What’s New in Gastroenterology and Hepatology

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What’s New in Gastroenterology and Hepatology

Overview

• GERD management: PPIs (and beyond)
• Functional GI Disorders (FGID) and IBS
• Colon Cancer Screening
• Non-alcoholic Fatty Liver Disease (NAFLD)
GERD Management
PPIs (and Beyond)
PPI (Over) Use in the US

- Proton pump inhibitors (PPIs) among most widely used drug class in all of medicine
  - 8-10% of ambulatory adults prescribed PPI in past 30 days
- PPI use particularly prevalent in elderly (3.5x higher use >60 yrs)
- In 2009: $7 billion spent on PPI prescriptions (not including OTCs!)
- “Indications” for PPI use often unclear or inappropriate

PPI Indications in the Ambulatory Setting

Over 1/3 Rx have NO clearly documented indication!

- Documented UGI Diagnosis (appropriate)
- Empiric for Extraesophageal Sx
- Gastroprotection
- No appropriate documented indication

N=946, 1034 patient-years of PPI use

## Benefits of PPI Therapy

<table>
<thead>
<tr>
<th>Definitive indications</th>
<th>Consequences of stopping PPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastroesophageal reflux disease (GERD)</td>
<td>Erosive esophagitis</td>
</tr>
<tr>
<td>Erosive esophagitis, especially higher grades</td>
<td>Stricture recurrence</td>
</tr>
<tr>
<td>NERD with abnormal ambulatory reflux monitoring</td>
<td>Persistent symptoms</td>
</tr>
<tr>
<td>Long segment Barrett’s esophagus</td>
<td>Reduced quality of life</td>
</tr>
<tr>
<td>Peptic strictures</td>
<td>(Barrett’s progression)</td>
</tr>
<tr>
<td>Erosive esophagitis, especially higher grades</td>
<td>Increased health care costs</td>
</tr>
<tr>
<td>Eosinophilic esophagitis</td>
<td>Food impaction, dysphagia</td>
</tr>
<tr>
<td>Peptic ulcer disease including bleeding (short term therapy)</td>
<td>Bleeding, perforation, penetration, gastric outlet obstruction, death</td>
</tr>
<tr>
<td>Helicobacter pylori eradication</td>
<td>Persisting <em>H pylori</em>, atrophic gastritis, small risk of gastric cancer</td>
</tr>
<tr>
<td>Mucosa associated-lymphoid tissue (MALT) syndrome</td>
<td>Persisting MALT, symptoms</td>
</tr>
<tr>
<td>Gastro-protection with long term NSAID therapy</td>
<td>Peptic ulcer complications, dyspepsia</td>
</tr>
<tr>
<td>Hypersecretory states (Zollinger Ellison syndrome)</td>
<td>Peptic ulcer complications</td>
</tr>
<tr>
<td>Stress ulcer bleeding (short term therapy)</td>
<td>Bleeding, death</td>
</tr>
<tr>
<td>Chronic pancreatitis and refractory steatorrhea on pancreatic enzyme replacement therapy</td>
<td>Persisting steatorrhea</td>
</tr>
</tbody>
</table>

Proton Pump Inhibitors (PPIs)

Multiple Harmful Associations Identified

- Acute cholecystitis
- Cholangitis
- Pancreatic cancer
- Atopic dermatitis
- Esophageal adenoCA
- Depression
- Gynecomastia
PPI Use: An Unfavorable Risk: Benefit Balance?
False Alarms and Pseudo-epidemics*
Most reported associations in observational clinical research are FALSE!

Weaker associations usually are related to study **BIAS** rather than **CAUSALITY**!

*CGrimes DA, Schultz KF. Obstet Gynecol 2012;120:920-7*
PPI and Enteric Infections

*Increased risk of C. difficile and other enteric infections*

**Clostridium difficile colitis**

Summary meta-analysis plot [random effects]

- Shah 2000
- Cunningham 2003
- Dial 2004 coh
- Dial 2004
- Yip 2001
- Gillis 2005
- Kyne 2002
- Modina 2005
- Muto 2005
- Al-Turki 2005
- Loo 2005
- Dial 2005
- combined

RR PPI = 2.05 (1.47, 2.85)
RR H2 = 1.47 (1.06, 2.05)

**Other enteric infections**

Odds ratio meta-analysis plot [random effects]

- Rodriguez 1997
- Neal 1996
- Neal 1997
- Doordyn 2006 (Salmonella)
- Doordyn 2006 (Campylobacter)
- combined [random]

RR PPI = 3.33 (1.84, 6.02)
RR H2 = 2.03 (1.05, 3.92)

