Grant Wood “The Family Doctor” 1941
Chronic Constipation

New Treatment Options for Irritable Bowel Syndrome with Constipation and Chronic Idiopathic Constipation

Brian K. Cooley, M.D. FACG

Plano, Texas
Drug Store
Edward Hooper 1927 Museum of Fine Arts Boston
Definition of IBS

IBS is a functional bowel disorder with abdominal pain or discomfort associated with changes in bowel habits

Functional = absence of structural or biochemical abnormalities (eg. celiac disease, inflammatory bowel disease, GERD)

Main IBS subtypes
- IBS-C: Constipation predominant
- IBS-D: Diarrhea predominant
- IBS-M: Mixed bowel pattern
- IBS-U: Unclassified

Definition of CIC

CIC is a disorder of defecation characterized by infrequent bowel movements (less than 3/week), difficult passage of stool or both.

Chronic = 3 or more months

Idiopathic = unknown cause, not related to medications, structural (colon cancer) or biochemical abnormalities (e.g., hypothyroidism)

Difficult stool passage includes straining, incomplete evacuation, hard/lumpy stools, prolonged time between bowel movements, need for manual removal of stool.
IBS Potential Risk Factors

• Age (25-55)
• Sex (60-70 percent of patients are women)
• Gastrointestinal infection and inflammation
• Food intolerance
• Psychiatric disorders
• History of sexual abuse
CIC Potential Risk Factors

- Age (more common in elderly)
- Sex (three times more women than men)
- Diet (low fiber and low caloric intake)
- Inactivity
- Multiple Medications
- Hemorrhoids and fissures
Differentiating Signs and Symptoms of Chronic Constipation (CC) and IBS-C

Chronic constipation

IBS with constipation

Abdominal Pain/Discomfort

Visceral Hypersensitivity

<3 BMs/Week

Normal Stool Frequency

*3 BMs/day to 3 BMs/week is considered range of normal stool frequency

Pathophysiology of IBS is Multifactorial

Pathophysiology of CIC is Multifactorial


Altered GI Motility

Altered Secretion
Prevalence and Impact of IBS-C and CIC

• US prevalence of IBS-C as many as 13 million
• US prevalence of CIC as many as 35 million

• IBS-C bothersome symptoms 135 days per year
• CIC bothersome symptoms 99 days per year

• IBS-C utilization of health care system 1.5 x more than age matched controls
• CIC utilization of health care system 1.4 x more than age matched controls
Increased Healthcare Utilization

- Increased healthcare utilization leads to higher costs of care for IBS-C and CIC patients
- Greater incidence of:
  - Outpatient visits
  - Surgeries
  - Prescription drugs
  - Radiology, lab tests

*Data based on survey of 2613 managed care plan members
Associated Symptoms of IBS-C and CIC

- Patients may present with:
  - Migraine Headaches
  - Insomnia
  - Chronic Fatigue
  - Fibromyalgia
  - Depression, anxiety
Patient and Provider Frustration

• Chronicity and lack of effective treatment options often leads to frustration for both patient and physician.

• Patients can be very demanding and difficult to care for.

• This can lead to fragmented care and overutilization of the health care system
Medical “Profile” of Constipated Patient circa 1915

Classic Patient described as:
“generally a woman.”
“Lean cadaverous, flat chested.”
“Cold and clammy” hands.
Skin “bears many crops of pimples.”
Body odor “is apt to be distressingly noticeable.”
Medical “Profile” of Constipated Patient circa 1915

Her “abdominal muscles …are flabby and flaccid and all the viscera which they should hold up are fallen in greater or less degree.”

She suffers “flatulence, and inveterate and incoercible constipation.”
Medical “Profile” of Constipated Patient circa 1915

She is “morose, querulous, and often suspicious,”

She exhibits “a complete absence of the joy of life.”

