ROME Update from DDW 2013
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Attention

• The abstracts discussed in this presentation were presented at Digestive Disease Week 2013. As such, they have not been subjected to a full peer-review process. These abstracts discuss uses of particular agents that are outside of their indications and/or agents that have not yet received approval for the uses discussed herein.
Nortriptyline for Idiopathic Gastroparesis: A Multicenter, Randomized, Double-Masked, Placebo-Controlled Trial (NORIG)

DD- #1

Parkman HP, Van Natta M, Abell TL et al.

Abstract 5
Tricyclic Antidepressant Actions in FGIDs

Antidepressant action

Visceral analgesia

Changes in motility

Smooth muscle relaxation

Adapted from Rome Foundation Functional GI Disorders Specialty Modules.

FGID = functional gastrointestinal disorder
Background and Methods

• Background
  – Tricyclic antidepressants (TCAs) are frequently used as neuromodulators for treatment of nausea, vomiting, and abdominal pain in patients with gastroparesis
  – This practice is *not yet* based on evidence from well-designed clinical trials

• Study design
  – 15-week, multicenter, randomized, placebo-controlled, double-blind, parallel group, dose escalation trial

• Patients
  – 130 patients with confirmed gastroparesis with delayed gastric emptying by scintigraphy and symptom scores >21 on Gastroparesis Cardinal Symptom Index (GCSI)

• Treatments
  – Nortriptyline (escalated at 3-week intervals: 10, 25, 60, 75 mg/day)
  – Placebo

• Primary end point
  – Decrease from the baseline GCSI score of ≥50% on 2 consecutive visits over 15 weeks of follow-up
Efficacy Results

• Overall symptomatic improvement did not differ between nortriptyline and control patients

Primary End Point
(Decrease from the baseline GCSI score of ≥50% on 2 consecutive visits over 15 weeks of follow-up)
Results: Additional End Points and Safety

• Nortriptyline was associated with:
  – Greater decrease in nausea ($P=.04$) and abdominal pain ($P=.03$) at 3 weeks but not after
  – Greater improvement in appetite ($P=.03$) and ability to finish a meal ($P=.08$) at week 15
  – Greater increase in body mass index (0.5 vs -0.2 kg/m$^2$; $P=.03$)
  – Improved symptoms in subgroup with impaired satiety testing (<250 ml Ensure; $P=.06$))

• Safety
  – Nortriptyline was associated with a high rate of discontinuation (19 vs 6 placebo patients)
  – Adverse effects were the primary reason for discontinuation
Conclusions

• In this first adequately powered randomized clinical trial of a neuromodulator in idiopathic gastroparesis, nortriptyline did not improve overall symptom endpoint in idiopathic gastroparesis over a 15 week period

• Improvements in appetite, satiety and BMI were noted

• An early improvement in nausea and abdominal pain was seen early in the trial, but this was not sustained

• Nortriptyline was associated with early treatment discontinuation in 29% (19 vs 6 placebo) patients
The Functional Dyspepsia Treatment Trial: Key Results
DD- #2

Locke GR et el.
Abstract 810
Methods

• Design: Prospective, randomized, double-blind parallel group trial:
• 3 arms
  – Placebo
  – Amitriptyline 50 mg
  – Escitalopram 10 mg
• Patients completed questionnaires, nutrient drink test, gastroesophageal study, SPECT, and blood testing before and after treatment

SPECT=single photon emission computed tomography.
Results: Primary Endpoint

Adequate Relief (%)
≥5/12 weeks of adequate relief

P=0.05

Patients ()

40% 53% 38%

Placebo, n=97 Amitriptyline, n=97 Escitalopram, n=98

Patients with ulcer-like but not dysmotility-like disease improved with amitriptyline
Conclusions

• Amitriptyline, but not escitalopram, was efficacious for the global symptoms of functional dyspepsia

• Treatment effect of amitriptyline was greatest in the ulcer-like functional dyspepsia subgroup and in males

• Response was not predicted by patient characteristics (eg, anxiety, BMI) or baseline GI physiology test results
Do Co-Morbid Mental Disorders Impact Differently on Perceived Symptom Severity in Patients With Gastrointestinal Diseases? A Comparison of Functional Dyspepsia and Intestinal Graft-Versus-Host Disease

Adam B, Klisanin V, Junne FP et al.

Abstract Sa1338
**Background and Methods**

**Background**

- Anxiety and depression are associated with functional dyspepsia (FD) but their role in symptom severity in organic gastrointestinal diseases is not well known.

