What's New in Motility Disorders of the Small and Large Intestine

2019 DDW and Recent Publications

Henry P. Parkman, MD
Director of GI Motility Laboratory
Temple University Hospital
Philadelphia, PA
Goals

• How to assess small intestinal and colonic motility in clinical practice

• Understand use of new agents to treat small intestinal and colonic motility disorders
The Escalators at DDW 2019
Efficacy and Safety of Prucalopride in Chronic Constipation: An Integrated Analysis of Six Randomized, Controlled Clinical Trials.

Prucalopride, a selective, high-affinity 5-hydroxytryptamine 4 receptor agonist, stimulates GI and colonic motility and alleviates common symptoms of chronic constipation (CC). Prucalopride 2 mg daily in CC from 6 randomized, controlled trials.

Primary efficacy endpoint was percentage of patients with mean of ≥3 spontaneous complete bowel movements (SCBMs) per week over 12 weeks of treatment.

Side effects (>5%):  
Nausea  
Diarrhea  
Abdominal pain  
Headache

Cardiovascular effects:  
No EKG changes  
No MI, CVA

Camilleri, Tack, et al.  
DDS 2016;61:2157
**Benefit of Prucalopride for Symptom Control and Gastric Emptying Enhancement in Idiopathic Gastroparesis: A Controlled Cross-Over Trial**

Single center, double-blind, randomized, placebo controlled, crossover study
4 weeks of prucalopride 2 mg po qd versus placebo
28 idiopathic gastroparesis patients. GEBT T1/2, GCSI (0-5)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Prucalopride</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric emptying (T1/2; min)</td>
<td>128±19</td>
<td>86±13*</td>
<td>141±17</td>
</tr>
<tr>
<td>Fullness/satiety</td>
<td>3.2±0.3</td>
<td>2.2±0.2*</td>
<td>3.3±0.3</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>1.6±0.2</td>
<td>1.0±0.3*</td>
<td>1.8±0.3</td>
</tr>
<tr>
<td>Bloating/distension</td>
<td>2.5±0.3</td>
<td>1.5±0.3*</td>
<td>3.1±0.3</td>
</tr>
<tr>
<td>Pain/discomfort</td>
<td>2.9±0.3</td>
<td>1.8±0.3*</td>
<td>2.3±0.3</td>
</tr>
<tr>
<td>PAGI-QOL</td>
<td>1.6±0.3</td>
<td>1.2±0.3*</td>
<td>1.9±0.4</td>
</tr>
</tbody>
</table>

No correlation between improvement in GE and symptoms

In idiopathic gastroparesis, 4 weeks prucalopride improved gastric emptying, symptoms and quality of life compared to placebo and to baseline. Carbone, Rotondo, Tack. Gastro 2016 (abstract)
Prucalopride for Gastroparesis

Prucalopride 2 mg po qd and 4 mg po qd
Did not help symptoms of gastroparesis

Cabrone, Tack, et al.
DDW 2019 Poster
AGA FDA Town Hall Meeting: Tegaserod

FDA Submission for approval of tegaserod (Zelnorm) 6 mg po BID for IBS-constipation in adult women.
Withdrawn approval for Zelnorm in 2007 for increased cardiovascular risks increase suicidal ideation/behavior

Secondary NDA submission filed in 2018. Company bought from Novartis
Cardiovascular events from tegaserod after re-review: 3/19,000
Females with IBS-C without cardiovascular disease and risk factors
Suicidal ideation/behavior (SIB):
Tegaserod 8/10,003=0.08%; Placebo 1/5,425=0.03%
Suggested warning; monitor patients

Discontinue if no response after 4-6 weeks

DDW 2019 Symposium
AGA FDA Town Hall Meeting: Prucalopride

FDA Submission for approval of prucalopride (Motegrity) 2 mg po qd for chronic idiopathic constipation in adults

Efficacy:
Used European data to supplement application

Side effects:
Cardiovascular: no signal seen
   Prucalopride: 1/1545=0.1%; Placebo: 2/2019=0.1%
Suicidal ideation/behavior (SIB)
   Prucalopride: 1 patient suicide in trials; open label 2 pts

DDW 2019 Symposium
A Cheaper Solution
Magnesium Oxide for Chronic Constipation

Magnesium Oxide 500 mg po TID
Increased SBM from 2 to 8 per week, compared to placebo 2 to 4 per week
Softened stool, reduced straining
Chronic functional constipation is strongly linked to vitamin D deficiency.