Berkeley 1915
“The Dreaded Colic”
George Cruikshank 1819
Philadelphia Museum of Art
IBS Typical Patient Profile

• Abdominal pain/discomfort associated with altered bowel habits
  1
• Female
  2
• Age 25 to 54 years
  2
• Patients may also present with:
  – Headache
  3,4
  – Poor sleep/fatigue
  3,4
  – Fibromyalgia
  4
  – Depression, anxiety
  5

CIC Typical Patient Profile

- Age 65
- Female
- Many years of constipation
- Has tried multiple medications without lasting success
- Constipation causes more discomfort than pain
Approach to the Patient with IBS-C and CIC

- Physician patient relationship is very important
- Ask the patient to describe the symptoms including frequency and severity of discomfort
- Encourage the patient to describe their stools
### The Bristol Stool Form Scale

<table>
<thead>
<tr>
<th>Slow Transit</th>
<th>Fast Transit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>Type 7</td>
</tr>
<tr>
<td>Type 2</td>
<td>Type 6</td>
</tr>
<tr>
<td>Type 3</td>
<td>Type 5</td>
</tr>
<tr>
<td>Type 4</td>
<td>Type 4</td>
</tr>
<tr>
<td>Type 5</td>
<td>Type 3</td>
</tr>
<tr>
<td>Type 6</td>
<td>Type 2</td>
</tr>
</tbody>
</table>
Consider the Diagnosis in women with chronic abdominal pain.

Frans Van Mieris, The Elder
The Doctor’s Visit.
1657
Kunsthistorisches Museum, Vienna
Diagnosis of IBS-C and CIC
A Symptom-Based Approach

• Identify current symptom complex (abdominal pain, bloating, alteration in bowel habits)
• Look for Red Flags on history, physical, and lab tests
• Perform selected physical and diagnostic tests to rule out organic disease.
• Make a positive diagnosis
• Initiate a treatment plan based on symptoms
• Follow up office visit in 3-6 weeks
Red Flags

- **History**
  - New onset of symptoms
  - Onset after age 50
  - Weight loss
  - Anorexia
  - Fever
  - Rectal bleeding
  - Family history of GI cancer, IBD, or celiac disease

- **Initial Labs**
  - ↓ HGB  - ↑ Sed Rate
  - ↑ WBC  - Abnormal chemistry
  - ↑ TSH  - abnormal Celiac Profile

- **Physical**
  - Abnormal exam (malleable mass)
  - Rectal exam
  - Positive occult blood test
The Physical Exam is of Limited Value in Diagnosing IBS!

William Chandler

Dr. William Gleason

1785

Ohio Historic Society
Collaborative Relationship Results in Improved Treatment Outcomes

• Basic principles of effective clinician-patient collaboration:
  – Show empathy, acknowledge the pain
  – Listen actively
  – Reassure
  – Educate
  – Encourage the patient to participate by keeping a symptom diary
  – Negotiate and set reasonable treatment goals
  – Provide follow-up care

# Treatments for IBS and CIC

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulking Agents</td>
<td>Eg, wheat bran, corn fiber, psyllium</td>
<td>Often cause gas and bloating. Occasionally make constipation worse.</td>
</tr>
<tr>
<td>Antispasmodics</td>
<td>Eg, hyoscyamine, dicyclomine</td>
<td>Helpful for pain and spasm, but can worsen constipation and have anticholinergic side effects (dry mouth, decreased sweating)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Eg, TCAs, SSRIs</td>
<td>Trycyclics work well to decrease visceral hypersensitivity but can worsen constipation. SSRIs have lots of GI side effects but are good for depressed patients</td>
</tr>
<tr>
<td>Serotonergic Agents</td>
<td>Eg, Tegaserod and Cisapride</td>
<td>Promotility drugs removed from marked due to cardiovascular side effects</td>
</tr>
<tr>
<td>Osmotic Laxatives</td>
<td>MOM, MiraLax</td>
<td>Effective and safe cut can bloat and are often unpredictable</td>
</tr>
<tr>
<td>Stimulant Laxatives</td>
<td>Cascara, Dulcolax</td>
<td>Effective short term but can lead to side effects like colonic atony long term</td>
</tr>
</tbody>
</table>
IBS-C: Key Takeaways

