Can Pancreatic Enzymes Relieve Symptoms in Irritable Bowel Syndrome?

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Outline
- Objectives
- Background
- Review Primary Literature
- Final Thoughts and Recommendations

Objectives
- Understand pathophysiology of IBS and the symptoms
- Summarize current guideline recommendations
- Analyze recent primary literature
- Develop recommendations based on literature

Pt Case
- MS is a 58 year old Caucasian female presenting to your pharmacy. She has had an extensive history of irritable bowel syndrome-mixed for about 7 years. For her diarrhea, her physician has trialed loperamide. Also for constipation she has trialed linaclotide and polyethylene glycol. She states the polyethylene glycol helps only minimally. She is currently on amitriptyline 10mg ½ tablet PO daily. Even at a low dosage she still unable to tolerate the amitriptyline stating it "makes me feel horrible and messes with my mood."
- She comes to you asking for advice on what other medications are available to treat IBS

Background
- Cause is unknown!
- Theories
  - Dysmotility
  - Abnormal GI tract movements
  - Visceral hypersensitivity
  - Increased awareness of bodily functions
  - Brain-Gut dysfunction
  - Miscommunication

Pathophysiology
Epidemiology worldwide

IBS Global Impact Report 2018 [Internet]. Gastrointestinal Society, Canadian Society of Intestinal Research. 2018 April 3

Epidemiology in United States

- Impacts 35 million Americans
- Development of symptoms incidence rate of 7.6 per 1000 person-years.
- 30% of people with symptoms consult physician, of those 80% are diagnosed


Symptoms

- Abdominal pain
- Bloating & gas
- Constipation
- Diarrhea
- Flatulence
- Unusual stools
- Urgent need
- Cramps


Multiple forms of IBS

IBS-D
- Diarrhea
- Loose stools
- Urgent need
- Cramps

IBS-C
- Constipation
- Hard to move bowels
- Urge to go but can not

IBS-M
- Mixed
- Both symptoms

Forms of IBS prevalence


Triggers

- Food
  - Wheat
  - Dairy Products
  - Citrus fruits
  - Cabbage
  - Carbonated drinks

- Stress
  - Aggravates symptoms
  - Hormones
Diagnosis*

▪ Diagnosis based on symptom based criteria
▪ Alarming features
  ▪ Anemia, rectal bleeding, nocturnal symptoms, weight loss, recent ABX use, onset after 50 years old, FX of colorectal cancer
▪ Need to rule out differentials
  ▪ Carcinoid tumor, cell, colorectal cancer, diverticular disease, drug use, GI infection, hyper or hypothyroidism, IBD, ischemic colitis, celiac disease and lactose intolerance
▪ Rome Foundation

*Rome Foundation

See Appendix


Rome 2

▪ At least 12 week (which need not be consecutive) in the preceding 12 months of abdominal discomfort or pain that has 2 of 3 features
  ▪ Relieved by defecation
  ▪ Onset associated with a change in frequency of stool
  ▪ Onset associated with a change in stool consistency

Differentials

Irritable Bowel Disorder

▪ Similar symptoms as IBS
  ▪ Abdominal pain/cramping, diarrhea,
  ▪ Inflammation
  ▪ Structural tests
  ▪ Treatment

Exocrine Pancreatic Insufficiency

▪ Similar symptoms as IBS
  ▪ Stomach pain, gas and bloating
  ▪ Weight loss
  ▪ Stool consistency
  ▪ Stress/hormone involvement
  ▪ Treatment

Guideline Recommendations

Overview

▪ No cure, only control symptoms through diet, stress management and meds
▪ Non-Pharmacologic Treatment
  ▪ Diet-avoid triggers
  ▪ Increase fluids
  ▪ Exercise
  ▪ Sleep
  ▪ Stress management

Pharmacologic Recommendations

▪ IBS-D
  ▪ Rifaximin (Xifaxan®)
  ▪ Alosetron (Lotronex®)
  ▪ Loperamide (Imodium®)

▪ IBS-C
  ▪ Linacotide (Linzess®)
  ▪ Lubiprostone (Amitiza®)
  ▪ Polyethylene glycol Laxatives (Miralax®)

▪ General
  ▪ Tricyclic antidepressants
  ▪ Antispasmodics
  ▪ Dicyclomine (Bentyl®)
Efficacy of Pharmacologic Agents

**PEG laxatives**
- Loperamide
- TCA
- Dicylomine

**Low Quality Evidence**

**Lubiprostone**

**Medium Quality Evidence**

**Rifaximin**

**Alosetron**

**High Quality Evidence**

**Linaclotide**

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**Pancreas**

**Pancreas Review**

**Endocrine**

**Exocrine**

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**Pancreatic Enzymes**

- Prescription
  - Pancrelipase
    - Creon®
    - Ultresa®
    - Pancrease®
    - Zenpep®
  - OTC
    - Herbal Supplements
    - Some products mixed with probiotics

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**Literature Review**

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**Research Articles Timeline**

- Suarez F
- Leeds JS
- Money ME
- Ciacci C

- 1999
- 2010
- 2011

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Leeds et al: 2010

Some patients with irritable bowel syndrome may have exocrine pancreatic insufficiency

Objective
- Primary: To determine the frequency of exocrine pancreatic insufficiency in patients meeting Rome 2 criteria for IBS
- Secondary: Investigate the effect of pancreatic enzyme supplementation

