# XPERT PERSPECTIVES ...from DDW

## Reporting on IBS


***Anthony Lembo, MD***
*Beth Israel Deaconess Medical Center*
*Boston, MA*

***Mark Pimentel, MD***
*Cedars-Sinai Medical Center*
*Los Angeles, CA*

***Nicholas Talley, MD***
*University of Newcastle*
*Callaghan, NSW Australia*



Accredited by
PURDUE UNIVERSITY

GastroIntestinal Health Foundation

XPERT PERSPECTIVES
...from DDW

Reporting on IBS

***Special thanks to our supporter for providing an educational grant:***

Salix®
PHARMACEUTICALS, INC.

Accredited by
PURDUE UNIVERSITY

GastroIntestinal Health Foundation

XPERT PERSPECTIVES ...from DDW

Reporting on IBS

# Pathophysiology and Epidemiology

Accredited by
PURDUE UNIVERSITY

GastroIntestinal Health Foundation

XPERT PERSPECTIVES
...from DDW

Reporting on IBS

# Functional Gastrointestinal Disorders (FGIDs) and Psychological Disorders: Strong Evidence That the Link Is Bidirectional, but Psychological Distress Is More Likely to Precede a New Diagnosis of an FGID

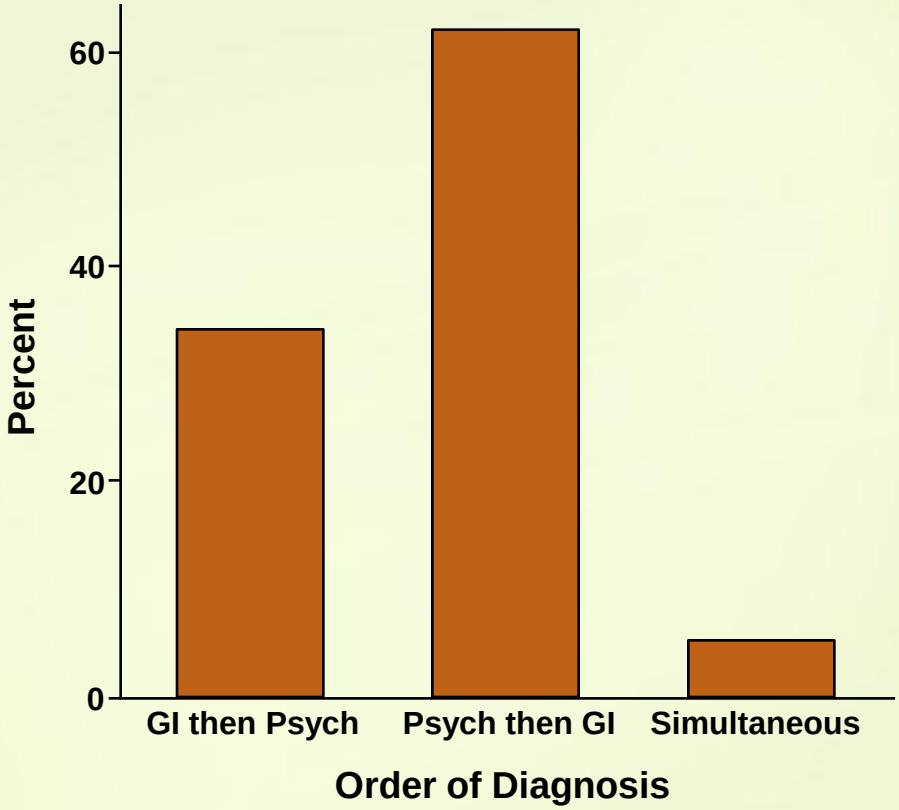
*Jones MP et al. Abstract Mo1007*

# Design

- Background
  - FGIDs, particularly IBS are heterogeneous conditions but all are strongly associated with mood and psychological disorders
  - The causal direction of this association remains undetermined although the biopsychosocial model suggests bidirectionality
- Objective
  - Describe the order of incidence of these conditions in a community setting and examine associations with patient factors
- Methods
  - Electronic medical records were examined for 3 FGIDs; IBS, dyspepsia and chronic constipation and common psychological disorders

# Results

- Psychological conditions preceded GI conditions in 61%
- GI conditions were observed first in 34%
- GI and psychological conditions were recorded simultaneously in 5%
- Females (59%) were more likely to have a psychological condition recorded before GI compared with males (55%, *P*=.01)