• Wide range of symptoms with hallmarks being:
  – Abdominal pain/discomfort
  – Altered bowel habits
• Often undiagnosed
• Predominantly affects women age 25 to 54 years
• Decreases quality of life
• Fewer than one third of patients are satisfied with their remedies
• Clinician-patient collaboration is important in establishing diagnosis and treatment plan
CIC: Key Takeaways

- Affects older patients most commonly
- Women affected more than men 2.2:1
- Major symptoms include infrequent or difficult to evacuate stools.
- Pain is not a primary symptom
- Quality of life may be diminished
- Most patients are unhappy with treatment outcome
- Good provider patient relationship important
Historical Perspective

- Constipation viewed as unhealthy
- "Autointoxication" theory of late 1800's contributed to habitual use of laxatives
- Treatments of Constipation include:
  - Enemas
  - Laxatives
  - Mechanical and Electrical Devices
  - Physical Therapy and Exercise
  - Surgery
The Enema throughout the ages:
“An emblem of Medical Skill and a sign of a caring physician.”
Galen 2nd Century instructing on the use of mild enemas for relief of constipation and stronger therapy for “flux, constant lustful desires and putrid ulcers”
Clyster (enema pump) 17th Century
France
Smoke Enema Technique perfected by John Woodall 1639
“Rectal Fumigation”
“Seat Enema” for Self administration 1920’
Warm Oil Enema
1920’s
Laxatives and Purgatives

See how these children take and ask for more
Of the same oil they sickened at before
What no one young or old could once endure
Now tastes pleasant, sweet and pure.
Patent Medicines were popular.

Clark Stanley's Snake Oil Liniment

Is for sale by all druggists. If your druggist fails to have it, tell him he can get it for you from any wholesale druggists or it will be sent to you by any part of the United States or Canada upon the receipt of fifty cents in stamps by addressing the

Clark Stanley Snake Oil Liniment Co.
Helped settle the West!
A good bowel movement!
BOWEL BLOAT

A horrible, slimy monster that makes man’s life a misery.
After eating: a bloated belly, belching of gas from the stomach, a foul, ill-smelling scurf on the tongue, dizziness, headache, a sour rising and spitting up of half-digested food, — it’s Bowel Bloat.

When the bowels stop working they become filled with putrid, rotting matter, forming poisonous gases that go through the whole body. If you don’t have a regular, natural movement of the bowels at least once a day your fate is bowel bloat, with all the nasty, disgusting symptoms that go with it.

There’s only one way to set it right.
Clean yourself out gently but thoroughly and tone up your bowels with CASCARETS. Every form of bowel trouble is quickly and permanently cured by CASCARETS.

CANDY CATHARTIC
BEST FOR THE BOWELS
ALL DRUGGISTS

To any needy mortal suffering from bowel troubles and too poor to buy CASCARETS we will send a box free. Address Sterling Remedy Company, Chicago or New York, mentioning advertisement and paper.
French Sponge Laxative "promotes inner hygiene"

Figure 4-2. Advertisement for the French product Jubol, which claimed to sponge and wipe the intestine, giving it a “sweet, prolonged and persuasive massage.” “Be good to your intestine,” the ad urges. “Jubolize it.” [The William H. Helfand Collection, New York].
Laxatives Help you Lose Weight!
The Babe can't be wrong!
"Good Moms give it to their children!"

[Image of a cartoon showing a man giving a child a medicine called 'Feen-a-mint: The Chewing LAXATIVE. No Taste but the Mint—Chew it like Gum.']
The ideal place to rest; to accurately learn your exact physical condition, to have applied the physiological and dietetic methods necessary to eliminate the causes of your illness and to build up permanent health. Luxurious modern appointments, moderate rates, delicious health cuisine, 200 kinds of baths, electricity, swimming pools, indoor palm garden, tonic Michigan climate, 860 feet above sea level; 300 trained nurses, 30 physicians; accommodations for 1000 guests. Illustrated Catalogue free.