12 papers, 2948 patients

6 papers, 11,280 patients

PPI and Bone Fractures

*Increased risk of hip, spine, and all-site fractures*

**Hip**

<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yang, 2006 (16)</td>
<td>1.44 (1.30, 1.59)</td>
</tr>
<tr>
<td>Vestergaard, 2006 (17)</td>
<td>1.45 (1.28, 1.65)</td>
</tr>
<tr>
<td>Targownik, 2008 (18)</td>
<td>1.09 (0.88, 1.34)</td>
</tr>
<tr>
<td>Yu, 2008a (19)</td>
<td>1.16 (0.80, 1.67)</td>
</tr>
<tr>
<td>Yu, 2008b (19)</td>
<td>0.62 (0.26, 1.44)</td>
</tr>
<tr>
<td>Corley, 2010 (21)</td>
<td>1.30 (1.21, 1.39)</td>
</tr>
<tr>
<td>Gray, 2010 (22)</td>
<td>1.00 (0.71, 1.40)</td>
</tr>
<tr>
<td>Chiu, 2010 (23)</td>
<td>2.11 (1.45, 3.07)</td>
</tr>
<tr>
<td>Pouwels, 2011 (24)</td>
<td>1.20 (1.04, 1.40)</td>
</tr>
<tr>
<td>Khalili, 2012 (25)</td>
<td>1.36 (1.13, 1.63)</td>
</tr>
<tr>
<td>Fraser, 2013 (26)</td>
<td>1.75 (0.94, 3.26)</td>
</tr>
<tr>
<td>Reyes, 2013 (27)</td>
<td>1.24 (0.93, 1.65)</td>
</tr>
<tr>
<td>Soriano, 2014 (29)</td>
<td>1.09 (1.01, 1.17)</td>
</tr>
<tr>
<td>Ding, 2014 (31)</td>
<td>1.32 (1.01, 1.71)</td>
</tr>
<tr>
<td>Adams, 2014 (32)</td>
<td>1.12 (1.03, 1.21)</td>
</tr>
<tr>
<td><strong>Overall (I-squared = 71.9%, p = 0.000)</strong></td>
<td>1.26 (1.16, 1.38)</td>
</tr>
</tbody>
</table>

18 studies, 244,109 fracture cases included in analysis

**Any site**

<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any-site Vestergaard, 2006 (17)</td>
<td>1.18 (1.12, 1.43)</td>
</tr>
<tr>
<td>Targownik, 2008 (18)</td>
<td>0.99 (0.90, 1.11)</td>
</tr>
<tr>
<td>Yu, Zijia (19)</td>
<td>1.34 (1.10, 1.64)</td>
</tr>
<tr>
<td>Yu, 2008b (19)</td>
<td>1.21 (0.91, 1.62)</td>
</tr>
<tr>
<td>Roux, 2009 (20)</td>
<td>0.79 (0.41, 1.52)</td>
</tr>
<tr>
<td>Gray, 2010 (22)</td>
<td>1.25 (1.15, 1.36)</td>
</tr>
<tr>
<td>Fraser, 2013 (26)</td>
<td>1.40 (1.11, 1.76)</td>
</tr>
<tr>
<td>Moberg, 2014 (28)</td>
<td>2.53 (1.28, 4.99)</td>
</tr>
<tr>
<td>Lewis, 2014 (30)</td>
<td>2.17 (1.25, 3.77)</td>
</tr>
<tr>
<td>Ding, 2014 (31)</td>
<td>1.27 (1.12, 1.43)</td>
</tr>
<tr>
<td><strong>Subtotal (I-squared = 86.4%, p = 0.000)</strong></td>
<td>1.33 (1.15, 1.54)</td>
</tr>
</tbody>
</table>

**Spine**

<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any-site Vestergaard, 2006 (17)</td>
<td>1.60 (1.25, 2.04)</td>
</tr>
<tr>
<td>Roux, 2009 (20)</td>
<td>3.10 (1.14, 8.44)</td>
</tr>
<tr>
<td>Gray, 2010 (22)</td>
<td>1.47 (1.18, 1.82)</td>
</tr>
<tr>
<td>Ding, 2014 (31)</td>
<td>1.09 (1.20, 1.27)</td>
</tr>
<tr>
<td><strong>Subtotal (I-squared = 0.0%, p = 0.498)</strong></td>
<td>1.58 (1.38, 1.82)</td>
</tr>
</tbody>
</table>

Zhou B *et al.* Osteoporosis Int 2016.
PPI and Kidney Disease

Increased risk of acute and chronic kidney disease

Acute kidney injury (AKI)

Chronic kidney disease (CKD)

RR=1.44 (1.08-1.91), n=2,140,913

RR=1.36 (1.07-1.72), n=689,953

PPI and Dementia

**Decreased dementia-free survival with PPI use**

![Graph showing cumulative dementia-free survival with PPI use and no PPI use.](image)