# Conclusions

- In individuals with comorbid FGID and psychological conditions, the psychological morbidity is almost twice as likely to precede the FGID as the other way around

- While this observation does not in itself prove causation it is supportive of the bidirectional hypothesis suggested by the biopsychosocial model

XPERT PERSPECTIVES ...from DDW

Reporting on IBS

# Disturbed Sleep Worsens IBS Pain Symptoms: an Effect of Gastrointestinal (GI) Specific Anxiety?

*Patel A et al. Abstract 35*

Accredited by
PURDUE UNIVERSITY

GastroIntestinal Health Foundation

# Design

- Objective
  - Determine the effect of sleep disturbances on IBS symptoms and IBS-specific quality of life (IBS-QOL)
  - Examine the role of GI-specific anxiety as a mediator of the relationship of sleep disturbance and IBS symptoms
- Patients
  - Healthy controls (n=23)
  - IBS (n=20)
- Design
  - Sleep patterns of IBS subjects were compared to healthy controls via wrist-mounted actigraphy data over 7 days
  - All subjects completed a validated IBS symptom measure (GI Symptom Rating Scale-IBS, GSRS-IBS), the Visceral Sensitivity Index (VSI) as a measure of GI-specific anxiety, and the IBS-QOL disease specific quality-of-life instrument

# Results

- IBS subjects slept longer than controls ($P<.001$)
- IBS subjects demonstrated more waking episodes during sleep (WEDS, 11.7 vs 8.9; $P=.001$), and shorter mean undisturbed sleep periods (63.5 vs. 99.7 min, $P<.001$).
- In IBS, shorter mean undisturbed sleep episodes and WEDS number correlated with abdominal pain ($P=.04$ and $P=.02$, respectively) and GI distress ($P=.003$ and $P=.001$) the following day
- In the control population, sleep parameters were not significantly associated with any bowel measures in controls
- Among IBS patients, WEDS number significantly correlated with both IBS-QOL scores and VSI scores
- Only the VSI score ($P<.001$) was a significant predictor of IBS pain scores

# Conclusions

- IBS subjects suffer more sleep disturbances despite spending greater amounts of time dedicated to sleep
- Sleep disturbances correlate with greater IBS-related pain, distress, and GI-specific anxiety, as well as poorer IBS-related QOL
- GI-specific anxiety, as determined by VSI, may mediate these observed relationships between sleep disturbances and IBS symptoms

XPERT PERSPECTIVES ...from DDW

Reporting on IBS

# Effect of Gender on Prevalence and Subtype of Irritable Bowel Syndrome: a Systematic Review and Meta-Analysis

*Lovell RM, Ford AC. Abstract Su1016*

# Design

- Objective
  - Estimate true prevalence of IBS by gender
- Methods
  - Literature review of studies reporting prevalence of IBS
  - Data extracted and pooled with a random effects model to estimate prevalence of IBS according to gender

# Results

## Prevalence of IBS in Men vs Women by Rome Criteria

| IBS Criteria used | Number of studies | Number of subjects | Pooled prevalence in women (95% CI) | Pooled prevalence in men (95% CI) | Odds ratio for women compared to men (95% CI) |
|---|---|---|---|---|---|
| Manning | 15 | 33304 | 17 (12-22) | 12 (9-16) | 1.55 (1.35-1.78) |
| Rome I | 19 | 48336 | 12 (9-16) | 7 (5-8) | 1.99 (1.76-2.25) |
| Rome II | 26 | 67534 | 10 (8-13) | 8 (6-10) | 1.40 (1.24-1.59) |
| Rome III | 4 | 21869 | 12 (2-26) | 7 (1-18) | 1.81 (1.36-2.39) |

- Prevalence of IBS-C was significantly higher in women with IBS vs men IBS (OR 2.38; 95% CI 1.45-3.92)
- Prevalence of IBS-D was lower in women with IBS vs men with IBS (OR 0.45; 95% CI 0.32-0.65)
- Prevalence of IBS-M was not significantly different by gender (OR 1.07; 95% CI 0.84-1.38)

# Conclusions

- Prevalence of IBS was modestly increased in women, and this observation remained stable according to the various diagnostic criteria used
- Among individuals with IBS, women were more likely to have IBS-C than men, and less likely to have IBS-D
- Suggests that gender may influence IBS subtype