The Sanitarium, Box 75, Battle Creek, Mich.
John Kellogg and the Road to Wellville
Exercise Helps Prevent Constipation
Mechanical and Electrical Devices
Mechanical Horse
Rotary Wheel Massage
External Vibrator
Oxygen “Bath”
Scotch “Douche”
Electric Cabinet Featuring Galvanic, Faradic, High Frequency, and Sinusoidal Currents
Surgical Treatment of Constipation

- Lane’s Kinked Colon theory
- Appendectomy
- Cecostomy with lavage
- Sigmoid Resection
- Sub total Colectomy
New Treatments for IBS-C and CIC

- Amitiza (Lubiprostone)
- Linzess (Linaclotide)
- Trulance (Plecanatide)

These drugs work by opening chloride channels in the gut which leads to increased intra-luminal fluid which causes increased motility.

Amitiza reduces pain in theory by tightening intracellular junctions.

Linzess reduces pain through a direct effect of Cyclic GMP on intracellular nerves.

Trulance does not have an IBS indication yet.
AMITIZA® (lubiprostone): Approved for Treatment of CIC and IBS-C

- AMITIZA is indicated for the treatment of:
  - IBS-C in women ≥18 years old
  - Chronic idiopathic constipation (CIC) in adults
  - Opioid induced constipation (OIC) in adults with chronic non cancer pain

**Dosing**

<table>
<thead>
<tr>
<th>IBS-C</th>
<th>CIC and OIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 mcg BID with food &amp; water</td>
<td>24 mcg BID with food &amp; water</td>
</tr>
</tbody>
</table>
AMITIZA® (lubiprostone) in IBS-C: Proposed Mechanism of Action

• The mechanism of action of AMITIZA in IBS-C is unknown

• Ex-vivo studies using ischemic porcine intestine suggest that activation of ClC-2 by lubiprostone has been shown to stimulate recovery of mucosal barrier function via the restoration of tight junction protein complexes¹

• The following illustrates the proposed mechanism of action of AMITIZA

AMITIZA® (lubiprostone)

• An orally active, functional fatty acid with a unique mechanism of action
  – Selectively activates type-2 chloride channels (ClC-2)\(^1\)
  – Enhances intestinal fluid secretion without altering serum electrolyte levels\(^2\)
  – Animal studies suggest that AMITIZA stimulates recovery of mucosal barrier function in ischemic porcine ileum and colon\(^3\)
  – Approved for treatment of women ≥18 years old with IBS-C (8 mcg BID) and adults with chronic idiopathic constipation (24 mcg BID)\(^4\)
  • Evaluated in >2200 patients in numerous clinical studies

AMITIZA® (lubiprostone): Phase III IBS-C Studies Used Balanced 7-Point Symptom Relief Scale

• In 2 clinical studies, patients were asked weekly how they felt about their relief:
  – “How would you rate your relief of IBS-C symptoms (abdominal discomfort/pain, bowel habits, and other IBS-C symptoms) over the past week, compared to how you felt before you entered the study?”

*Significantly relieved and moderately relieved were considered to be responders

AMITIZA® (lubiprostone) IBS-C: Overall Responder* Rates

Therapeutic Gain† = Treatment response rate minus placebo response rate

Overall responders defined as subjects who were monthly responders for ≥2 out of any 3 months

**Phase III-1**
- Placebo: 7.8% (n=193)
- AMITIZA: 13.8% (n=390)

**Phase III-2**
- Placebo: 5.7% (n=192)
- AMITIZA: 12.1% (n=379)

*Overall responders defined as subjects who were monthly responders for ≥2 out of any 3 months

†Therapeutic gain = treatment response rate minus placebo response rate

## AMITIZA® (lubiprostone): Incidence of AEs* Across All IBS-C Studies

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo (%) n=435</th>
<th>AMITIZA (%) n=1011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

*Treatment-related (possibly or probably related) adverse events reported by ≥1% of subjects during double-blinded treatment (safety evaluable subjects) who took AMITIZA 8 mcg twice daily and that occurred more frequently with study drug than placebo.