HR incident dementia = 1.44 (1.36, 1.52)

German statutory health insurer (Allgemeine Ortskrankenkassen), n=73,679 PPI users, n=70,729 controls >75 years old

# PPI and Pneumonia

Increased risk of community acquired pneumonia (CAP)

26 studies, n=226,769 cases of CAP

**Relative Risk (RR) PPI=1.49 (1.16, 1.92)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Measure of Association</th>
<th>Effect Estimate (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Almirall 2008</td>
<td>OR</td>
<td>1.38 (0.87, 2.18)</td>
<td>4.26</td>
</tr>
<tr>
<td>Chen 2013</td>
<td>HR</td>
<td>2.28 (1.64, 3.15)</td>
<td>4.58</td>
</tr>
<tr>
<td>Lubnion 2010</td>
<td>OR</td>
<td>1.13 (0.88, 1.44)</td>
<td>4.13</td>
</tr>
<tr>
<td>Piltz 2013</td>
<td>OR</td>
<td>1.05 (0.89, 1.25)</td>
<td>4.85</td>
</tr>
<tr>
<td>Gau 2010</td>
<td>OR</td>
<td>1.18 (0.90, 1.54)</td>
<td>4.44</td>
</tr>
<tr>
<td>Hermes 2012</td>
<td>OR</td>
<td>1.29 (1.15, 1.45)</td>
<td>4.90</td>
</tr>
<tr>
<td>Jena 2013</td>
<td>RR</td>
<td>1.80 (1.71, 1.89)</td>
<td>4.05</td>
</tr>
<tr>
<td>Juthani–Mehta 2013</td>
<td>HR</td>
<td>0.81 (0.57, 1.14)</td>
<td>4.35</td>
</tr>
<tr>
<td>Ihejir 2003</td>
<td>OR</td>
<td>18.70 (7.00, 51.00)</td>
<td>1.06</td>
</tr>
<tr>
<td>Labaj 2004</td>
<td>OR</td>
<td>1.73 (1.33, 2.25)</td>
<td>4.70</td>
</tr>
<tr>
<td>Liu 2012</td>
<td>OR</td>
<td>1.63 (1.25, 2.12)</td>
<td>4.70</td>
</tr>
<tr>
<td>Long 2013</td>
<td>OR</td>
<td>1.15 (1.04, 1.26)</td>
<td>4.92</td>
</tr>
<tr>
<td>Mastromarco 2009</td>
<td>OR</td>
<td>7.24 (4.14, 15.19)</td>
<td>0.58</td>
</tr>
<tr>
<td>Mejias 2011</td>
<td>OR</td>
<td>1.60 (1.20, 2.20)</td>
<td>4.63</td>
</tr>
<tr>
<td>Merri 2013</td>
<td>OR</td>
<td>1.85 (1.03, 3.26)</td>
<td>0.77</td>
</tr>
<tr>
<td>Nilsson 2012</td>
<td>OR</td>
<td>3.49 (2.40, 3.60)</td>
<td>4.95</td>
</tr>
<tr>
<td>Posina 2011</td>
<td>OR</td>
<td>7.77 (1.16, 5.07)</td>
<td>3.47</td>
</tr>
<tr>
<td>Quagliarello 2005</td>
<td>HR</td>
<td>0.92 (0.61, 1.37)</td>
<td>4.40</td>
</tr>
<tr>
<td>Ramsey 2013</td>
<td>RR</td>
<td>1.55 (1.44, 1.67)</td>
<td>4.93</td>
</tr>
<tr>
<td>Rodriguez 2009</td>
<td>RR</td>
<td>1.16 (1.03, 1.31)</td>
<td>4.90</td>
</tr>
<tr>
<td>Roughend 2009</td>
<td>RR</td>
<td>1.16 (1.11, 1.22)</td>
<td>4.95</td>
</tr>
<tr>
<td>Sarker 2008</td>
<td>OR</td>
<td>1.02 (0.97, 1.08)</td>
<td>4.84</td>
</tr>
<tr>
<td>Schilman 2011</td>
<td>OR</td>
<td>0.26 (0.09, 1.46)</td>
<td>1.96</td>
</tr>
<tr>
<td>Sugano 2011</td>
<td>OR</td>
<td>1.04 (0.06, 16.68)</td>
<td>0.70</td>
</tr>
<tr>
<td>Sugano 2012</td>
<td>OR</td>
<td>7.51 (1.50, 37.65)</td>
<td>1.65</td>
</tr>
<tr>
<td>van de Geur 2006</td>
<td>OR</td>
<td>7.71 (1.85, 7.97)</td>
<td>4.76</td>
</tr>
<tr>
<td>Overall (I-squared = 99.2%, p = 0.000)</td>
<td></td>
<td>RR PPI=1.49 (1.16, 1.92)</td>
<td>100.00</td>
</tr>
</tbody>
</table>
PPI and Mortality

Excess risk of death among PPI users

HR PPI vs H2= 1.25 (1.23,1.28)

“False Alarms and Pseudo-Epidemics”?  