**Study design**

- This study compared the role of anxiety and depression in a functional GI disorder, functional dyspepsia, and an organic GI disease, graft-vs.-host disease which is a major cause of non-relapse mortality and morbidity. GVHD can occur after allogenic stem cell transplantation.
Background and Methods

• Study design (cont.)
  – 67 patients with GVHD and 45 patients with Rome III + FD were studied.
  – GI symptoms were assessed using a standardized Gastrointestinal Symptom Score for epigastric pain, cramps, fullness, early satiety, nausea and vomiting
  – Anxiety and depression were measured using the Hospital Anxiety and Depression (HAD) scale
    • HAD scores of 0-7 were considered to be indicative of no psychological co-morbidity
    • HAD scores between 8-10 were categorized as probably anxiety and depression
    • Scores >= 11 were indicative of relevant anxiety and depression
## Results

<table>
<thead>
<tr>
<th></th>
<th>Probable Anxiety</th>
<th>Relevant Anxiety</th>
<th>Probable Depression</th>
<th>Relevant Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>aGVHD</td>
<td>12/67 (17.9%)</td>
<td>6/67 (9.0%)</td>
<td>4/67 (6.0%)</td>
<td>8/67 (11.9%)</td>
</tr>
<tr>
<td>FD</td>
<td>12/45 (26.7%)</td>
<td>8/45 (17.7%)</td>
<td>11/45 (24.4%)</td>
<td>6/45 (13.3%)</td>
</tr>
</tbody>
</table>

Overall anxiety and depression scores did not differ between FD and GVHD.
Results

• Anxiety in GVHD correlated with:
  – Severity of pain ($r=.25$, $P=.04$)
  – Fullness ($r=.43$, $P<.001$)
  – Satiety ($r=.40$, $P=.001$)
  – Nausea ($r=.36$, $P=.003$)
  – Vomiting ($r=.40$, $P=.001$)

• Anxiety in functional dyspepsia correlated with:
  – Pain ($r=.44$, $P<.028$)
  – Fullness ($r=.38$, $P<.001$)
  – Satiety ($r=.23$, $P=.03$)
  – Vomiting ($r=.32$, $P=.002$)
Results

- Functional dyspepsia patients without anxiety showed significantly more severe cramps and nausea but less vomiting compared to GVHD without anxiety.

- In FD patients with anxiety, pain was more prominent while vomiting was less evident compared to GVHD with anxiety.
Results

• Depression in GVHD was associated with:
  – Pain \((r=.58, P\leq.001)\)
  – Cramps \((r=.53, P<.001)\)
  – Fullness \((r=.64, P<.001)\)
  – Satiety \((r=.50, P<.001)\)
  – Nausea \((r=.43, P<.001)\)
  – Vomiting \((r=.48, P<.001)\)

• Depression was associated with:
  – Pain \((r=.23, P<.001)\)
Conclusions

• While patients with functional dyspepsia experience more pain, vomiting is more severe in GVHD

• Psychological co-morbidity is closely linked to symptom severity in both functional dyspepsia and organic GI disease

• Anxiety and depression appeared to be associated with pain in FD and a number of GI symptoms in GVHD

• These differences may indicate different underlying pathophysiological mechanisms rather than psychologically driven factors
Mirtazapine Improves Early Satiation, Nutrient Intake, Weight Recovery, and Quality of Life in Functional Dyspepsia With Weight Loss: A Double-Blind, Randomized, Placebo-Controlled Pilot Study

DD- #4

Ly HG, Carbone F, Holvoet L et al.

Abstract 161
Background and Methods

• Background
  – In up to 40% of cases, weight loss accompanies functional dyspepsia symptoms (eg, early satiation, postprandial fullness, epigastric pain/burning)

• Study design
  – 8-week, randomized, placebo-controlled study

• Patients
  – 34 functional dyspepsia patients who lost ≥10% of original body weight without major depression or anxiety disorder

• Treatments
  – Mirtazapine 15 mg orally in the evening
  – Placebo

• End points
  – Functional dyspepsia symptom severity (8 symptoms score 0-3)
  – Weight
  – Functional dyspepsia-specific quality of life
  – Results of nutrient challenge test
## Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Week 0 vs Week 8 Mirtazapine</th>
<th>Week 0 vs Week 8 Placebo</th>
<th>Mirtazapine vs Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Symptoms</strong></td>
<td>10.9 ± 0.9 vs 7.5 ± 1.1</td>
<td>11.4 ± 0.9 vs 9.9 ± 1.2</td>
<td>-3.3 ± 0.9 vs 2.1 ± 1.0</td>
</tr>
<tr>
<td></td>
<td>(P=.017)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Early Satiety</strong></td>
<td>1.9 ± 0.2 vs 1.1 ± 0.26</td>
<td>1.53 ± 0.2 vs 1.7 ± 0.2</td>
<td>-0.8 ± 0.2 vs 0.27 ± 0.2</td>
</tr>
<tr>
<td></td>
<td>(P=.001)</td>
<td>NS</td>
<td>(P=.005)</td>
</tr>
<tr>
<td><strong>Quality of Life</strong></td>
<td>31.7 ± 1.8 vs 24.5 ± 2.6</td>
<td>30.9 ± 0.38 vs 30.5 ± 2.9</td>
<td>-7.3 ± 1.8 vs 0.1 ± 1.9</td>
</tr>
<tr>
<td></td>
<td>(P=.003)</td>
<td>NS</td>
<td>(P=.030)</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>67.0 ± 3.5 vs 68.8 ± 3.8</td>
<td>59.0 ± 2.7 vs 58.4 ± 2.8</td>
<td>4.2 ± 0.8 vs -0.1 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>(P=.0002)</td>
<td>NS</td>
<td>(P=.0002)</td>
</tr>
<tr>
<td><strong>Nutrient Intake (cal)</strong></td>
<td>542.7 ± 42.3 vs 715.2 ± 72.3</td>
<td>668.4 ± 75.0 vs 658.9 ± 85.7</td>
<td>160.7 ± 55.0 vs -32.1 ± 38.1</td>
</tr>
<tr>
<td></td>
<td>(P=.036)</td>
<td>NS</td>
<td>(P=.023)</td>
</tr>
</tbody>
</table>
Results