Pooled Safety Analysis from placebo-controlled 12-week trials=Phase II, Phase III-1, and Phase III-2 data.
AMITIZA (lubiprostone) 24 mcg Twice Daily: Demonstrated Rapid Relief in Majority of CIC Patients\textsuperscript{1-3}

![Bar chart showing response rates in Phase 3 Study 1 and Phase 3 Study 2.](chart)

- **Phase 3 Study 1**
  - Placebo: 37% (n=122)
  - AMITIZA: 57% (n=120)

- **Phase 3 Study 2**
  - Placebo: 32% (n=116)
  - AMITIZA: 63% (n=116)

Rapid relief defined as SBM within 24 hours.

\*P<0.0024 vs placebo. \textsuperscript{†}P<0.0001 vs placebo

Please see Important Safety Information in this presentation.

3. Data on file. Sucampo Pharma Americas, LLC.
Treatment with AMITIZA (lubiprostone) 24 mcg Twice Daily vs Placebo: Symptom Improvement in Two 4-Week CIC Studies

- Symptoms* included¹-³:
  - Abdominal bloating
  - Abdominal discomfort
  - Stool consistency
  - Straining
  - Constipation severity

- In patients with CIC, the most common adverse reactions (incidence >4%) were nausea, diarrhea, headache, abdominal pain, abdominal distension, and flatulence¹

* Secondary endpoint in phase 3 studies

Please see Important Safety Information in this presentation

AMITIZA® (lubiprostone)

• An orally active, functional fatty acid with a unique mechanism of action
  – Selectively activates type-2 chloride channels (ClC-2)\(^1\)
  – Enhances intestinal fluid secretion without altering serum electrolyte levels\(^2\)
  – Animal studies suggest that AMITIZA stimulates recovery of mucosal barrier function in ischemic porcine ileum and colon\(^3\)
  – Approved for treatment of women \(\geq\)18 years old with IBS-C (8 mcg BID) and adults with chronic idiopathic constipation (24 mcg BID)\(^4\)
    • Evaluated in >2200 patients in numerous clinical studies

AMITIZA® (lubiprostone): Important Safety Information

- AMITIZA® (lubiprostone) is indicated for the treatment of Chronic Idiopathic Constipation (24 mcg) in adults and for Irritable Bowel Syndrome with Constipation (8 mcg) in women ≥18 years old.
- AMITIZA is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction. Patients with symptoms suggestive of mechanical gastrointestinal obstruction should be thoroughly evaluated by the treating physician to confirm the absence of such an obstruction prior to initiating AMITIZA treatment.

Please see Takeda representative for full prescribing information.

• The safety of AMITIZA in pregnancy has not been evaluated in humans. AMITIZA should be used during pregnancy only if the benefit justifies the potential risk to the fetus. Women who could become pregnant should be capable of complying with effective contraceptive measures.
Patients taking AMITIZA may experience nausea. If this occurs, concomitant administration of food with AMITIZA may reduce symptoms of nausea. Patients who experience severe nausea should inform their physician.

AMITIZA should not be prescribed to patients that have severe diarrhea. Patients should be aware of the possible occurrence of diarrhea during treatment and inform their physician if the diarrhea becomes severe.

Patients taking AMITIZA may experience dyspnea within an hour of first dose. This symptom generally resolves within three hours, but may recur with repeat dosing. Patients who experience dyspnea should inform their physician.

Please see Takeda representative for full prescribing information.

