New Pharmacologic Treatments for Chronic Idiopathic Constipation

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Overview

- Review the pathophysiology of chronic constipation
- Distinguish various subtypes of constipation
- Common causes of secondary constipation
- Review traditional treatments for chronic constipation
- Review new therapies for CIC
Constipation

- Affects ~28% percent of the general U.S. population
  - 12% of men
  - 16% of women
  - 25-40% of the elderly
- > 2.5 million physician visits annually
- > 92,000 hospitalizations annually
Economic and Social Impact

- Significant direct costs
  - Doctor visits, medications, procedures

- Significant indirect costs
  - 12% of constipated people report missing work or school an average of 2.4 days/month
  - 13.7 million days of restricted activity/yr
  - 60% report impairment at work because of symptoms

*Pharmacoeconomics* 2006;23:451-76.
Economic and Social Impact

- Patients with chronic constipation have half the health related quality of life scores of someone without constipation
- Higher rate of psychological symptoms
  - Distress
  - Depression

Subtypes of Constipation

- Acute constipation
- Slow transit constipation
- Dyssynergic defecation
- Secondary constipation
- IBS
- Normal transit constipation
Chronic Constipation Definition

- Unsatisfactory defecation characterized by infrequent stool, difficult stool passage, or both
- Difficult stool passage
  - straining, hard lumpy stool, difficulty passing stool, incomplete evacuation, prolonged time to stool, manual maneuvers to pass stool
- Symptoms must be reported for at least 3 months

Case Study

- Tess is a 65 year old with 9 - 10 year history of progressively increasing constipation
  - 1 bowel movement a week
  - Frequent straining and occasional blood
  - Stools are hard and pellet-like
  - Frequent feeling of incomplete emptying
  - No abdominal pain but has bloating & gassiness
Secondary Constipation

- Endocrine/metabolic
  - diabetes, thyroid disorders, hypercalcemia

- Neurologic
  - spinal cord injury, multiple sclerosis, Parkinson’s disease, stroke, Hirschsprung disease

- Anorectal
  - fissures and strictures, inflammatory bowel disease
Secondary Constipation

- Psychogenic
  - depression, eating disorders
- Iatrogenic
  - medications, surgery
- Dietary
  - low residue diet
Selected Constipating Medications

- Analgesics (narcotics, NSAIDs)
- Aluminum or bismuth antacids
- Anticholinergics (TCAs, sedating antihistamines, phenothiazine)
- Calcium channel blockers
- Calcium (supplements or antacids)
- Cholestyramine
- Colestipol
- Diuretics
- Iron supplements
- Polysterene
- Sucralfate
Case Study - Tess

- Current medications: Claritin for seasonal allergies, occasional ibuprofen for headaches, lisinopril
- Medical: hypertension, seasonal allergies
- Family history: No colon cancer, no chronic constipation or IBS that she knows about
Diagnosis of Chronic Constipation

Constipation

Presence of Red Flags

Yes → Need to be evaluated

No

Occasional constipation

< 3 months

Treat empirically

Duration of Symptoms

> 3 months

Chronic constipation

Primary

Abdominal pain

No

Chronic idiopathic

Yes

IBS-C

Secondary
Red Flags

- Marked abdominal pain
- Significant distention
- Fever
- Nausea and/or vomiting
- Unexplained changes in bowel habits accompanied by weight loss
- Blood in stool or dark/tarry stool
- Change in caliber of stool (pencil thin)
Diagnosis of Chronic Constipation

Constipation → Presence of Red Flags

Occasional constipation < 3 months → Treat empirically

Duration of Symptoms

> 3 months → Chronic constipation

< 3 months → Primary Chronic idiopathic

Chronic idiopathic No → Abdominal pain

Yes → IBS-C

Need to be evaluated → Secondary
Pathophysiology of Chronic Idiopathic Constipation

- **Serotonin**
  - Important for visceral sensitivity (sensation), motility, and secretion
  - Primary neurotransmitter in regulating bowel activity

- **Fluid balance**
  - ~9 L/day goes in gut (dietary intake + gut secretions)
  - ~8.9 L/day is reabsorbed
  - Chloride channels – allow fluid release into gut

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  - Chloride channels – allow fluid release into gut
Treatment Goals