Dyspeptic symptoms

- Placebo
- Mirtazapine

Symptom score

Week
Conclusions

• Mirtazapine significantly improves early satiation and quality of life in FD with weight loss

• The favorable effect of mirtazapine is associated with improved nutrient intake and superior recovery of weight loss
Effect of the H1-Receptor Antagonist Ebastin on Visceral Perception and Clinical Symptoms in IBS

LC- #5

Van Wanrooij S, Wouters MM, Van Oudenhove L et al.
Abstract 901
Background and Methods

• Background
  – Previous studies suggest that ketotifen (mast cell stabilizer/H1 antagonist) improves visceral hypersensitivity and IBS symptoms but doesn’t appear to have this effect by decreasing mast cell mediators and therefore may have a beneficial effect via H1 blockade

• Study design
  – 12-week, randomized, placebo-controlled study evaluating the effects of the H1-antagonist ebastin in IBS
  – 55 Rome III+ IBS patients stratified by normal or increased visceral sensitivity determined by barostat balloon distension
  – Measured visceral sensitivity before and after treatment
Background and Methods

• Primary end point
  – Reduction in visual analog score during +21 mm Hg distensions of ≥15 points

• Symptom measures served as secondary endpoints
  – IBS symptoms by subjective global assessment, Gastrointestinal Symptom Rating Scale (GSRS), and health-related quality of life (IBS-QOL) scored before, during, and after treatment
Results

- 55 IBS patients (62% women, mean age = 35 yrs)
- Visceral hypersensitivity was seen in 45%
- Symptom scores evoked by rectal distension were not significantly influenced by ebastin
Results

SGA Abdominal pain (100mm VAS)

- SGA = Subjects Global Assessment (100mm visual analog scale [VAS]). Linear mixed models: treatment and time as categorical and continuous independent variables, respectively. A time-by-treatment effect was added to the test difference in evolution over time (linear slopes) between both groups. Ebastin (linear slope effect = -1.35, p<0.0001), placebo (slope -0.29, p=0.4)
- Ebastin resulted in a significant reduction in abdominal pain (P=.03)

Figure 1A.

Treatment Period by Treatment Interaction Effect (P=.03)

w1-w12: weeks of treatment
w13 & w14: run-out post treatment

N=26 Placebo  N=21 Ebastin
Results

Figure 1B. Percentage of patients with at least considerable relief of global symptoms SGA = Subjects Global Assessment; *p<0.05 x2-test.

- Significantly more patients treated with ebastin vs. placebo had at least considerable relief of symptoms (46% vs 12%; P=0.001)
- No difference in other GI symptoms by the GSRS
- IBS-QOL scores showed improvement with ebastin vs. placebo
Conclusions

- Trial failed to show a significant effect on visceral perception assessed by rectal distension
- Ebastin resulted in a significant improvement in global symptom relief, abdominal pain, and quality of life compared to placebo
- These data suggest a poor relationship between barostat findings and clinical response
- Study suggests that H1-receptor blockade may represent an effective treatment for IBS
- Ebastin is not available in the US
Randomized, Placebo-Controlled Trial of Glutamine for the Treatment of Diarrhea-Predominant IBS

DD- #6

Basra S, Verne GN, Zhou Q.