AMITIZA® (lubiprostone): Important Safety Information

• In clinical trials of AMITIZA (24 mcg) in patients with Chronic Idiopathic Constipation, the most common adverse reactions (incidence >4%) were nausea (29%), diarrhea (12%), headache (11%), abdominal pain (8%), abdominal distention (6%), and flatulence (6%).

• In clinical trials of AMITIZA (8 mcg) in patients with Irritable Bowel Syndrome with Constipation, the most common adverse reactions (incidence >4%) were nausea (8%), diarrhea (7%), and abdominal pain (5%).
Linzess® (linaclotide) capsules
290 mcg for IBS-C • 145 mcg for CIC

A Clinical Review

Please see Important Safety Information section in this presentation and full Prescribing Information provided to you at this presentation and at LINZESShcp.com.
LINZESS Acts Locally and is Minimally Absorbed

- LINZESS is a guanylate cyclase-C (GC-C) agonist
- LINZESS selectively binds with high affinity to the GC-C receptor, which is located almost exclusively in the intestines
- LINZESS is minimally absorbed with low systemic availability
  - LINZESS is expected to be minimally distributed to tissues
  - While no drug-drug interaction studies have been conducted, no systemic drug-drug interactions are anticipated
- LINZESS is metabolized within the GI tract

LINZESS acts locally in the intestines
LINZESS is Thought to Work in Two Ways, Based on Nonclinical Studies

1. Increases fluid secretion and accelerates transit
2. Decreases pain-sensing nerve activity*

*Clinical relevance of the effect on pain fibers in nonclinical studies has not been established.
IBS-C: Responder Criteria

Trials evaluated Abdominal Pain Responders, CSBM Responders, and Combined Responders in the same week.

**Combined Responders** demonstrated significant improvement on 2 measures:

<table>
<thead>
<tr>
<th>Measure</th>
<th>Area of Improvement</th>
<th>Threshold for Weekly Response</th>
<th>Combined Responder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal Pain</td>
<td>At least 6 of 12 weeks</td>
<td>≥30% reduction over baseline</td>
<td>✔</td>
</tr>
<tr>
<td>CSBM</td>
<td></td>
<td>Increase of ≥1 over baseline</td>
<td></td>
</tr>
</tbody>
</table>
IBS-C: Significant Responder Rates vs Placebo in Abdominal Pain and in CSBMs Combined

Responder Rates:

at least 6 out of 12 Weeks

34% of LINZESS-treated Patients were Combined Responders

Results from 2 Phase 3 clinical trials with identical designs comparing LINZESS 290 mcg vs placebo for 12 weeks. The data above represent a primary endpoint in individual trials. Trial 1: Trt Diff 12.6%, 95% CI (6.5%, 18.7%). Trial 2: Trt Diff 19.8%, 95% CI (14.0%, 25.5%).

- In IBS-C clinical trials, the most common adverse reactions in LINZESS-treated patients were diarrhea, abdominal pain, flatulence, headache, viral gastroenteritis, and abdominal distension

1. LINZESS Prescribing Information.
Summary of Additional IBS-C Efficacy

Time to Maximum Effect: CSBM

Max CSBM effect occurred and was maintained until end of study; Abdominal pain effect separated from placebo

Time to Maximum Effect: Abdominal Pain

Max abdominal pain effect occurred and was maintained until end of study

Bowel Movement Frequency

LINZESS increased CSBM frequency by more than 2 CSBs, ~1.5 more than placebo
CIC: Primary Endpoint

Trials Evaluated CSBM Responders Based on 2 Criteria

- At least 3 CSBMs
- An increase of at least 1 CSBM vs baseline

In the Same Week for $\geq 9$ of 12 Weeks

Adapted from the LINZESS Prescribing Information
CIC: CSBM Responders

More Than Twice as Many CSBM Responders with LINZESS vs Placebo

- In CIC clinical trials, the most common adverse reactions in LINZESS-treated patients were diarrhea, abdominal pain, flatulence, upper respiratory tract infection, sinusitis, and abdominal distension.
Summary of Additional CIC Efficacy