- Improve symptoms and restore normal bowel function
  - Accelerate colonic transit
  - Simulate gut motility
  - Facilitate defecation
  - Promote intestinal secretion
What lifestyle modifications would you recommend for patients complaining of constipation?
- Increase fluid
- Increase fiber
- Increase exercise
- None of the above
- All of the above
Lifestyle Modifications

- Increase fluid intake
  - Increase stool volume by augmenting luminal fluid
  - Limited efficacy because majority of fluid is absorbed before reaching colon

- Increase exercise
  - Improve motility by decreasing transit time
  - Moderately effective, some evidence suggests this is beneficial

- Increase dietary fiber
  - Increase stool bulk
  - Limited benefit compared with placebo
# Chronic Constipation Treatment Options –

<table>
<thead>
<tr>
<th>Agent/Example</th>
<th>Mechanism of Action</th>
<th>Level of supporting evidence</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fiber/psyllium</td>
<td>Increases stool volume</td>
<td>B</td>
<td>Improves stool frequency and consistency</td>
</tr>
<tr>
<td>Bulking agent/ methylcellulose</td>
<td>Increases water and stool volume</td>
<td>B</td>
<td>Insufficient data to recommend</td>
</tr>
<tr>
<td>Stool softeners/docusate</td>
<td>Allows water to react with stool</td>
<td>B</td>
<td>Insufficient data to recommend</td>
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# Treatment Options

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<tr>
<td>Osmotic laxative/lactulose, PEG</td>
<td>Draw water into intestines to stimulate peristalsis</td>
<td>A</td>
<td>Improves stool frequency and consistency</td>
</tr>
<tr>
<td>Stimulant laxative/bisacodyl, cascara, senna</td>
<td>Increases intestinal motility and secretion</td>
<td>B</td>
<td>Insufficient data to recommend, potential for adverse effects</td>
</tr>
</tbody>
</table>

Case Study - Tess

- Tried fiber tablets but these made her “blow up with gas”
- Currently uses a tea from a health food store once every few weeks and spends most of next day in the bathroom with cramping
- Misses work or cancels plans about twice a month because she feels so bad
Tegaserod (Zelnorm®)

- 5-HT$_4$ receptor agonist
  - it mimics serotonin
  - increases motility, increases intestinal secretion, and inhibits visceral sensitivity

Tegaserod

- 6 mg bid before meals
- Early onset of relief
- Significant relief of symptoms over 12 weeks (straining, hard stools, bloating/distension, infrequent bowel movements, etc.)
- No rebound effect seen
- Approved for CIC in patients < 65 and IBS-C (in women)
Tegaserod

- **Adverse effects**
  - Headache, diarrhea, nausea, abdominal pain

- **Drug interactions**
  - None
  - Beware combining with other agents that can cause diarrhea

- **Cautions/Warnings**
  - Severe renal impairment, mod – severe liver impairment, significant gallbladder disease, sphincter of Oddi dysfunction, abdominal adhesions
Lubiprostone (Amitiza®)

- GI targeted bicyclic functional fatty acid
- Selectively activates chlorid channel-2
- Enhances fluid secretion to facilitate increased motility

Lubiprostone

- 24 mcg bid
- Early onset of relief
- Effective in increasing spontaneous BMs and decreasing related symptoms
- Approved for CIC in adults
  - works in > 65 population
Lubiprostone

- **Adverse effects**
  - Nausea, diarrhea, headache, abdominal pain, flatulence, vomiting
  - Take with food to minimize nausea

- **Drug interactions**
  - None
  - Beware combining with other agents that can cause diarrhea

- **Cautions/Warnings**
  - Mechanical GI obstruction
FDA Approved Treatments for Constipation

Constipation

Occasional constipation

< 3 months

Duration of Symptoms

> 3 months

Chronic constipation

Laxatives
PEG/Lactulose

Chronic idiopathic

Lubiprostone or Tegaserod

IBS-C

Tegaserod
Case Study - Tess

- Treatment for her chronic constipation
  - Lifestyle modifications
  - PEG – has not tried that we know
  - Lubiprostone
    - > 65
  - Important counseling points
Conclusions

- Idiopathic chronic constipation is a common chronic condition
  - Affects all ages
  - Affects females and the elderly disproportionately
  - Affects quality of life
- Serotonin and intestinal fluid secretion are involved in pathophysiology
  - Agents are now available to specifically target these two areas
- Goal is to restore normal bowel function and improve symptoms
Questions