<table>
<thead>
<tr>
<th>BENEFITS</th>
<th>0.1</th>
<th>0.25</th>
<th>0.33</th>
<th>0.5</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>10+</th>
</tr>
</thead>
<tbody>
<tr>
<td>HARMSS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| CP=chest pain, ENT=laryngopharyngeal symptoms, HB=heartburn, CKD=chronic kidney disease, SIBO=small intestinal bacterial overgrowth, FGP=fundic gland polyps

Grimes DA, Schultz KF. Obstet Gynecol 2012;120:920-7
Studies Reporting Risk of PPIs have Major Limitations

- Retrospective design
  - Bias and misinterpretation
  - Suboptimal design to assess safety
- Channeling bias
- Failure to satisfy Hill criteria
- Often not confirmed (or even refuted) by better quality studies
Channeling bias

• Tendency of clinicians to prescribe a treatment based on the patient’s prognosis
  – i.e., OLDER and SICKER patients are more likely to be prescribed a PPI than are younger, healthier individuals
Studies Reporting Risk of PPIs have Major Limitations

• Retrospective design
  – Bias and misinterpretation
  – Suboptimal design to assess safety
• Channeling bias
• Failure to satisfy Hill criteria
### Hill Criteria and PPIs

**Soft evidence of causation**

<table>
<thead>
<tr>
<th>Strength</th>
<th>Enteric infection</th>
<th>Fracture</th>
<th>Renal dysfunction</th>
<th>Dementia</th>
<th>Pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consistency</td>
<td>Moderate</td>
<td>Weak</td>
<td>Weak</td>
<td>Very weak</td>
<td>Weak</td>
</tr>
<tr>
<td>Specificity</td>
<td></td>
<td>Weak</td>
<td>Weak</td>
<td>Very weak</td>
<td></td>
</tr>
<tr>
<td>Temporality</td>
<td>Moderate</td>
<td>Weak</td>
<td>Weak</td>
<td>Very weak</td>
<td>Weak</td>
</tr>
<tr>
<td>Gradient</td>
<td>Moderate</td>
<td>Weak</td>
<td>Weak</td>
<td>Very weak</td>
<td></td>
</tr>
<tr>
<td>Plausibility</td>
<td>Moderate</td>
<td>Weak</td>
<td></td>
<td>Very weak</td>
<td></td>
</tr>
<tr>
<td>Coherence</td>
<td>Moderate</td>
<td></td>
<td></td>
<td>Very weak</td>
<td></td>
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<tr>
<td>Experiment</td>
<td></td>
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<tr>
<td>Analogy</td>
<td>Moderate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Studies Reporting Risk of PPIs have Major Limitations

- Retrospective design
  - Bias and misinterpretation
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- Channeling bias
- Failure to satisfy Hill criteria
- Often not confirmed (or even refuted) by better quality studies
Prospective PPI Safety Data

- Randomized, double-blinded study on patients ≥65 with stable CV disease
  - ASA 100 mg a day
  - ASA 100 mg a day + rivaroxaban 2.5 mg bid
  - Rivaroxaban 5 mg bid
- Pts NOT on PPI randomized to pantoprazole 40 mg a day or placebo
- 3 year followup, 53,000 pt-years

## Prospective PPI Safety Data

*(Mostly) lack of significant effect*

<table>
<thead>
<tr>
<th></th>
<th>Pantoprazole 40 mg <em>qd</em> (N=8791)</th>
<th>Placebo <em>qd</em> (N=8807)</th>
<th>Pantoprazole v. placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. (%) of first events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. difficile</td>
<td>9 (0.1)</td>
<td>4 (&lt;0.1)</td>
<td>2.26 (0.70 to 7.34)</td>
</tr>
<tr>
<td>Other enteric infections</td>
<td>119 (1.4)</td>
<td>90 (1.0)</td>
<td>1.33 (1.01 to 1.75)</td>
</tr>
<tr>
<td>Fracture</td>
<td>203 (2.3)</td>
<td>211 (2.4)</td>
<td>0.96 (0.79 to 1.17)</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>184 (2.1)</td>
<td>158 (1.8)</td>
<td>1.17 (0.94 to 1.45)</td>
</tr>
<tr>
<td>Dementia</td>
<td>55 (0.6)</td>
<td>46 (0.5)</td>
<td>1.20 (0.81 to 1.78)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>318 (3.6)</td>
<td>313 (3.6)</td>
<td>1.02 (0.87 to 1.19)</td>
</tr>
</tbody>
</table>