Abstract 902
Background and Methods

• Background
  – IBS symptoms (abdominal pain, diarrhea, urgency) may be related to intestinal hyperpermeability
  – IBS-D patients have decreased intestinal glutamine synthase levels

• Study design
  – 8-week, randomized, double-blind, placebo-controlled study

• Patients
  – 61 patients with IBS-D
  – Patients completed a IBS Symptom Severity Scale (IBSS), lactulose/mannitol intestinal permeability test and intestinal biopsies for Claudin-1 expression before and after study

• Treatments
  – Glutamine 10 g orally three times daily
  – Placebo
Results

• Significant improvements ($P<.01$) were observed in:
  – Abdominal pain
  – Bloating
  – Diarrhea

• Intestinal permeability was restored in patients who received glutamine ($P<.05$)

• A positive correlation was observed between improvement in IBS symptoms and colonic Caludin-1 expression following glutamine therapy ($r=0.7$)
Conclusions

• Oral glutamine supplementation improves gastrointestinal symptoms and restores normal intestinal permeability in D-IBS patients

• Improvements in symptoms and intestinal permeability correlated with Claudin-1 expression

• Glutamine may be a useful therapeutic agent to treat D-IBS patients who have intestinal hyperpermeability
Efficacy of Ibodutant, a Selective Antagonist of Neurokinin 2 Receptors, in IBS-D: Results of a Double-Blind, Placebo-Controlled, Parallel-Group Phase II Study (IRIS-2)
LC- #7

Tack JF, Dochev YS, Bochenek A et al.
Abstract 520
Background and Methods

• Background
  – Ibodutant is a selective antagonist of neurokinin 2 (NK2) receptors in clinical development
  – In animal models, ibodutant did not alter sensorimotor function, but reverted intestinal hypermotility and hyperalgesia
The NK2 Receptor: Role in Gastrointestinal Function

• G-protein-linked receptors
  – Three distinct subtypes (neurokinin 1, 2, 3)

• Physiologic ligand: Tachykinins (excitatory neuropeptides)
  – Substance P
  – Neurokinin A
  – Neurokinin B

• Sources of tachykinins
  – Intrinsic neurons located in myenteric plexus, projecting to the muscle layers
  – Intrinsic neurons located in the submucous plexus, projecting to the mucosa and submucosal blood vessels
Methods

• Study design
  – Multinational, double-blind, dose-finding, placebo controlled study with 2-week treatment-free run-in and 8 week treatment period

• Patients
  – 559 patients with IBS-D (Rome III criteria)- 60% women
  – ≥25% loose/watery stool, ≥3 stools/day, at least moderate abdominal pain/discomfort on ≥3 days during run-in period

• Treatments
  – Placebo or ibodutant 1 mg, 3 mg, 10 mg once daily (1:1:1:1 ratio)

• Primary end point:
  – Combined response of satisfactory relief of overall IBS symptoms and abdominal pain/discomfort (yes/no) in ≥6 of 8 weeks
Baseline Characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>46 years</td>
</tr>
<tr>
<td>Mean abdominal pain intensity</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td>Mean number of bowel movements</td>
<td>4.5/day</td>
</tr>
<tr>
<td>Stool consistency*</td>
<td>5.7</td>
</tr>
</tbody>
</table>

*According to Bristol Stool Scale (Type 1 = separate hard lumps; Type 7 = entirely liquid)
Efficacy Results

- Trend toward increased response with escalating ibodutant dose
  - Best efficacy with highest (10 mg) dose

Responders by 75% Rule
(Overall Population)

*P*=0.032 vs placebo (not significant after Hochberg correction for multiple testing).
Efficacy Results

Responders by 75% Rule
(Males vs Females)

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>31.2</td>
<td>24.4</td>
</tr>
<tr>
<td>Ibodutant 1 mg</td>
<td>25.5</td>
<td>36</td>
</tr>
<tr>
<td>Ibodutant 3 mg</td>
<td>21.6</td>
<td>40.2</td>
</tr>
<tr>
<td>Ibodutant 10 mg</td>
<td>30</td>
<td>46.8</td>
</tr>
</tbody>
</table>

*P=.003 vs placebo.
Safety

- 94% of patients completed the study
- Incidence of adverse events <10%
- 5 serious adverse events occurred
Conclusions

• The NK2 receptor plays a demonstrated role in modulating symptoms of IBS

• In this well-designed study, ibodutant demonstrated a dose-dependent trend toward efficacy in the overall population
  – “75% rule” end point difficult to achieve

• This effect was driven by positive outcomes in women, with little if any effect in men
Plecanatide, a Novel Guanylate Cyclase C (GC-C) Receptor Antagonist, is Efficacious and Safe in Patients With Chronic Idiopathic Constipation: Results from a 951-Patient, 12-Week, Multicenter Trial

Miner PB, Surowitz R, Fogel R et al.

