td>
</tr>
<tr>
<td><strong>Pharmacodynamic efficacy in humans</strong></td>
<td>Accelerated colonic transit in health and chronic constipation</td>
<td>Accelerated colonic transit in health in dose-related fashion</td>
<td>Accelerated colonic transit in health</td>
</tr>
<tr>
<td><strong>Clinical trial efficacy</strong></td>
<td>Phase II and III portfolio in chronic constipation</td>
<td>Phase IIB</td>
<td>Phase IIB</td>
</tr>
<tr>
<td><strong>Open label effectiveness</strong></td>
<td>Open label experience of ~1000 cumulative patient-years</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><strong>Arrhythmogenicity</strong></td>
<td>No arrhythmic activity in human atrial cells; inhibited hERG channel only at (1 \mu\text{mol/l}) concentration (IC\textsubscript{50} \approx 4.9 \times 10^{-6} \mu\text{mol/l}); no clinically relevant cardiac AEs in clinical trials of &gt; 4000 humans</td>
<td>At 3 \mu mol/l, no effect on hERG channel current; safety ratio versus cisapride &gt;1000-fold; no effect on QT in health or 400 patients with constipation</td>
<td>At 100 \mu mol/l, no effect on hERG channel; affinity ratio between (I_{\text{p}}) and 5-HT\textsubscript{4} receptors of &gt;1000-fold.</td>
</tr>
<tr>
<td><strong>Cardiovascular safety including elderly</strong></td>
<td>Healthy subjects ‘through’ QTc study; safety in elderly cohort 80% on CV drugs</td>
<td>Healthy subjects ‘through’ QTc study; transient increase in heart rate not different from placebo</td>
<td>Healthy subjects ‘through’ QTc study;</td>
</tr>
<tr>
<td><strong>Commonest AEs</strong></td>
<td>Diarrhoea, headache</td>
<td>Diarrhoea, nausea, headache</td>
<td>Diarrhoea, headache</td>
</tr>
<tr>
<td><strong>Approval status</strong></td>
<td>EMEA</td>
<td>—</td>
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EMEA, European Medicines Agency; hERG, human ether-a-go-go-related gene.

but may also function as endocrine hormones in gut—kidney communication and as regulators of ion transport in extra-intestinal epithelia. Activation of GC-C occurs by inducing a conformational change in the extracellular portion of the homotrimeric GC-C complex, which allows two of the three intracellular catalytic domains to dimerise and form two active catalytic clefts. In the intestine, activation of GC-C results in stimulation of chloride and bicarbonate secretion through the opening of apical CFTR chloride channels and inhibition of sodium absorption through blockade of an apical Na/H exchanger. The principal effector of the GC-C effect on ion transport is cGMP-dependent protein kinase type II which, together with GC-C and the ion transporters, may form a supra-molecular complex at the apical border of epithelial cells.

Linaclotide

Linaclotide is a 14 amino acid peptide that contains three disulphide bonds required for GC-C activation. The active metabolite, MM-419447, is produced after loss of the C-terminal tyrosine through the action of carboxypeptidase A. By increasing cyclic guanosine monophosphate (cGMP), linaclotide induces signalling pathways which stimulate chloride and bicarbonate secretion through CFTR channel-dependent and, to a lesser extent, channel-independent mechanisms.\textsuperscript{67} Linaclotide also inhibits sodium absorption from the lumen by a sodium proton exchanger.\textsuperscript{68} Phase IIA placebo-controlled studies of 2 weeks and 5 days in duration showed that linaclotide improved symptoms and accelerated colonic transit.\textsuperscript{69–71} A phase IIB study of 310 patients with chronic constipation who were treated with placebo or one of four doses of linaclotide (75, 150, 300 or 600 µg once daily) for 4 weeks confirmed that all four doses improved constipation symptoms.\textsuperscript{72} Table 3 summarises the properties of these two chloride secretagogues.