Approach to Responsible PPI Use

• Review indication for PPI therapy
• Review dose of PPI therapy
  – Lowest effective dose
• Discuss risk-benefit with patient
GERD Management

"Therapy gap"

Acid manipulation
60-70% successful
20 million Americans

Over the counter medications: H2, antacids, alginates

Lifestyle

Surgical management (fundoplication) - 1%

Not responding to medical management
Mild-moderate symptoms
Unwilling to consider surgery
Poor surgical candidate

Gyawali CP, Fass R. Gastroenterology 2018;154:302
Anti-reflux surgery

A good alternative to PPI?

• **Objective**: restore antireflux barrier, ↓ GERD
• Success rates variable (67-95%)
  – Dependent on: surgical expertise, pre-op eval, patient selection
• Serious peri-operative (30-day) complications low
  – Mortality (0.1-0.2%), infection (1.1%), bleeding (0.9%), perforation (0.9%)
  – BUT: acute dysphagia: 50%
• Prolonged complications are common
  – Structural: 30% (disruption, herniation, slippage, stenosis)
  – Functional: dysphagia, gas-bloat, inability to belch/vomit, chest pain, diarrhea (18-31%)
• 62% surgical patients back on PPI *within a decade!*

Magnetic LES Sphincter Augmentation (MSA, LINX)
Magnetic Sphincter Augmentation (MSA) Advantages
Magnetic Sphincter Augmentation vs BID PPI

MSA vs. Nissen

Meta-analysis of 3 studies

• 688 patients (n=273, Lap Nissen, n=415 MSA)
  – Better with MSA:
    • Belching (95.2 vs. 65.9%, p<0.00001)
    • Emesis (93.5 vs 49.5%, p<0.0001)
  – No difference:
    • Dysphagia
    • Bloating
    • PPI dependence

The Ideal MSA Patient

- Typical GERD Sx (heartburn, regurgitation)
- Normal esophageal peristalsis on manometry
- Good symptom correlation on pH testing
- Want a quick recovery
- Smaller hiatal hernia
- No anticipated need for MRI
Functional GI Disorders (FGID) & Irritable Bowel Syndrome (IBS)
Defining and Characterizing IBS

Rome IV Criteria for IBS\(^1\)

Recurrent **abdominal pain**, on average, \(\geq 1\) day per week in the last 3 months, associated with \(\geq 2\) of the following:

- Related to *defecation*
- Change in *frequency* of stool
- Change in *form* (appearance) of stool

Criteria should be fulfilled for the *last 3 months* with symptom *onset* \(\geq 6\) months before diagnosis

IBS-C, irritable bowel syndrome with constipation; IBS-D, irritable bowel syndrome with diarrheal IBS-M, irritable bowel syndrome with mixed symptoms.

The Dichotomy of IBS Diagnostic Approaches

Rome criteria + for IBS

Diagnose IBS

IBS is a “diagnosis of exclusion”

Rule out ALL other diagnoses

Basic laboratories

Specialized lab testing

Stool studies

Multiple endoscopic procedures

Multiple imaging studies

Diagnose IBS

The Dichotomy of IBS Diagnostic Approaches

Rome criteria + for IBS

- No red flag symptoms
- High somatization/anxiety
- Normal CBC, Hb, CRP

Diagnose IBS

LR +17.3, Specificity 99%

IBS is a diagnosis of exclusion

Rule out ALL other diagnoses

- Basic laboratory tests
- Specialized lab testing
- Stool studies
- Multiple endoscopic procedures
- Multiple imaging studies

Diagnose IBS

“Diagnosis IBS and Treat…”
Reconsider if No Response or New Symptoms Develop

Rome criteria + for IBS
- No red flag symptoms
- High somatization/anxiety
- Normal CBC, Hb, CRP

Diagnose IBS and Treat

Expand Differential To Consider Additional Diagnoses, & Pursue Further Evaluation

No Response to Rx, New Red Flags

IBS Pharmacotherapy

Remember when?
IBS Pharmacotherapy

Tegaserod for IBS with constipation

Find out more
Tegaserod for IBS with constipation

“Not all smiles”

• March 30, 2007: FDA “discontinued marketing” of tegaserod “for safety reasons.”

• Retrospective review of 29 premarketing trials (11,614 tegaserod-treated subjects):
  • 10-fold increase in the RR of significant pooled cardiovascular events:
    • 0.1% in tegaserod vs. 0.01% in placebo
    • Number needed to harm (NNH) was 1,111
  • FDA: because tegaserod was used for a “nonlife-threatening condition”, risk of serious cardiovascular events was felt to be disproportionate to any potential benefit.