Abstract 925G
Background and Methods

• Background
  – Plecanatide is a GC-C receptor agonist; mimics effect of the natriuretic peptide uroguanylin

• Study design
  – 12-week, randomized, placebo controlled study

• Patients
  – 951 CIC patients (Rome III criteria)
  – <3 complete spontaneous bowel movements (CSBMs)/week at baseline

• Treatments
  – Plecanatide (0.3, 1, 3 mg) orally once daily
  – Placebo once daily

• Primary end point
  – Number of CSBMs/week
  – Weekly responder: >3CSBMs/wk + increase of 1 CSBM from baseline
# Efficacy Results

<table>
<thead>
<tr>
<th></th>
<th>PBO n=234</th>
<th>PLE 0.3 mg n=237</th>
<th>PLE 1 mg n=238</th>
<th>PLE 3 mg n=237</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders for ≥9 weeks (%)</td>
<td>11.5</td>
<td>19.0*</td>
<td>17.2</td>
<td>21.5*</td>
</tr>
<tr>
<td>Responders including last 3 of 4 weeks</td>
<td>10.7</td>
<td>18.6*</td>
<td>16.8</td>
<td>19.0**</td>
</tr>
<tr>
<td>Median time to first SBM (hours)</td>
<td>27.3</td>
<td>21*</td>
<td>21.3*</td>
<td>12.5*</td>
</tr>
<tr>
<td>Change in CSBM frequency from baseline</td>
<td>1.03</td>
<td>1.54*</td>
<td>1.76*</td>
<td>2.13*</td>
</tr>
<tr>
<td>Change in SBM frequency from baseline</td>
<td>1.30</td>
<td>2.08*</td>
<td>2.23*</td>
<td>2.88*</td>
</tr>
<tr>
<td>Change in stool consistency (BSFQ)</td>
<td>1.04</td>
<td>1.47</td>
<td>1.71*</td>
<td>2.01*</td>
</tr>
<tr>
<td>Change in straining score</td>
<td>-1.24</td>
<td>-1.38</td>
<td>-1.68*</td>
<td>-2.07*</td>
</tr>
</tbody>
</table>

*Significant difference vs placebo.

BSFQ=Bristol Stool Form Questionnaire
# Safety Results

<table>
<thead>
<tr>
<th></th>
<th>PBO n=234</th>
<th>PLE 0.3 mg n=237</th>
<th>PLE 1 mg n=238</th>
<th>PLE 3 mg n=237</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serious adverse events</strong></td>
<td>5 (2.1%)</td>
<td>1 (0.4%)</td>
<td>1 (0.4%)</td>
<td>2 (0.8%)</td>
</tr>
<tr>
<td><strong>Patients with TEAE(s)</strong></td>
<td>96 (40.7%)</td>
<td>99 (41.8%)</td>
<td>103 (43.3%)</td>
<td>106 (44.7%)</td>
</tr>
<tr>
<td><strong>Diarrhea with TEAE(s)</strong></td>
<td>3 (1.3%)</td>
<td>13 (5.5%)</td>
<td>20 (8.4%)</td>
<td>23 (9.7%)</td>
</tr>
<tr>
<td><strong>Patient withdrew due to TEAE</strong></td>
<td>8 (3.4%)</td>
<td>9 (3.8%)</td>
<td>16 (6.7%)</td>
<td>13 (5.5%)</td>
</tr>
<tr>
<td><strong>Patient withdrew due to diarrhea</strong></td>
<td>1 (0.4%)</td>
<td>2 (0.8%)</td>
<td>8 (3.4%)</td>
<td>7 (3.0%)</td>
</tr>
</tbody>
</table>

TEAE=Treatment-emergent adverse event
Conclusions

• The 3-mg dose of plecanatide appears effective, safe, and well-tolerated

• Dose-related efficacy was shown in this trial
Qualitative Assessment of Symptom Experience in Patients With IBS for the Development of Patient-Reported Outcome Instruments

LC- #9

Abstract Su2065
Background and Methods

• Background
  – There are currently no patient-reported outcome (PRO) measures that are accepted as well-defined and reliable by the FDA

• Aim
  – Conduct qualitative research with IBS patients to elicit their symptom experience in accordance with the FDA-mandated guidance for development of a PRO instrument

• Study design
  – Face-to-face interviews conducted in a representative sample of patients with physician-confirmed IBS

• Patients
  – Irritable bowel syndrome with diarrhea (IBS-D) (n=17)
  – Irritable bowel syndrome with constipation (IBS-C) (n=14)
  – Irritable bowel syndrome with mixed symptoms (IBS-M) (n=18)
### Results: Spontaneously Reported IBS Concepts by Subtype with ≥50% Reporting Frequency

