Efficacy and Safety of Lubiprostone
Objectives

- Brief overview of constipation
- Review of article
- Discussion
Constipation in Children

- 3-5% of all pediatric visits
- 25% of pediatric gastroenterology visits
- Peaks during preschool years
- More common in boys
- +Family history in up to 50%
- Anxiety-causing for parents
- Painful for children

Constipation in Adults

- Prevalence of approximately 15%
- Higher rates in older adults and women
- Increase in the number of physician visits
- Decrements in quality of life
## Normal Frequency of Bowel Movements

<table>
<thead>
<tr>
<th>Age</th>
<th>BMs per week(^1)</th>
<th>BMs per day(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3mos breast-fed</td>
<td>5-40</td>
<td>2.9</td>
</tr>
<tr>
<td>0-3mos formula-fed</td>
<td>5-28</td>
<td>2.0</td>
</tr>
<tr>
<td>6-12mos</td>
<td>5-28</td>
<td>1.8</td>
</tr>
<tr>
<td>1-3years</td>
<td>4-21</td>
<td>1.4</td>
</tr>
<tr>
<td>&gt;3years</td>
<td>3-14</td>
<td>1.0</td>
</tr>
</tbody>
</table>

\(^1\) Mean 2 SDs  
\(^2\) Mean  

Etiology of Constipation

- Most commonly functional (95% cases)
  - Idiopathic
  - Fecal retention
  - Fecal withholding
- Hirschsprung disease
- Endocrine/Metabolic
- Obstruction
- Neurogenic
- Medications
Definition of Constipation: Adults

- ≥ 2 of the following for ≥ 12 weeks in the past 12 months
  - < 3 BMs per week
  - Straining during ≥ 25% of BMs
  - Lumpy or hard stools for ≥ 25% of BMs
  - Sensation of incomplete evacuation for ≥ 25% of BMs
  - Sensation of anorectal obstruction/blockage ≥ 25% of the time
  - Manual maneuvers to facilitate ≥ 25% of BMs
  - Loose stools not present, no IBS

Treatment of Constipation

- Education
- Disimpaction
- Dietary modifications
- Behavioral modifications
- Maintenance therapy
Maintenance Therapy

- Lubricants
  - Mineral oil
- Emollients/Softeners
  - Docusate
- Stimulants
  - Senna
  - Bisacodyl
  - Glycerin suppositories
- Bulk-forming agents
  - Psyllium
- Laxatives
  - Magnesium hydroxide
  - Magnesium citrate
  - Lactulose
  - Miralax
Laxatives

- High levels of dissatisfaction
  - 75% with predictability
  - 60% with relief of bloating and other symptoms
  - 50% with lack of efficacy and improvement in quality of life
- Large fluid intake can be difficult
- Lack of long-term efficacy

Efficacy and Safety of Lubiprostone in Patients with Chronic Constipation

Charles F. Barish · Douglas Drossman · John F. Johanson · Ryuji Ueno
Lubiprostone (Amitiza)

- Bicyclic fatty acid that activates ClC-2 chloride channels on GI epithelial cells, producing a chloride-rich fluid secretion
  - Softens the stool
  - Increases motility
  - “Stablizes” mucosal membranes
Lubiprostone (Amitiza)

- FDA-approved in January 2006 for chronic constipation
- FDA-approved in April 2008 for IBS-C
Specific Aims

- To assess the efficacy and safety of lubiprostone in adults with chronic constipation
Study Design

- Phase III trial
- Multicenter (20 sites)
- 2-week pre-randomization washout period
- 4-week randomized treatment period
  - Double blind
  - Placebo-controlled
- Follow-up visit 2 weeks later
- IRB approved, written consent obtained
Study Participants: Eligibility

- ≥ 18 years of age
- History of constipation confirmed during 2-week pre-randomization period
  - < 3 SBMs per week
- Fulfill Rome II criteria
  - Hard stools (or little balls)
  - Incomplete evacuation
  - Straining at defecation
Study Participants: Exclusion Criteria

- Mechanical obstruction
- Megacolon/megarectum
- Pseudo-obstruction
- Any GI or surgical procedure during the 3 months prior
- Secondary causes of constipation
Study Procedures

- Physical exam, baseline labs
- < 50 years: Flex sig or colonoscopy
- ≥ 50 years: Flex sig with barium enema or colonoscopy
- Pre-randomization: Daily diary to confirm constipation
Randomization Period

- 24mcg lubiprostone BID (with food and at least 8 ounces of water) vs. placebo
- Advised not to change their diet/lifestyle
- Daily diaries to record
  - Occurrence of all BMs
  - Consistency of each BM (0-4)
  - Degree of straining (0-4)
Study Assessments

- 1 week office visit
- 2 weeks telephone evaluation
- 4 weeks end-of-treatment office visit
- 2 weeks following the end of treatment

- Severity of constipation (0-4)
- Treatment effectiveness (0-4)
- Bloating and discomfort upon waking (0-4)
Rescue Meds