# Diagnosis and Treatment

XPERT PERSPECTIVES
...from DDW

Reporting on IBS

# Patient Response to Lubiprostone for the Treatment of Moderate to Severe Irritable Bowel Syndrome With Constipation (IBS-C)

*Joswick TR et al. Abstract Su1198*

# Design

- Objective
  - Investigate improvements among the subset of patients receiving lubiprostone who reported more severe IBS-C symptoms at baseline
- Design
  - Used pooled data from 2 pivotal, 12-week trials of lubiprostone in patients with IBS-C
- Patients
  - Patients reporting a weekly baseline of moderate or greater abdominal pain and <3 spontaneous bowel movements (SBMs) were assessed for composite response rate
- Outcome measures
  - Response: ≥30% improvement from baseline in mean abdominal pain scores, ≥1 SBM per week improvement over baseline, and ≥3 SBMs for 9 of 12 weeks

# Results

- Lubiprostone 8 mcg BID was associated with higher proportions of responders for 6 of 12 weeks (*P*=.0031) and 9 of 12 weeks (*P*=.0109)
- Patients with severe abdominal pain at baseline reported greater improvements with lubiprostone treatment vs placebo (*P*=.0002)
- Among patients with severe or very severe abdominal pain at baseline, 35.1% reported improvements of ≥30% with lubiprostone 8 mcg BID compared with pretreatment abdominal pain ratings
- Across the range of abdominal pain improvements (≥10% to ≥60% change from baseline), the percentage of patients reporting improvement in abdominal pain at each level was significantly higher with lubiprostone (*P*<.0001)

# Conclusions

- Patients reporting more severe symptoms of IBS-C at baseline showed improvement when treated with lubiprostone 8 mcg BID vs placebo

- Lubiprostone 8 mcg BID is a viable treatment option for IBS-C patients; in particular, those with moderate to very severe abdominal pain

XPERT PERSPECTIVES
...from DDW

Reporting on IBS

# Effects of 26 Weeks of Linaclotide Treatment on Adequate Relief and IBS Severity in Patients With IBS-C

*Chey WD et al. Abstract Tu1381*

# Design

- Background
  - Few long-term studies have evaluated treatments for IBS
- Objective
  - To determine the effects of 26 weeks of linaclotide on adequate relief and IBS severity
  - Examine relationship between long-term improvement in adequate relief with improvements in abdominal pain and complete spontaneous bowel movement (CSBM) frequency
- Methods
  - Data used from 2 double-blind, placebo-controlled trials of linaclotide 290 mcg once daily or placebo for 26 weeks

# Results

**Approximately half of linaclotide patients (49.1%) were Adequate Relief Responders, compared with 25.1% of placebo patients**

| | Placebo (n=403) | Linaclotide (n=401) |
|---|---|---|
| Responder[1] n (%) | 101 (25.1) | 197 (49.1) |
| Difference in Responder Rate (Linaclotide – Placebo) | 24.1 | |
| p-value[2] | <0.0001 | |
| Number Needed to Treat (NNT) | 4.2 | |