<table>
<thead>
<tr>
<th>Concepts Spontaneously Reported: n(%)</th>
<th>IBS-D (n=17)</th>
<th>IBS-C (n=14)</th>
<th>IBS-M (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea: 17 (100%)</td>
<td></td>
<td>Constipation: 14 (100%)</td>
<td>Constipation: 18 (100%)</td>
</tr>
<tr>
<td>Loose or Watery Stools: 16 (94%)</td>
<td></td>
<td>Infrequent BMs: 14 (100%)</td>
<td>Abdominal Pain: 17 (94%)</td>
</tr>
<tr>
<td>Urgency: 15 (88%)</td>
<td></td>
<td>Bloating: 13 (93%)</td>
<td>Infrequent BMs: 17 (94%)</td>
</tr>
<tr>
<td>Abdominal Pain: 15 (88%)</td>
<td></td>
<td>Can’t go: 12 (86%)</td>
<td>Diarrhea: 16 (89%)</td>
</tr>
<tr>
<td>Cramping: 12 (71%)</td>
<td>Abdominal Pain: 11 (79%)</td>
<td>Recurrent BMs: 16 (89%)</td>
<td></td>
</tr>
<tr>
<td>Recurrent BMs: 12 (71%)</td>
<td>Small Stools: 11 (79%)</td>
<td>Loose or Watery Stools: 15 (83%)</td>
<td></td>
</tr>
<tr>
<td>Too Frequent BMs: 12 (71%)</td>
<td>Straining: 10 (71%)</td>
<td>Too Frequent BMs: 14 (78%)</td>
<td></td>
</tr>
<tr>
<td>Gas: 10 (59%)</td>
<td>Gas: 9 (64%)</td>
<td>Cramping: 13 (72%)</td>
<td></td>
</tr>
<tr>
<td>Abdominal Discomfort: 9 (53%)</td>
<td>Abdominal Discomfort: 9 (64%)</td>
<td>Urgency: 13 (72%)</td>
<td></td>
</tr>
<tr>
<td>Feeling of Fullness: 8 (57%)</td>
<td></td>
<td>Can’t go: 12 (67%)</td>
<td></td>
</tr>
<tr>
<td>Hard Stools: 8 (57%)</td>
<td></td>
<td>Long Time in Bathroom: 12 (67%)</td>
<td></td>
</tr>
<tr>
<td>BM = Bowel Movement</td>
<td></td>
<td>Unsuccessful Attempts: 12 (67%)</td>
<td></td>
</tr>
</tbody>
</table>

- BM = Bowel Movement
## Results: Summary of Single Most Bothersome IBS Symptom

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Number of Patients Reporting Symptom as the Most Bothersome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IBS-D (n=17)</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>4</td>
</tr>
<tr>
<td>Urgency</td>
<td>6</td>
</tr>
<tr>
<td>Cramping</td>
<td>1</td>
</tr>
<tr>
<td>Bloating</td>
<td>0</td>
</tr>
<tr>
<td>Infrequent BMs</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>1</td>
</tr>
<tr>
<td>Gas</td>
<td>0</td>
</tr>
<tr>
<td>Too frequent BMs</td>
<td>1</td>
</tr>
<tr>
<td>Accidents</td>
<td>1</td>
</tr>
<tr>
<td>Loose or watery stools</td>
<td>1</td>
</tr>
<tr>
<td>Hard Stools</td>
<td>0</td>
</tr>
<tr>
<td>Recurrent BMs</td>
<td>1</td>
</tr>
<tr>
<td>Vomitting</td>
<td>0</td>
</tr>
<tr>
<td>Contractions</td>
<td>1</td>
</tr>
</tbody>
</table>

BM = Bowel Movement

<sup>a</sup>One IBS-C participant did not report a most bothersome symptom.

<sup>b</sup>Two IBS-M participants reported two most bothersome symptoms.
Conclusions

• IBS patients report a range of gastrointestinal symptoms that includes but is not limited to abdominal pain and abnormal stool consistency and frequency

• This is not a test of a proposed PRO instrument
  – Preliminary step in identifying symptom domains that will determine which items are developed for the PRO

• None of the findings are surprising
  – Pain, urgency, cramping, and bloating are likely to be heavily weighted in the eventual PRO instrument

• Sample size is relatively small given the implications for clinical trials
Efficacy and Safety of Naloxegol in Patients With Opioid-Induced Constipation: Results from 2 Prospective, Randomized, Controlled Trials

DD- #10

Chey WD, Webster L, Sostek M et al. Abstract 900
Study Design (KODIAC-04 and KODIAC-05)

- Outpatients with OIC aged ≥18 to <85 years receiving oral morphine equivalent: 30–1000 mg/day for ≥4 weeks before screening for noncancer pain

*Diagnosis of OIC and opioid dose stability confirmed by eDiary (provided at screening).
†Bisacodyl (10–15 mg; maximum of 3 doses/episode) and one-time use enema permitted as rescue.
‡Patients could either complete the follow-up visit or enroll in a safety extension study.
EOT=end of treatment; OIC=opioid-induced constipation.
Primary Endpoint: Responder Rates (Weeks 1–12) ITT Population

**Placebo** | **Naloxegol 12.5 mg/day** | **Naloxegol 25 mg/day**
---|---|---
KODIAC-04 | 29.4 | 40.8 | 44.4
KODIAC-05 | 29.3 | 34.9 | 39.7

*Significant vs placebo under the multiple testing procedure.
†Calculated as (% responders naloxegol – % responders placebo).