Time to Max. Effect
Max CSBM effect occurred and maintained until end of study

Bowel Movement Frequency
LINZESS increased CSBM frequency by more than 2 CSBMs, ~1.5 more than placebo
LINZESS increased SBM frequency by more than 3 SBMs, ~2 more than placebo

Stool Consistency
LINZESS improved stool consistency versus placebo

Study Week
0  2  4  6  8  10  12  14  16
1 WK  12 WK
## Most Common Adverse Reactions in IBS-C and CIC Trials

Adverse Reactions Reported in ≥2% of LINZESS-treated Patients and at an Incidence Greater Than in the Placebo Group

<table>
<thead>
<tr>
<th>IBS-C</th>
<th>LINZESS 290 mcg N=807</th>
<th>Placebo N=798</th>
<th>CIC</th>
<th>LINZESS 145 mcg N=430</th>
<th>Placebo N=423</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse Reactions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>20%</td>
<td>3%</td>
<td>Diarrhea</td>
<td>16%</td>
<td>5%</td>
</tr>
<tr>
<td>Abdominal pain*</td>
<td>7%</td>
<td>5%</td>
<td>Abdominal pain*</td>
<td>7%</td>
<td>6%</td>
</tr>
<tr>
<td>Flatulence</td>
<td>4%</td>
<td>2%</td>
<td>Flatulence</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>Abdominal distention</td>
<td>2%</td>
<td>1%</td>
<td>Abdominal distention</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral gastroenteritis</td>
<td>3%</td>
<td>1%</td>
<td>Upper respiratory tract infection</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>4%</td>
<td>3%</td>
<td>Sinusitis</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Severe diarrhea</td>
<td>2%</td>
<td>&lt;1%</td>
<td>Severe diarrhea</td>
<td>2%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Discontinuation due to diarrhea</td>
<td>5%</td>
<td>&lt;1%</td>
<td>Discontinuation due to diarrhea</td>
<td>5%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

* "Abdominal pain" term includes: abdominal pain, upper abdominal pain, and lower abdominal pain.*

Adapted from the LINZESS Prescribing Information
Going shouldn’t mean going to extremes
Trulance met the most stringent primary endpoint in CIC

Patient fulfills both ≥3 CSBMs* in a given week + an increase of ≥1 CSBM from baseline in the same week

Same patient must be a weekly responder for 9 out of the 12 treatment weeks

Same patient must be a weekly responder for ≥3 of the last 4 treatment weeks (sustained)

Trulance was evaluated in the largest Phase 3 CIC clinical trials to date, involving more than 2600 patients¹-⁴
The percentage of efficacy responders (CSBM)* to Trulance was significantly greater than placebo\(^1\)

Primary endpoint: Efficacy responders over the 12-week treatment period vs placebo\(^1\)

Only Trulance met the most stringent criteria, evaluated in the largest Phase 3 CIC clinical trials to date\(^1\).
Established safety and tolerability

Trulance has well-established safety and tolerability, involving more than 1700 patients across 2 placebo-controlled, Phase 3 studies\(^1\,^2\)

<table>
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<th>Most Common Adverse Events (AEs) in Trulance Studies(^1)</th>
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<tbody>
<tr>
<td>AE</td>
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<tr>
<td>Diarrhea</td>
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4% discontinuation rate for Trulance vs 2% on placebo\(^1\)
- 2% discontinuation rate due to diarrhea vs 0.5% for placebo

No drug-drug interactions occur with Trulance\(^1\)
- Trulance therapy is minimally absorbed with negligible systemic availability

- Severe diarrhea was reported in 0.6% of patients receiving 3 mg of Trulance vs 0.3% of placebo-treated
IMPORTANT SAFETY INFORMATION

WARNING: RISK OF SERIOUS DEHYDRATION IN PEDIATRIC PATIENTS
Trulance™ is contraindicated in patients less than 6 years of age; in nonclinical studies in young juvenile mice administration of a single oral dose of plecanatide caused deaths due to dehydration. Use of Trulance should be avoided in patients 6 years to less than 18 years of age. The safety and efficacy of Trulance have not been established in pediatric patients less than 18 years of age.