Brandt LJ. Am J Gastroenterol 2008.
Tegaserod for IBS with constipation

*Evidence against a CV risk*

- Large matched, case-control study of tegaserod-treated patients (n = 2603), matched 1:6 with untreated (n = 15,618) patients, followed for an average of 2.5 years.
- Cardiovascular event rates were low and similar in both cohorts
  - Primary composite CV endpoint, 54 (0.35%) untreated and 12 (0.46%) treated pts (untreated OR = 1.27, 95% CI: 0.68-2.38, P = .46).
  - A total of 12 (0.1%) untreated and 1 (<0.1%) treated pts were hospitalized for a myocardial infarction (MI).
  - A total of 6 (<0.1%) untreated and NO treated pts died from cardiac causes.
- Failed to confirm a reported large event differential for tegaserod incidentally noted in earlier clinical trials database
  - **Suggesting that the prior observation may have been due to chance.**
FDA approves reintroduction of Zelnorm for IBS-C in certain women

April 3, 2019

The FDA has approved the reintroduction of Zelnorm, a twice-daily oral treatment for irritable bowel syndrome with constipation in women aged under 65 years, according to a company press release.

The FDA originally approved tegaserod (Zelnorm, Sloan Pharmaceuticals) in 2002 for the treatment of IBS-C in women. However, Novartis, the drug's previous manufacturer, voluntarily pulled tegaserod from the U.S. market in 2007 due to possible cardiac-related side effects.

Tegaserod has been available in the U.S., but only through an FDA-authorized expanded access program.

"We are excited about what the reintroduction of Zelnorm means for patients suffering from irritable bowel syndrome with constipation," P. Brockinridge Jones, CEO of U.S. WorldMeds, said in the press release. "We have continually heard from patients and clinicians alike that the IBS-C community is eager to have Zelnorm return to the U.S. as an available treatment option."
IBS Pharmacotherapy

“What’s old is new again”

Women with IBS-C <65 yrs, without CV risk
Prucalopride as a “Newer” prescription option

- 5-HT<sub>4</sub> receptor agonist
  - Improves colonic motility, (decreases colonic transit time)
  - Increase spontaneous complete bowel movements (SCBMs)
  - In chronic idiopathic constipation [NNT ~5]

- More specific 5-HT<sub>4</sub> receptor activity than predecessors
- No observed increase in cardiac events or QTc
- Systemic effects: Nausea, headache
- “Suicidal ideation and behavior” warning

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Diet and IBS… *circa 2000*
Diet and IBS...2019
What are FODMAPs?

Fermentable Oligo-, Di-, Monosaccharides And Polyols

**Excess Fructose**
- Honey, apples, pears, peaches, mangos, fruit juice, dried fruit

**Fructans**
- Wheat (large amounts), rye (large amounts), onions, leeks, zucchini

**Sorbitol**
- Apricots, peaches, artificial sweeteners, artificially sweetened gums

**Raffinose**
- Lentils, cabbage, brussels sprouts, asparagus, green beans, legumes

Dietary Management of IBS

FODMAP > mNICE for abdominal pain and bloating

Average Daily Abdominal Pain Scores (0-10)

Average Daily Abdominal Bloating Score (0-10)

P values refer to the change WITHIN group comparing to baseline score.

*P≤0.05; ⁰P≤0.001; §P≤0.0001.

Prebiotics for IBS
As effective as low FODMAP diet (with continued benefit!)

Psychiatric and Extra-intestinal Comorbidities in IBS

Additive worsening of HRQOL and Bowel Symptoms

Cognitive Behavioral Therapy (CBT) for IBS

Minimal contact (and standard) CBT improves refractory IBS symptoms

MC-CBT = minimal contact cognitive behavioral therapy
S-CBT = standard cognitive behavioral therapy
EDU = education control

Cognitive Behavioral Therapy (CBT) for IBS

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Colon Cancer Screening
Bowel Prep for Colonoscopy

Poor prep = poor study

- Even with excellent prep, colonoscopy is imperfect
  - 5% miss rate clinically significant lesions (polyp ≥1cm)
- Prep is inadequate in up to 25% of examinations
- Split-dose better than single dose (85 vs. 63% adequate)
- Inadequate bowel preparation increases:
  - Risk of adverse events during procedure
  - Missed polyps
  - Insertion time, overall procedure time
  - Incomplete procedures
  - Number of procedures needed

Patient risk factors for poor bowel prep

- Prior inadequate preparation
- Hx constipation
- Constipating medications (e.g., TCAs and opioids)
- Dementia or Parkinson disease
- Male sex

- Low health literacy/cognitive skills
- Low patient engagement
- Overweight/obese
- Diabetes mellitus
- Previous colorectal surgery
- Cirrhosis

Bowel prep quality

*Boston Bowel prep score (BBPS) and Bubble score*

A Recent Case...
Simethicone helps reduce colon bubbles

But... Is Simethicone safe?