**ACHIEVING A BALANCE IN THE CLINICAL MANAGEMENT OF CHRONIC CONSTIPATION**

While the stepwise approach shown in figure 2 has not been formally evaluated, it is widely employed and, in our experience, provides a logical, balanced and effective approach to managing constipation in clinical practice. This algorithm is underpinned by the concepts that: (1) dietary fibre supplementation and osmotic agents should be initially tried for patients with chronic constipation, particularly in...
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Table 3  Comparison of secretagogues, lubiprostone and linaclotide

<table>
<thead>
<tr>
<th></th>
<th>Lubiprostone</th>
<th>Linaclotide</th>
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</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td>Bicyclic fatty acid called a prostone</td>
<td>14 amino acid peptide, analogue of guanylin</td>
</tr>
<tr>
<td>Target receptor</td>
<td>Chloride channel (ClC2); ? CFTR involved</td>
<td>Guanylate cyclase C receptor activation with CFTR-meditated secretion</td>
</tr>
<tr>
<td>Pharmacodynamics in humans</td>
<td>Accelerated small bowel and colonic transit in health</td>
<td>Accelerated colonic transit in IBS-C in dose-related fashion</td>
</tr>
<tr>
<td>Clinical trial efficacy</td>
<td>Phase II and III portfolio in chronic constipation and C-IBS</td>
<td>Phase IIB in chronic constipation and IBS-C</td>
</tr>
<tr>
<td>Open label effectiveness</td>
<td>Clinical practice experience</td>
<td>—</td>
</tr>
<tr>
<td>Arrhythmogenicity</td>
<td>No arrhythmic activity</td>
<td>Low bioavailability, no arrhythmic activity</td>
</tr>
<tr>
<td>Cardiovascular safety</td>
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<tr>
<td>Commonest AEs</td>
<td>Diarrhoea, nausea</td>
<td>Diarrhoea</td>
</tr>
<tr>
<td>Potential other actions</td>
<td>Mucosal protection</td>
<td>Anti-neoplastic</td>
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<tr>
<td>Approval status</td>
<td>FDA</td>
<td>—</td>
</tr>
</tbody>
</table>

Box 1

- Diagnostic tests are useful for identifying defaecatory disorders and characterising colonic transit in chronic constipation; this classification facilitates management.
- Controlled studies suggest that behavioural and pharmacological treatments improve symptoms in patients with and without defaecatory disorders respectively.
- Rigorous trials support the efficacy of simple measures (fibre supplementation, osmotic and stimulant laxatives) for chronic constipation.
- Newer agents should be considered for patients who do not respond to older therapies.

For patients with normal or slow transit constipation, it is customary to start treatment with fibre and an osmotic laxative such as a magnesium salt or polyethylene glycol, adding a stimulant laxative such as bisacodyl on an as-needed basis. These agents are relatively safe, inexpensive, widely used, and in many cases their efficacy has been proven in controlled trials. Newer medications that seem to be efficacious and safe should be considered in patients who do not respond to these older agents or do not tolerate them. These agents include 5-HT4 agonist prokinetics, of which prucalopride is approved in Europe, and secretagogues like lubiprostone, which is approved in the United States. Colonic motor assessments with intraluminal techniques are useful for identifying colonic motor dysfunction and identifying patients who may benefit from subtotal colectomy. A subtotal colectomy should be considered in patients with medically refractory chronic constipation who do not have a defaecatory disorder.

Defaecatory disorders can be diagnosed by careful clinical assessments and ano-rectal testing and are managed by biofeedback therapy. However, the expertise necessary to provide pelvic floor retraining is not widely available. Many patients with defaecatory disorders have structural abnormalities (ie, rectoceles, rectal mucosal intussusception, enterocoele, and descending perineum syndrome), which may be transient (ie, related to straining) or persistent, and may occur in isolation or in association with functional disturbances.

Managing structural abnormalities is guided by several considerations. Not all abnormalities (eg, small rectoceles) cause symptoms and some may be secondary to a functional disturbance (eg, excessive straining, non-relaxing pelvic floor). Thus, pelvic floor retraining should be considered even in some patients with structural abnormalities. However, the response to pelvic floor retraining in patients with structural abnormalities has not been evaluated in controlled studies. Surgery should be considered for anatomical abnormalities (eg, large enterocoeles) that obstruct defaecation.

In controlled trials, up to 75% of patients with a defaecatory disorder have satisfactory bowel habits after pelvic floor retraining at specialised centres. Non-behavioural options (eg, sacral nerve stimulation, pelvic floor botulinum toxin) for patients with pelvic floor dysfunction persistent despite retraining are of unproven efficacy. Persistent constipation after resolution of pelvic floor dysfunctions may be due to colonic motor dysfunction which may need specific treatment with laxatives, prokinetics and rarely colectomy, as described above.

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REFERENCES

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Behavioural and new pharmacological treatments for constipation: getting the balance right

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