Contraindications
• Trulance is contraindicated in patients less than 6 years of age due to the risk of serious dehydration.
• Trulance is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction.

Warnings and Precautions
Risk of Serious Dehydration in Pediatric Patients
• Trulance is contraindicated in patients less than 6 years of age. The safety and effectiveness of Trulance in patients less than 18 years of age have not been established. In young juvenile mice (human age equivalent of approximately 1 month to less than 2 years), plecanatide increased fluid secretion as a consequence of stimulation of guanylate cyclase-C (GC-C), resulting in mortality in some mice within the first 24 hours, apparently due to dehydration. Due to increased intestinal expression of GC-C, patients less than 6 years of age may be more likely than older patients to develop severe diarrhea and its potentially serious consequences.
• Use of Trulance should be avoided in patients 6 years to less than 18 years of age. Although there were no deaths in older juvenile mice, given the deaths in young mice and the lack of clinical safety and efficacy data in pediatric patients, use of Trulance should be avoided in patients 6 years to less than 18 years of age.

Diarrhea
• Diarrhea was the most common adverse reaction in the two placebo-controlled clinical trials. Severe diarrhea was reported in 0.6% of patients.
• If severe diarrhea occurs, the health care provider should suspend dosing and rehydrate the patient.

Adverse Reactions
• In the two combined CIC clinical trials, the most common adverse reaction in Trulance-treated patients (incidence ≥2% and greater than in the placebo group) was diarrhea (5% vs 1% placebo).

Indication
• Trulance (plecanatide) 3 mg tablets is indicated in adults for the treatment of chronic idiopathic constipation (CIC).

Please also see the full Prescribing Information, including Box Warning, for additional risk information.

Medications for opioid induced constipation

• Relistor (methylnaltrexone bromide) this narcotic antagonist is now available in both parenteral and enteral forms (SC and PO)

• Movantic (naloxegol) another narcotic antagonist available only in tablet form

• Amitiza (lubiprostone) a chloride channel activator approved for OIC
Efficacy of OIC Medications

- Relistor injection 12 mg daily 59 percent responders vs 38 percent for placebo
- Relistor tablets 450 mg daily 52 percent responders vs 38 percent for placebo
- Movantick 25 mg tablets 44 percent response rate vs 29 percent for placebo
- Amitiza 24 mcg bid 27 percent responders vs 19 percent for placebo
Side Effects of OIC Medications

• Amitiza side effect similar to what was seen in CIC and IBS-C (nausea, abdominal pain, diarrhea, etc)

• Relistor and Movantik side effects include
  Opioid withdrawal
  Severe abdominal pain and diarrhea
  Gastrointestinal perforation
Summary IBS-C and CIC

• Common Conditions
• More women affected than men
• Often Under diagnosed and patients often self medicate
• Presents a Significant Economic Burden
• Abdominal discomfort and altered bowel habits are hallmark symptoms of IBS, but CIC patients c/o difficult deification
• Often associated with other symptoms (headache, depression, fatigue, etc)
• Physicians should look for Red Flags (weight loss, bleeding, etc)
• Organic conditions should be ruled out by selective testing
• In the past, treatment options have been limited and patient satisfaction has been low.
• A positive therapeutic relationship between the physician and patient is important
• Newer treatments are available
When your skin becomes sallow, rough, blotchy or disfigured with pimples — it is nature’s way of telling you that there is something wrong with your system.

Use EX-LAX regularly to cleanse your system — and you’ll do more toward helping nature give you a clear, healthy complexion and bright sparkling eyes, than by using the best cosmetics you can buy. The best cold creams or soaps cannot rub blemishes away.
Gastroenterologist’s search for “Inner Hygiene”