Prospective case-control study

Patients with chronic constipation with intestinal motility disorders. Glucose/lactulose breath tests, radiopaque markers (multiple capsule techniques) and wireless motility capsule analysis were used to assess colonic and oro-cecal transit time. 25-hydroxyvitamin D level measured.

86 patients with chronic functional constipation associated to intestinal motility disorders and 86 matched healthy subjects.

Patients with intestinal motility disorders had lower 25-hydroxyvitamin D levels ($P < 0.001$).

Multivariate analysis: vitamin D low levels remained a significant independent risk factor for the occurrence of intestinal motility disorder (odds ratio = 1.19; 95% confidence interval: 1.14-1.26, $P < 0.001$).

Vitamin D deficiency is associated with chronic functional constipation induced by intestinal motility disorders.

Vitamin D serum levels should be routinely measured in these patients.
Opiate-Induced Constipation (OIC)

Drugs approved

- Lubiprostone (Amitiza)
- Naloxegol (Movantik)
- Methylnaltrexone (Relistor)

In addition to delaying colonic transit, patients on opiates can have

- functional evacuation disorders
- rectal hyposensitivity

DDW 2019
Poster Sunday 1627
Bile Acid Diarrhea (BAD): A Clinical Symposium

An underappreciated disorder: causes 28% of chronic unexplained diarrhea
Key points: increased fecal bile acid loss, responds to bile acid sequestrants
  Type 1. Secondary. Ileal resection
  Type 2. Primary. Idiopathic
  Type 3. Misc. Post-cholecystectomy, gastric surgery, microscopic colitis
UK experience (where easier to diagnose with SeHCAT test)
  87% increased urgency
  82% explosive, foul smelling, watery diarrhea
  68% bloating
Rx: cholestyramine, colestipol, colesevelam
Response if <100 cm ileum removed; not if >100 cm
If bile binder not working:
  Ensure optimal dosing
  Add anti-motility drug
  Try alternative sequestrant

DDW 2019 Symposium
Bile Acid Diarrhea: Mayo Clinic Experience

Dx: 48 hour fecal bile acids while on 100 gram fat diet
Primary bile acids better than total bile acids
Other ways: fasting serum samples: C4 (high), FGF-19 (low)

Pts: BAD present in 26% of pts with chronic unexplained diarrhea
Risk factors: prior cholecystectomy, nocturnal diarrhea

Tx:
Cholestyramine effective in 75%
Colesevelam effective in 71%

Camilleri et al.
DDW 2019
Oral Presentation
SIBO: Is it useful to test for?

Prospective study in IBS-D, IBS-M patients
Breath hydrogen test using glucose 75 grams
All patients treated with Rifaximin 550 mg TID for 14 days

Positive SIBO test seen in 14% of patients; Response 90%
Negative SIBO test seen in 86% of patients: Response 80%

Overall, study suggested to treat empirically for SIBO, rather than testing for SIBO

DDW 2019
Oral Presentation
Risk of small intestinal bacterial overgrowth in patients receiving proton pump inhibitors *versus* proton pump inhibitors plus prokinetics.

Intestinal dysmotility is considered a risk factor for SIBO.

Evaluate presence of SIBO in patients taking PPI compared with those taking PPI plus prokinetics.

Single-center, cross-sectional study.

Patients divided into 2 groups: patients taking PPIs for more than 3 months (Group A) and those taking PPIs with prokinetics for more than 3 months (Group B).

147 patients, SIBO was documented in 13.2% patients in Group A but only 1.8% in Group B, \( P = 0.018 \).

Median OCTT in Group A was 130 (105-160) min compared with 120 (92.5-147.5) min in Group B (\( P = 0.010 \)).

Use of prokinetics in patients on PPI may reduce the risk of SIBO by enhancing intestinal motility and may reduce SIBO risk associated with long-term PPI use.