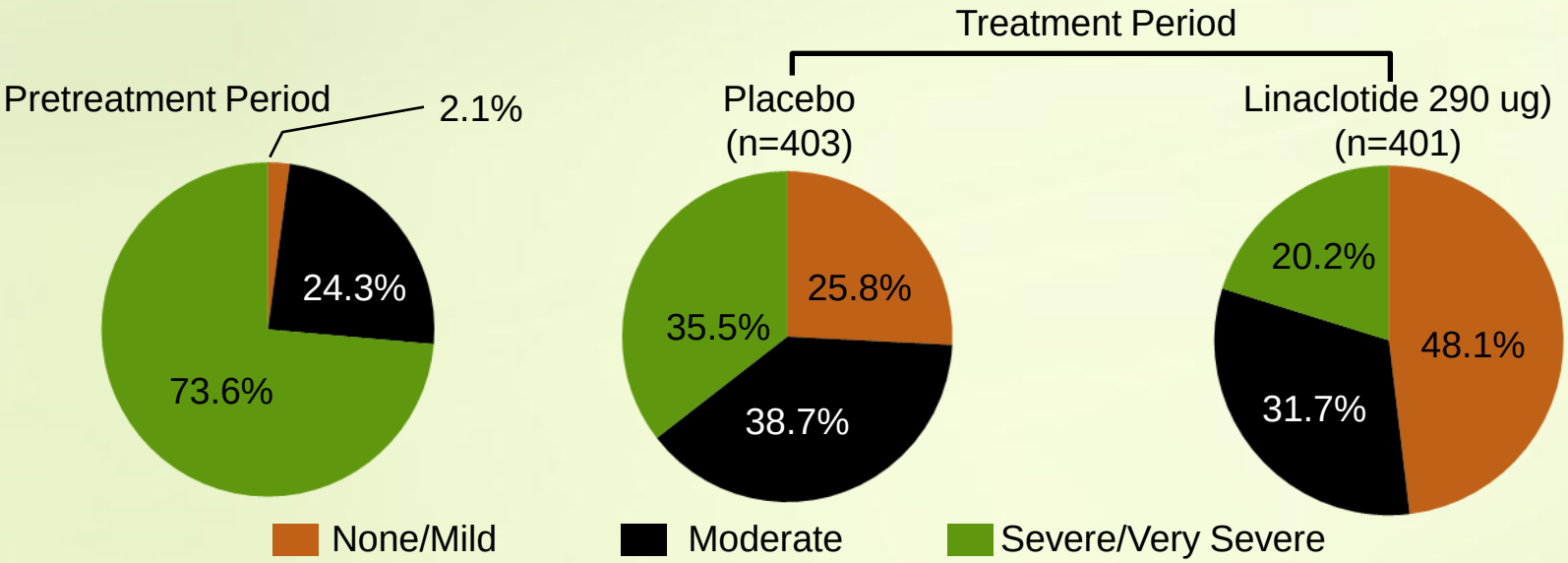
[1]Adequate relief responder=reported adequate relief of IBS symptoms for at least 13 of 26 weeks of the treatment period

[2]*P* values derived using CMH test controlling for geographic regions

# Results

**48% of linaclotide patients rated their IBS severity as “none/mild,” compared to 26% of placebo patients**

**Figure: Percent of Patients by IBS Severity (Week 26, LOCF)**




LOCF = Last Observation Carried Forward

# Results

- Adequate Relief responders had a 26-week mean decrease in abdominal pain of 52% vs 18% for non-responders (*P*<.0001)
- Adequate Relief responders had an increase from baseline in mean CSBM frequency of 3.0 per week vs 0.8 for non-Responders (*P*<.0001)
- Improvements in abdominal pain and CSBM frequency were well correlated with Adequate Relief

# Conclusions

- IBS-C patients receiving linaclotide were significantly more likely than those receiving placebo to report Adequate Relief of IBS symptoms and improvement of IBS Severity during 26 weeks of treatment

- Gains in the percentage of patients reporting Adequate Relief strongly correlated to improvements in abdominal pain (52% improvement) and CSBM frequency (3.0 per week)

XPERT PERSPECTIVES
...from DDW

Reporting on IBS

# Systematic Review of Diagnostic Criteria for IBS Demonstrates Poor Validity and Utilization of ROME III

*Dang J et al. Abstract Mo1053*

# Design

- Background
  - Rome Criteria are commonly used to diagnose IBS
  - They have not been properly validated and have poor discriminatory ability
- Objective
  - Examine the validation and utilization of IBS criteria
- Design
  - Two-stage systematic review
  - Stage 1 identified articles on IBS, diagnosis, and diagnostic criteria from 1978 to present
  - Stage 2 identified articles from 1992 and 2011 and divided them into 3 segments: Rome I era (1992-1999), Rome 2 era (1999-2006), Rome 3 era (2007-2011)

# Results

- The first stage of identified only 19 published studies validating diagnostic tests for IBS
- These studies showed a considerable range in sensitivity and specificity
  - Manning (42%-94%, and 55%-93%, respectively)
  - Kruis (47%-81%, and 91%-99% respectively)
  - Rome I (62%-85%, and 70%-100% respectively)
  - Rome II (64%-89%, and 66%-73% respectively)
- Although overlap was seen, differing populations are identified with each
- Rome II, but not Rome III was quickly adopted
  - After excluding RCT studies since these can be long duration and from overlapping eras, the rate of utilization of Rome III was low and used in only 26.6% of all published studies from 2007-2011

# Conclusions

- Since Rome I, there have been several changes to the Rome criteria defining IBS
- There is minimal validation of the Rome criteria
- Are drugs approved using Rome II criteria relevant if IBS is now defined as Rome III?