Primary efficacy endpoint: ≥3 SBM/week with ≥1 SBM/week increase over baseline for ≥9 of the 12 weeks and ≥3 of the last 4 weeks of treatment.

$P$ vs placebo: 0.015, 0.001, 0.202, 0.021
No. needed to treat: 8.8, 6.7, NS, 9.7
## Safety

<table>
<thead>
<tr>
<th></th>
<th>KODIAC-04</th>
<th>KODIAC-05</th>
<th>KODIAC-05</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo</strong></td>
<td>46.9%</td>
<td>58.9%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Naloxegol 12.5 mg/day</strong></td>
<td>49.3%</td>
<td>59.6%</td>
<td>0.9%</td>
</tr>
<tr>
<td><strong>Naloxegol 25 mg/day</strong></td>
<td>61.2%</td>
<td>10.3%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Discontinuation due to an AE</strong></td>
<td>5.6%</td>
<td>5.2%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Deaths</strong></td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Serious AE</strong></td>
<td>5.2%</td>
<td>5.2%</td>
<td>6.1%</td>
</tr>
</tbody>
</table>

*Most frequent adverse events were gastrointestinal-related*
Conclusions

• In patients with OIC, naloxegol treatment increased the frequency of SBMs and resulted in significantly more OIC responders vs placebo
  – This effect was maintained over the 12-week treatment period

• There was no reversal or reduction of opioid-mediated analgesia as reflected by daily pain scores and opioid dose

• Naloxegol was generally well tolerated and safe with the most commonly reported AEs were GI-related and were found more in the higher dose of naloxegol

• Naloxegol is in late-phase clinical development
Dyssynergic Defecation Can Be Diagnosed by Questionnaire and Physical Examination
LC- #11

Chiarioni G, Kim SM, Whitehead WE et al.
Abstract Sa2038
Background and Methods

• Background
  – Dyssynergic defecation (DD) has a distinct pathologic mechanism vs other subtypes of constipation
  – Diagnosis currently depends on costly, invasive tests, not widely available

• Aim
  – Develop a questionnaire-based methodology for diagnosing dyssynergic defecation

• Patients
  – 238 patients with refractory constipation

• Assessments
  – Questionnaire and physical exam (PE)
  – Anorectal manometry (ARM)
  – Balloon evacuation test (BET)
  – Defecography
Methods

- Mechanical obstruction (MO) if rectal prolapse on physical exam or abnormal defecography + BET >2 min
- DD if paradoxical contraction or failure to relax pelvic floor muscles on ARM + BET >2 min
- Slow transit constipation (STC) if >5/24 sitzmarkers remained 5 days after ingestion + BET >2 min
- Normal transit constipation is absence of MO, DD and STC
- Predictive variables were symptoms and physical exam findings
Results

- 238 patients divided into 2 groups of 119- test sample and validation sample
- Avg age= 45 yrs, 92% women
- DD=102, STC= 31, MP=37, NTC=63, 5 not classifiable
- Best predictor of DD was question on which muscles used to defecate- response of anus identified 91% of DD
- PE finding of anal sphincter relaxing on straining correctly identified 97.8% of patients without DD

<table>
<thead>
<tr>
<th>Questionnaire:</th>
<th>Learning Sample</th>
<th>Validation Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
</tr>
<tr>
<td>Incomplete Evacuation</td>
<td>100</td>
<td>2.8</td>
</tr>
<tr>
<td>Anal Blockage</td>
<td>55.6</td>
<td>58.3</td>
</tr>
<tr>
<td>Digital Maneuvers</td>
<td>37.8</td>
<td>61.1</td>
</tr>
<tr>
<td>Squeeze anus to defecate</td>
<td>91.1</td>
<td>88.7</td>
</tr>
<tr>
<td>Physical Examination:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abd wall contracts to defecate</td>
<td>73.3</td>
<td>5.6</td>
</tr>
<tr>
<td>Anal sphincter relaxes to defecate</td>
<td>76.4</td>
<td>97.8</td>
</tr>
</tbody>
</table>
Conclusions

- Asking patients which muscles they use to defecate has an overall accuracy of 87% for distinguishing patients with dyssynergic defecation from those with other types of constipation.