FODMAPs

- FODMAPs: Fermentable Oligosaccharides, Disaccharides, Monosaccharides, and Polyols)

<table>
<thead>
<tr>
<th>FODMAP</th>
<th>Example Foods High in FODMAPs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oligosaccharides</td>
<td>Legumes, selected fruits and vegetables, cereals</td>
</tr>
<tr>
<td>Disaccharides</td>
<td>Lactose, milk-based foods</td>
</tr>
<tr>
<td>Monosaccharides</td>
<td>Sweeteners with fructose, selected fruits</td>
</tr>
<tr>
<td>Polyols</td>
<td>Sweeteners ending in “-ol” (eg, sorbitol), selected fruits and vegetables</td>
</tr>
</tbody>
</table>

- Poorly absorbed, short-chain fermentable carbohydrates
- Cause gas production, luminal distention, GI symptoms via fermentation by colonic bacteria
- Low FODMAP diet may benefit up to two thirds of patients with IBS


Slide credit: clinicaloptions.com
Lifestyle and dietary modifications
(usually tried BEFORE the pharmacological interventions and advanced management strategies outlined below)

If no response or refractory to these measures, base the sequence of treatments on:

- Predominant symptom
- Quality of the evidence
- Individual patient assessment
- Preference and availability

Management targeted at predominant symptom (order of use according to IBS subtype)

**IBS-D**
- Diarrhoea
  - Loperamide
  - Eluxadoline
  - Cholestyramine
  - Ondansetron
  - Rifaximin
- Bloating
  - Rifaximin
  - Eluxadoline
  - Low-FODMAP diet
  - Probiotics
- Pain
  - Antispasmodics
  - Eluxadoline
  - TCAs
  - Psychological therapy
  - Bile acid sequestrants
  - Probiotics

**IBS-C**
- Constipation
  - Water-soluble fibre
  - Laxatives
  - Linaclotide
  - Lubiprostone
  - Prokinetics
- Bloating
  - Linaclotide
  - Lubiprostone
  - Low-FODMAP diet
  - Probiotics
- Pain
  - Antispasmodics
  - Linaclotide
  - SSRIs
  - Psychological therapy
  - Probiotics

**IBS-M**
- Laxative user
  - Stop laxative
- Loperamide user
  - Stop loperamide
  - Low-FODMAP diet
- Pain
  - Antispasmodics
  - SSRIs or TCAs
  - Psychological therapy
  - Probiotics
Foods suitable on a low-fodmap diet

<table>
<thead>
<tr>
<th>Fruit</th>
<th>Vegetables</th>
<th>Grain Foods</th>
<th>Milk Products</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>banana</td>
<td>aubergine, bamboo shoots, broad beans, celery, chestnuts, fennel, feta, garlic, ginger, gluten-free bread or cereal products, green beans, grapes, greek yogurt, fennel, kiwi, lemon, passion fruit, pine nuts, pomegranate, pumpkin, quinoa, red pepper, rice, salads, seitan, sesame seeds, strawberries, sweet potato, temptation, thyme</td>
<td>tomatoes</td>
<td>milk, lactose-free milk, soy milk, rice milk, any milk?</td>
<td>honey, molasses, maple syrup, salt, sea salt</td>
</tr>
<tr>
<td>berries</td>
<td>artichokes, blackberries, blueberries, blackcurrant, blueberry, blackberry</td>
<td>corn, nutritional yeast</td>
<td>cheese, cheese, cheese</td>
<td>honey, molasses, maple syrup, salt, sea salt</td>
</tr>
<tr>
<td>apricots</td>
<td>avocados, bananas, blackberries, blueberries, black currant, blueberry, blackberry</td>
<td>corn, nutritional yeast</td>
<td>cheese, cheese, cheese, cheese, cheese</td>
<td>honey, molasses, maple syrup, salt, sea salt</td>
</tr>
<tr>
<td>prunes</td>
<td>beans</td>
<td>corn, nutritional yeast</td>
<td>cheese, cheese, cheese, cheese, cheese</td>
<td>honey, molasses, maple syrup, salt, sea salt</td>
</tr>
</tbody>
</table>