Inclusion
- Referred from their general practitioner w/o previous investigation
- Symptoms consistent with IBS
- Met Rome 2 criteria

Methods: Primary
- Intervention
- Group 1: IBS-D but normal Fel 1 level
- Both groups received Creon 30,000 units PO TID

Results
- 314 Subjects met IBS criteria
- 19 had Fel-1 <100
- 6.1% (95% CI, 3.7%-9.3%)

Results for Secondary outcome
- 94.7% had clinically significant response
- 6.7% had clinically significant response

Authors Conclusions
- Use of pancreatic enzymes led to improvements in stool frequency, stool consistency, and abdominal pain when compared to those with normal Fel-1.
- This study showed a significant reduction in bloating, flatulence and feeling full using pancreatic supplements.
- This could suggest that such therapy may be beneficial in alleviating symptoms of patients with IBS-D.

Limitations/final thoughts
- Those with greatest benefit were those who met IBS criteria and had pancreatic insufficiency, so of course the enzymes worked.
- Only 1/15 subjects without insufficiency had benefit from enzymes.
- The study was actually looking at pancreatic insufficiency percentage amongst IBS, so was it wasn’t really powered to look at the effectiveness of pancreatic enzymes in IBS patients.

Leeds et al: 2010

Patient demographics
- 314 patients
- Mean age: 46.3
- 33% (96/314) were men

Secondary outcome
- Table 3

Table 3: Baseline Characteristics of Patients Undergoing Trial of Pancreatic Supplementation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1</th>
<th>Group 2</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>56</td>
<td>59</td>
<td>.91</td>
</tr>
<tr>
<td>Number of males</td>
<td>7</td>
<td>3</td>
<td>.71</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>72.5</td>
<td>76.4</td>
<td>.56</td>
</tr>
<tr>
<td>Median number of stools per day</td>
<td>6</td>
<td>5</td>
<td>.08</td>
</tr>
<tr>
<td>Median BSS</td>
<td>2</td>
<td>6</td>
<td>.56</td>
</tr>
</tbody>
</table>
Objective
- Test the effectiveness of pancrealipase (PEZ) compared with placebo in the reduction of the symptoms in patients who have IBS-D after eating known triggering agents

Inclusion
- Inclusion:
  - Postprandial IBS-D
  - 18 years or older
  - At least 5 years of only IBS-D symptoms before age 50 years
  - At least 12 times annually which had to occur within 3 h of eating at least two different triggering foods (specific for each patient)

Exclusion
- Intolerance only to milk products was not acceptable
- Unexplained weight loss
- Felt symptoms were due to medication
- Pt had been diagnosed with other gastrointestinal disorders which might explain the symptoms

Primary outcome
- The effectiveness of PEZ compared with placebos in reduction of postprandial symptoms among the number of individuals who chose the enzymes as the effective agent for the prolonged use period

Results
- Screened: N=255
- Randomized N=49
- Drug 1: placebo N=24
- Drug 1: Enzymes N=25
- Wash Out

Final Choice
- Enzymes N=25
- Placebo N=14

Drug 2: Enzymes N=19
- Drug 2: Placebo N=22
- Enzymes N=19
- Placebo N=22

Enzymes N=17
- Placebo N=11

Patient characteristics were as follows:
- 14 men, 35 women, mean age 52 years (SD 15.3); Choice of effective agent
- 25 participants (64%) of the remaining 39 chose PEZ over placebo as the effective agent
- The 3 months open label follow up revealed 31 out of the 46 were using pancreatic enzymes
- Safety
- There were no serious adverse events during the trial.

Author’s conclusion
- Further studies are needed to study the effectiveness of PEZ compared with placebo in patients with this condition.
- Comparison of PEZ vs. placebo identified that the PEZ was significantly more effective in reducing bloating, borborygmi (stomach rumbling), cramping, pain, and urgency, as well as decreasing the number of bowel movements and increasing the firmness of stool.
- Because PEZ are relatively safe, patients might be offered them as a therapeutic option if their symptoms occur predominately after meals.
- The study was limited by the small sample size and a high drop-out rate.
Pipeline

• Irritable Bowel Syndrome Evaluation and Treatment in Primary Care
  ▪ Sponsored by American Academy of Family Physicians
  ▪ Completed in 2012 with last update in 2014. But not published
  ▪ Double-blind randomized control trial. Cross over with active treatment and placebo
  ▪ Aim: 1) Evaluate how well Genova Diagnostics (GDx) IBS tests can be integrated into primary care, 2) examine the effects of the Genova Diagnostics (GDx) test on treatment, and 3) observe and track patients’ health, quality of life and clinical outcomes related to IBS during the study period.
  ▪ Looked at: Bifidobacterium infantis (probiotic), pancrelipase, nitazoxanide (broad-spectrum antiparasitic and antiviral) and placebo.
  ▪ Unknown results

Conclusion

Final Thoughts

• Small amount of studies or quality of data for the treatment of IBS
• Insufficiency vs IBS?
• Pancreatic enzymes can be potentially used
  ▪ Data is limited to only IBS-D.
• Not harmful so if patient wants to try it, there likely won’t be much harm
• Drug-drug interactions
  ▪ No significant interactions

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Acknowledgements

• Dr Nathan Pope PharmD, BCACP, FACA
• Evaluator

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**References**