But…Is Simethicone safe?

“Olympus does not recommend the use of non-water-soluble additives with our flexible endoscopes or ancillary equipment. These products may be difficult to remove during manual cleaning and may reduce the efficacy of the reprocessing procedure.”

Yet….there are no published reports of adverse events related *specifically* to the use of simethicone.
Is Simethicone OK to use for colonoscopy?  
It depends on who you ask!

- **The Gastroenterology Society of Australia (2019):** “The *continued use* of simethicone is considered reasonable as it improves mucosal inspection during colonoscopy.”

- **The American Society for Gastrointestinal Endoscopy (2016):** “*Insufficient evidence to recommend a change* to current clinical practice.”

- **The Canadian Association of Gastroenterology:** “*Unable to make clear recommendations* on the use of simethicone at this time.”

- **The British Society of Gastroenterology (2017):** “*Concentration of simethicone should be kept to a minimum* and that it be administered orally or via the biopsy channel”

- **The European Society of Gastrointestinal Endoscopy:** “*Recommend adding simethicone to standard bowel preparation* for colonoscopy.”

The role of oral simethicone on the adenoma detection rate and other quality indicators of screening colonoscopy: a randomized, controlled, observer-blinded clinical trial

Sharareh Moraveji, MD, 1 Nancy Casner, CRC, 1 Mohammad Bashashati, MD, 2 Cesar Garcia, MD, 3 Alok Dwivedi, PhD, 4 Marc J. Zuckerman, MD, 1 Andres Carrion, MD, 1 Antonio Mendoza Ladd, MD 1

El Paso, Texas, USA

<table>
<thead>
<tr>
<th></th>
<th>PEG + SIM (n = 129)</th>
<th>PEG (n = 139)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cecal intubation time, mean (± SD), sec</td>
<td>363.6 (± 222.7)</td>
<td>371.6 (± 277.3)</td>
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<tr>
<td>Withdrawal time, mean (± SD), sec</td>
<td>395.7 (± 69.2)</td>
<td>399.0 (± 76.7)</td>
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<td>Effective procedure time, mean (± SD), sec</td>
<td>759.3 (± 253.1)</td>
<td>800.2 (± 459.6)</td>
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<tr>
<td>Polyp detection rate, %</td>
<td>46.5%</td>
<td>49.6%</td>
<td>.61</td>
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<tr>
<td>Adenoma detection rate, %</td>
<td>33.3%</td>
<td>38.8%</td>
<td>.88</td>
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<tr>
<td>Intraprocedural use of SIM, no. (%)</td>
<td></td>
<td></td>
<td>&lt; .05</td>
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<tr>
<td>Yes</td>
<td>2 (1.6%)</td>
<td>68 (48.9%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>127 (98.4%)</td>
<td>71 (51.1%)</td>
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<tr>
<th>Endoscopist 1: total mean (± SD)</th>
<th>PEG + SIM (n = 129)</th>
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<tr>
<td></td>
<td>Bubble scale</td>
<td>BBPS</td>
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<tr>
<td></td>
<td>0.1 (± 0.2)</td>
<td>8.9 (± 0.4)</td>
<td></td>
</tr>
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<td></td>
<td>2.1 (± 2.1)</td>
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<th>BBPS</th>
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<tr>
<td>Rectosigmoid colon</td>
<td>0.01 (± 0.09)</td>
<td>2.98 (±0.13)</td>
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<td></td>
<td>0.34 (±0.74)</td>
<td>2.98 (±0.15)</td>
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<td>.73</td>
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<td>Transverse colon</td>
<td>0.02 (± 0.13)</td>
<td>2.99 (±0.09)</td>
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<tr>
<td></td>
<td>1 (±1.05)</td>
<td>2.99 (±0.12)</td>
<td>&lt; .001</td>
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<td>.62</td>
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<tr>
<td>Ascending colon</td>
<td>0.01 (± 0.09)</td>
<td>2.97 (±0.18)</td>
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<td>0.75 (±0.89)</td>
<td>2.93 (±0.29)</td>
<td>&lt; .001</td>
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The Future?…Computer Aided Detection of Colon Polyps

Non-alcoholic Fatty Liver Disease (NAFLD)
12x increase in crude annual incidence of NAFLD since 2000
The Natural History of Non-Alcoholic Fatty Liver (NAFLD)