Eliminate foods containing fodmaps

<table>
<thead>
<tr>
<th>Excess Fructose</th>
<th>Lactose</th>
<th>Fructans</th>
<th>Galactans</th>
<th>Polysols</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fruit</td>
<td>milk</td>
<td>beans</td>
<td>vegetables</td>
<td>legumes</td>
</tr>
<tr>
<td>banana</td>
<td>milk</td>
<td>beans</td>
<td>vegetables</td>
<td>legumes</td>
</tr>
<tr>
<td>apple</td>
<td>milk</td>
<td>beans</td>
<td>vegetables</td>
<td>legumes</td>
</tr>
<tr>
<td>mango</td>
<td>milk</td>
<td>beans</td>
<td>vegetables</td>
<td>legumes</td>
</tr>
<tr>
<td>apricot</td>
<td>milk</td>
<td>beans</td>
<td>vegetables</td>
<td>legumes</td>
</tr>
<tr>
<td>banana</td>
<td>milk</td>
<td>beans</td>
<td>vegetables</td>
<td>legumes</td>
</tr>
<tr>
<td>apple</td>
<td>milk</td>
<td>beans</td>
<td>vegetables</td>
<td>legumes</td>
</tr>
<tr>
<td>mango</td>
<td>milk</td>
<td>beans</td>
<td>vegetables</td>
<td>legumes</td>
</tr>
<tr>
<td>apricot</td>
<td>milk</td>
<td>beans</td>
<td>vegetables</td>
<td>legumes</td>
</tr>
</tbody>
</table>

From
https://www.fortlangleycolonics.com/sibo/
Low FODMAP Diet: Long term effects

Low FODMAP Treatment
  Low FODMAP diet for 1 month
  Reintroduction of foods over 2 months
  Adaptive diet for patient

Trigger foods
  Lactose 70%
  Fructans 30%
  Fructose 25%
  Polyols 20%

Potential side effects of continuing Low FODMAP diet
  Change microbiota
  Constipation
  Nutritional deficiencies: Calcium
  Eating disorders (ARFID)
  Expense

DDW 2019
Oral Presentation
Road to Precision in Diet Therapy for Functional Bowel and Motility Disorders

IBS Chek: primarily for postinfectious IBS was not used by audience (10)

Low FODMAP Diet: Patient Guides
Monash app. Tells if foods contain FODMAPS
Web site: Kate Scarlatta (a nutritionist)

DDW 2019
Breakfast Meeting
Eswaran S.
## Neuromodulators for Treating Functional GI Disorders

<table>
<thead>
<tr>
<th>Condition</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Painful FGIDs</td>
<td>TCAs (Desipramine/Nortriptyline 25-50 mg qhs)</td>
</tr>
<tr>
<td></td>
<td>SNRIs (Duloxetine 30-60 mg, Venlafaxine 37.5-75)</td>
</tr>
<tr>
<td></td>
<td>DLA (pregabalin, gabapentin)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>Trazadone</td>
</tr>
<tr>
<td>IBS diarrhea</td>
<td>TCA (amitriptyline)</td>
</tr>
<tr>
<td>IBS constipation</td>
<td>SSRI (Escitalopram)</td>
</tr>
<tr>
<td>Functional Dyspepsia</td>
<td>Amitriptyline 25-50 mg qhs</td>
</tr>
<tr>
<td>Early Satiety</td>
<td>Buspirone 7.5 -15 mg BID</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>Mirtazapine 15-30 mg qhs</td>
</tr>
<tr>
<td></td>
<td>Olanzapine 2.5 to 5 mg qd</td>
</tr>
<tr>
<td>CVS</td>
<td>Amitriptyline</td>
</tr>
<tr>
<td></td>
<td>Topiramate</td>
</tr>
</tbody>
</table>

Sobin, Drossman. AJG 2017;112:2026
## Effect of Antidepressants in IBS: An updated systematic review and meta-analysis

<table>
<thead>
<tr>
<th></th>
<th>Improvement vs placebo</th>
<th>RR IBS Sx not improving</th>
<th>Number to treat (NNT)</th>
<th>RR Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TCAs</strong></td>
<td>57.3% vs 36.2%</td>
<td>0.65 (0.55-0.77)</td>
<td>4.5</td>
<td>1.59</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>drowsiness</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>dry mouth</td>
</tr>
<tr>
<td><strong>SSRIs</strong></td>
<td>54.5% vs 32.8%</td>
<td>0.69 (0.51-0.91)</td>
<td>5.0</td>
<td>1.53</td>
</tr>
</tbody>
</table>

**Abbreviations:**
- RR: relative risk
- NNT: number to treat for one patient improving

Ford, Lacy, Harris, et al. AJG 2018;
Enteral tolerance in critically ill patients.