- None allowed during pre-randomization
- Patients able to remain on daily fiber supplement if started >3 months prior
- Dulcolax PR or Fleet Enema if no BM for ≥3 days
  - Authorized by study investigator
Efficacy Variables

- **Primary:** SBM frequency during week 1
- **Secondary:**
  - SBM frequency during weeks 2, 3, 4
  - % of patients with SBM within 24 hours
  - Time to first SBM
  - Weekly responder rate (Full if ≥4 SBMs/week)
  - Symptomatic assessments
116 patients per group to detect a difference of 2 SBMs per week
Intention to treat
Descriptive statistics for demographic data
Wilcoxon signed-rank test
Van Elteren’s test
Total Patients Randomized (n=237)

Placebo (n = 118)
Number of Completed (n = 107, 90.7%)
Reason and Number of Discontinuations:
- Adverse event: 1 (0.8%)
- Voluntary withdrawal: 1 (0.8%)
- Lack of efficacy: 6 (5.1%)
- Lost to follow-up: 1 (0.8%)
- Other: 2 (1.7%)
Timing of Early Discontinuation:
- Week 1: 2 (1.7%)
- Week 2: 2 (1.7%)
- Week 3: 3 (2.5%)
- Week 4: 3 (2.5%)

Lubiprostone (n = 119)
Number of Completed (n = 99, 83.2%)
Reason and Number of Discontinuations:
- Adverse event: 15 (12.6%)
- Lack of efficacy: 1 (0.8%)
- Lost to follow-up: 4 (3.4%)
Timing of Early Discontinuation:
- Week 1: 11 (9.2%)
- Week 2: 7 (5.9%)
- Week 3: 1 (0.8%)
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Lubiprostone 24 mcg BID (N = 119)</th>
<th>Placebo BID (N = 118)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender n (%)</td>
<td></td>
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</tr>
<tr>
<td>Male</td>
<td>15 (12.6)</td>
<td>13 (11.0)</td>
</tr>
<tr>
<td>Female</td>
<td>104 (87.4)</td>
<td>105 (89.0)</td>
</tr>
<tr>
<td>Race n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>90 (75.6)</td>
<td>89 (75.4)</td>
</tr>
<tr>
<td>Black</td>
<td>13 (10.9)</td>
<td>12 (10.2)</td>
</tr>
<tr>
<td>Asian</td>
<td>4 (3.4)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>11 (9.2)</td>
<td>14 (11.9)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (0.8)</td>
<td>2 (1.7)</td>
</tr>
<tr>
<td>Age, mean years ± SD</td>
<td>46.2 ± 12.13</td>
<td>45.4 ± 13.24</td>
</tr>
<tr>
<td>SBMs/week, mean ± SD (P = 0.0382)*</td>
<td>1.3 ± 0.88 (n = 118)</td>
<td>1.5 ± 0.80</td>
</tr>
<tr>
<td>Constipation severity, mean ± SD</td>
<td>3.0 ± 0.82</td>
<td>3.0 ± 0.76 (n = 117)</td>
</tr>
<tr>
<td>Stool consistency, mean ± SD</td>
<td>2.7 ± 0.83 (n = 96)</td>
<td>2.8 ± 0.77 (n = 110)</td>
</tr>
<tr>
<td>Degree of straining, mean ± SD</td>
<td>2.3 ± 0.94 (n = 95)</td>
<td>2.4 ± 0.92 (n = 109)</td>
</tr>
<tr>
<td>Abdominal bloating, mean ± SD</td>
<td>2.3 ± 1.03</td>
<td>2.2 ± 0.91</td>
</tr>
<tr>
<td>Abdominal discomfort, mean ± SD</td>
<td>1.9 ± 1.02</td>
<td>1.8 ± 0.91</td>
</tr>
</tbody>
</table>
Frequency of SBMs

- Greater constipation relief observed at all study weeks
More Lubiprostone patients experienced a SBM within 24 hours of the first dose

Time to first SBM was shorter in Lubiprostone patients
Lubiprostone was associated with more full responders
Symptom Scores

- Lubiprostone associated with improvement in:
  - Stool consistency
  - Degree of straining
  - Constipation severity
  - Abdominal bloating
  - Global assessment
- 106/237 (44.7%) reported adverse events
- Higher incidence of treatment-related events in lubiprostone group (42.9% vs. 16.1%)
- No serious adverse events associated with lubiprostone
Conclusions

- Lubiprostone is an effective treatment for chronic constipation, with over 60% of patients having a SBM within 24 hours
- Improvements in SBM frequency, stool consistency, straining, and bloating
- Less of a need for rescue therapy
- Safe and generally well-tolerated
Discussion

- Can we use these medications in our patient population?
- Cases unsatisfied with laxatives
- Patients unable to tolerate large volumes
- Adolescents (especially those with IBS-C)
- Minimal data on long-term effects
Lubiprostone: Other Applications

- IBS-C: Lower dose (8mcg BID)
- Co-administration with GoLytely for improved bowel prep
- Uterine muscle
- Cystic fibrosis: Respiratory tissue

Thank you