Features of the Metabolic Syndrome:
- Abdominal Obesity
- Hypertriglyceridemia
- Low HDL
- Hypertension
- High fasting glucose

STEATOSIS
Histology:
- 5% steatotic hepatocytes

10-25% → NASH
Histology:
- Lobular inflammation
- Hepatocyte ballooning

20% → FIBROSIS
Histology:
- Perisinusoidal/pericellular fibrosis

2.5% → CIRRHOSIS
Histology:
- Regenerative nodules surrounded by fibrous bands

Complications:
- Hepatocellular carcinoma
- Portal hypertension
- Decompensated liver disease

Management of NAFLD…circa 2000

"You need to lose weight"

"You still need to lose weight"

"Keep working to lose weight"

Pray patient doesn’t develop cirrhosis/cancer

"You REALLY need to lose weight!"

Liver biopsy to confirm NAFLD/NASH
Bariatric surgery outcomes in NAFLD

Improvement/resolution fibrosis
30% (21-48%)

Improvement/resolution steatosis
88% (88-94%)

Improvement/resolution steatohepatitis
59% (38-78%)

RYGB more effective than other surgeries at improving NAFLD histology

N=2374 patients

Vitamin E and Pioglitazone

The good: Improvement in transaminases

247 non-diabetic patients with steatohepatitis

Vitamin E and Pioglitazone

*The good: Improvement in histology*

<table>
<thead>
<tr>
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<th>Placebo</th>
<th>Vitamin E</th>
<th>Pioglitazone</th>
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<tbody>
<tr>
<td>Steatosis</td>
<td>31</td>
<td>54</td>
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<tr>
<td>Lobular inflammation</td>
<td>35</td>
<td>54</td>
<td>60</td>
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<tr>
<td>Fibrosis</td>
<td>31</td>
<td>41</td>
<td>44</td>
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<tr>
<td>Resolution of NAFLD</td>
<td>21</td>
<td>36</td>
<td>47</td>
</tr>
</tbody>
</table>

Vitamin E and Pioglitazone

The not so good

Pioglitazone

• Diabetics only
• Weight gain!
• Heart failure
• Fracture risk
• ? Bladder cancer risk

Vitamin E

• Not studied in diabetics or decompensated cirrhosis
• Increase in all cause mortality?
• Increase risk prostate cancer (SELECT)

Management of NAFLD in 2019

Fibrosis is the key of liver-related and all-cause mortality

Suspected NASH/NAFLD
- Obesity, MetS
- Abnormal transaminases
- Liver ultrasound with steatosis
- Other etiologies excluded (Hx, labs)

Assess for liver fibrosis
- **FIB4 Score** (age, PLT, AST, ALT)
- **NAFLD fibrosis score** (age, BMI, fast glucose, AST, ALT, PLT, albumin)

High risk
- Hepatology referral
- Further imaging (fibroscan, MR)
- Implement MANAGEMENT

Low/intermediate risk
- Lifestyle changes encouraged
- Repeat scoring Q 2 years

HEPATIC STEATOSIS
- Exercise
- Weight loss (>7%), bariatric procedure
- CVD risk assessment/Rx

NASH AND FIBROSIS
- Vitamin E
- Pioglitazone (DM2 only)
- GLP-1 agonist? (liraglutide)

CIRRHOSIS
- Ultrasound ± AFP (HCC screening)
- Upper endoscopy
- Transplant evaluation

MetS= metabolic syndrome
CVD= cardiovascular disease

The Future of NAFLD Treatment?

The Future of NAFLD Treatment?

Obetacholic acid

Primary endpoint

Key Secondary Endpoints—72 wks

* Improvement in NAFLD Activity Score (NAS) ≥2
  [Steatosis (0-3) + Inflammation (0-3) + Ballooning (0-2)]

* No worsening of hepatic fibrosis

**BUT: worsening lipid profile (↑ LDL, ↓ HDL, pruritis)

What’s New in Gastroenterology and Hepatology

A Summary

• PPI’s overall are safe; use, where indicated, at lowest effective doses.
• Consider magnetic sphincter augmentation as a good GERD surgical option.
• Symptom are sufficient to diagnose IBS (99% accurate).
• IBS therapy: what’s new is old (tegaserod); use diet, prebiotic, and psychological strategies to control symptoms.
• Colonoscopy remains a mainstay of colon cancer screening; improving prep (recognize risk, split dose) and bubbles (simethicone) optimizes visualization.
• Computer aided detection of polyps is around the corner.
• NAFLD is increasing in incidence; aggressive weight loss (bariatrics) mainstay; Vit E and pioglitazone for some patients.
• Novel NAFLD therapies are on the horizon. Ultimate goal is to prevent fibrosis and cirrhosis.