Enteral nutrition (EN) can maintain the structure and function of the gastrointestinal mucosa better than parenteral nutrition. EN should be started as soon as possible with a small amount of EN first and gradually increased. EN itself may also promote intestinal peristalsis. One of the best ways to success for EN management is to continue as long as possible without interruption and discontinuation of EN easily by appropriate measures, even if gastrointestinal complications occur.

In critically ill patients, EN must be discontinued or interrupted, if gastrointestinal complications, particularly vomiting and bowel movement disorders, do not resolve with appropriate management. The measures to decrease the risk of reflux and aspiration include elevation the head of the bed (30° to 45°), switch to continuous administration, administration of prokinetic drugs or narcotic antagonists to promote gastrointestinal motility, and switch to jejunal access (postpyloric route). The control of bowel movement is also important for intensive care and management. Prolonged diarrhea can cause deficiency in nutrient absorption, malnutrition, and increase in mortality. In addition, diarrhea may cause a decrease the circulating blood volume, metabolic acidosis, electrolyte abnormalities, and contamination of surgical wounds and pressure ulcers. If diarrhea occurs in critically ill patients on EN management, it is important to determine whether diarrhea is EN-related or not. After ruling out the other causes of diarrhea, the measures to prevent EN-related diarrhea include switch to continuous infusion, switch to gastric feeding, adjustment of agents that improve gastrointestinal peristalsis or laxative, administration of antidiarrheal drugs, changing the type of EN formula, and semisolidification of EN formula. Tatsumi H. J Intensive Care. 2019;7:30
A multicenter, randomized, double-blind study of ulimorelin and metoclopramide in the treatment of critically ill patients with enteral feeding intolerance.

Enteral feeding intolerance (EFI) is a frequent problem in the intensive care unit (ICU), but current prokinetic agents have uncertain efficacy and safety profiles. The current study compared the efficacy and safety of ulimorelin, a ghrelin agonist, with metoclopramide in the treatment of EFI.

120 ICU patients were randomized 1:1 to ulimorelin or metoclopramide for 5 days. EFI was diagnosed by a gastric residual volume (GRV) ≥ 500 ml. A volume-based feeding protocol was employed, and enteral formulas were standardized. Primary end point was percentage daily protein prescription (%DPP) received by patients over 5 d of treatment. Secondary end points included feeding success, defined as 80% DPP; gastric emptying, assessed by paracetamol absorption; incidences of recurrent intolerance (GRV ≥ 500 ml); vomiting or regurgitation; aspiration, defined by positive tracheal aspirates for pepsin; and pulmonary infection.

120 patients randomized and received the study drug (ulimorelin 62, metoclopramide 58). Mean APACHE II and SOFA scores were 21.6 and 8.6, and 63.3% of patients had medical reasons for ICU admission. Ulimorelin and metoclopramide resulted in comparable %DPPs over 5 days of treatment (median [Q1, Q3]: 82.9% [38.4%, 100.2%] and 82.3% [65.6%, 100.2%], respectively, p = 0.49). Five-day rates of feeding success were 67.7% and 70.6% when terminations unrelated to feeding were excluded, and there were no differences in any secondary outcomes or adverse events between the two groups.

Both prokinetic agents achieved similar rates of feeding success, and no safety differences between the two treatment groups were observed.

Hayland DK et al
DDW 2019 oral presentation
Summary

How to assess small intestinal and colonic motility in clinical practice

Understand use of new agents to treat small intestinal and colonic motility disorders

Prucalopride for CIC
Bile acid sequestrants, cholestyramine: BAD
Low FODMAP Diets
Feeding Intolerance in ICU patients