- This question could be used in epidemiological studies to estimate the prevalence of dyssynergic defecation, in primary care to guide treatment, and in pharmaceutical trials to select patients for inclusion.
Epidemiology of Fecal Incontinence in US Adults From 2005 to 2010: Prevalence, Trends, and Risk Factors

LC- #12

Ditah IC, Devaki P, Jaiyeoba CO et al.
Abstract Sa2028
Background and Methods

• Background
  – Fecal incontinence (FI) is a common condition that can lead to poor self-image, social isolation and poor QOL
  – The prevalence of fecal incontinence may be increasing especially with our aging population

• Aim
  – To estimate the prevalence, analyze trends and identify risk factors for FI among non-industrialized US adults from 2005-2010

• Study design
  – Data from NHANES (National Health and Nutrition Examination Survey) used to estimate prevalence FI

• Participants
  – 14,759 participants in NHANES
Overall Prevalence of Fecal Incontinence

- 2005/2006: 8.26
- 2007/2008: 8.48
- 2009/2010: 8.41
Additional Results

- Fecal incontinence occurred weekly in 1.13% of study participants.
- Fecal incontinence was statistically significantly more common in women (9.45%) than men (7.27%).
- Fecal incontinence increased statistically significantly with age:
  - 2.91% in subjects aged 20 to 29 years
  - 16.16% among those aged ≥70 years
- Independent risk factors for FI: >55 years, diabetes, female gender, poor health status, urge incontinence, non-Hispanic whites, >21 stools/week and loose/watery stools.
# Risk Factors for Fecal Incontinence

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Univariate analysis</th>
<th>P value</th>
<th>Multivariate analysis</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age Groups (yrs)</strong></td>
<td></td>
<td></td>
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<tr>
<td>20-29</td>
<td>Baseline</td>
<td></td>
<td></td>
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<tr>
<td>30-39</td>
<td>1.70 (1.21, 2.40)</td>
<td>0.003</td>
<td>0.93 (0.50, 1.75)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>40-54</td>
<td>3.12 (2.24, 4.34)</td>
<td>&lt;0.001</td>
<td>1.50 (0.84, 2.69)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>55-69</td>
<td>4.56 (3.49, 5.95)</td>
<td>&lt;0.001</td>
<td>1.99 (1.12, 3.54)</td>
<td>0.02</td>
</tr>
<tr>
<td>&gt;70</td>
<td>6.44 (4.73, 8.76)</td>
<td>&lt;0.001</td>
<td>2.18 (1.10, 4.36)</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Body Mass Index</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt;25</td>
<td>Baseline</td>
<td></td>
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<tr>
<td>25-29.9</td>
<td>0.95 (0.79, 1.14)</td>
<td>&gt;0.05</td>
<td>0.91 (0.65, 1.25)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>&gt;30</td>
<td>1.30 (1.08, 1.56)</td>
<td>0.006</td>
<td>1.03 (0.76, 1.41)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td><strong>Self rated health</strong></td>
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<tr>
<td>Good</td>
<td>Baseline</td>
<td></td>
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</tr>
<tr>
<td>Poor</td>
<td>2.14 (1.79, 2.55)</td>
<td>&lt;0.001</td>
<td>1.43 (1.14, 1.81)</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>Baseline</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Female</td>
<td>1.28 (1.11, 1.47)</td>
<td>0.001</td>
<td>0.67 (0.51, 0.89)</td>
<td>0.008</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
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<tr>
<td>Hispanic</td>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non Hispanic White</td>
<td>1.15 (0.98, 1.35)</td>
<td>&gt;0.05</td>
<td>1.62 (1.16, 2.26)</td>
<td>0.005</td>
</tr>
<tr>
<td>Non Hispanic Black</td>
<td>1.12 (0.89, 1.41)</td>
<td>&gt;0.05</td>
<td>1.12 (0.73, 1.74)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td><strong>Urinary Incontinence</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.65 (1.27, 2.14)</td>
<td>&lt;0.001</td>
<td>1.65 (1.23, 2.22)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.20 (1.06, 1.35)</td>
<td>0.005</td>
<td>1.59 (1.17, 2.17)</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>Frequency of Bowel Movement/week</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 3</td>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-20</td>
<td>0.67 (0.50, 0.90)</td>
<td>0.009</td>
<td>0.94 (0.59, 1.51)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>&gt;21</td>
<td>1.85 (1.32, 2.59)</td>
<td>0.001</td>
<td>2.46 (1.42, 4.28)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Stool consistency</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Usual</td>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hard/lumpy</td>
<td>1.11 (0.82, 1.50)</td>
<td>&gt;0.05</td>
<td>0.86 (0.51, 1.44)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Loose/watery</td>
<td>3.52 (2.84, 4.36)</td>
<td>&lt;0.001</td>
<td>2.49 (1.76, 3.53)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Conclusions

• Fecal incontinence is a prevalent problem among non-institutionalized US adults, and rose steadily from 2005 to 2010
• Age is a strong risk factor
• Diabetes and chronic diarrhea are potential modifiable risk factors
• This is not the largest population-based study of fecal incontinence, but it is the most representative of the overall population
• Limitation: Study pooled males and females in multivariate analyses despite substantial differences in risk factors between genders