XPERT PERSPECTIVES ...from DDW

Reporting on IBS

# Impact of Concurrent Use of PPIs or Anti-Depressants on Efficacy of Rifaximin for IBS Without Constipation

*Lembo A et al. Tu1406*

# Design

- Background
  - It is unclear if concurrent use of antidepressants or PPIs with rifaximin would diminish or improve response to rifaximin
- Objective
  - To evaluate the concurrent PPI or antidepressants on rifaximin efficacy
- Methods
  - Data derived from two Phase III double-blind placebo-controlled trials (TARGET 1 and TARGET 2) in patients with non-C IBS
  - Patients received rifaximin 550 mg three times daily or placebo for 14 days
  - Improvement in global IBS symptoms and bloating correlated with antidepressant and PPI use

# Results

## Percentage of Responders

| No PPIs | | | | PPIs | | |
|---|---|---|---|---|---|---|
| **Symptoms** | **Rifaximin** | **Placebo** | **TRT Diff** | **Rifaximin** | **Placebo** | **TRT Diff** |
| Daily Global IBS | 40.2%* (194/482) | 29.7% (145/488) | 10.5% | 40.1% (57/142) | 28.8% (42/146) | 11.3% |
| Daily Bloating | 41.5%* (200/482) | 32.6% (159/488) | 8.9% | 40.8%* (58/142) | 28.8% (42/146) | 12% |
| **No Antidepressants** | | | | **Antidepressants** | | |
| | **Rifaximin** | **Placebo** | **TRT Diff** | **Rifaximin** | **Placebo** | **TRT Diff** |
| Daily Global IBS | 42.6%* (205/481) | 32.3% (153/474) | 10.3% | 32.2% (46/143) | 21.3% (34/160) | 10.9% |
| Daily Bloating | | 33.8% (160/474) | 9.7% | 34.3% (49/143) | 25.6% (41/160) | 8.7% |

# Conclusions

- Among patients with non-C IBS, concurrent use of PPIs or antidepressants does not appear to enhance or minimize response to rifaximin
- The observed non-significant trends in PPI users and antidepressant users may reflect small sample sizes
- Further research should examine why antidepressant users have lower responder rates overall while the magnitude of benefit of rifaximin over placebo is still similar in these patients

XPERT PERSPECTIVES
...from DDW

Reporting on IBS

# Evaluation of Treatment-Associated Harm for Irritable Bowel Syndrome With Constipation

*Shah ED et al. Abstract Mo1042*

# Design

- Background
  - Since IBS is common, harm is an important consideration when selecting therapy
- Objective
  - Examine the harms associated with IBS-C therapy
- Methods
  - Systematic review and meta-analysis of adverse events and related dropouts in controlled trials for C-IBS

# Results

- Eight clinical trials were included
  - 4 studies of SSRIs
  - 3 of lubiprostone
  - 2 of linaclotide
- Lubiprostone was not harmful relative to placebo and an NNH could not be calculated; NNT was 12.8
- The number of subjects that would benefit from linaclotide before 1 harm event would be 2.6
- Existing data from small trials suggested that SSRIs are less harmful than placebo and therefore the data were not interpretable

# Conclusions

- Lubiprostone appears to be safe in treating IBS-C with minimal harm leading to withdrawal
  - While nausea was a reported side effect, it did not lead to excessive withdrawal from study
- One patient withdrew from study due to side effects for every 2.6 with successful treatment on linaclotide
- The safety of SSRIs in treating IBS-C is not clear
  - Large-scale trials are required to assess the occurrence and severity of known side effects of these drugs

XPERT PERSPECTIVES
...from DDW
Reporting on IBS

# Functional Net Value (FNV): an Important Consideration in Clinical Evaluation of IBS Pharmacotherapy

*Shah D, Pimentel M. Abstract 1039*

# Design

- Background
  - Since IBS is a fluctuating condition, a better endpoint would be one that measures proximity to normal function
- Objective
  - Conduct a systematic review of the efficacy and GI specific harm of IBS to determine the functional net value (FNV) of each drug
- Methods
  - Systemic literature
  - Primary outcomes of interest: Summary efficacy of drug and prevailing GI side effect
  - Based on pooled efficacy and detriment, a functional net value was reported as the difference between the 2 numbers

# Results

- For C-IBS, selective serotonin inhibitors (SSRI) were not reported as there was inadequate data to evaluate FNV
- Diarrhea was as prominent side effect exceeding that seen with placebo for lubiprostone (3 trials), linaclotide (2 trials) and tegaserod (7 trials)
- In D-IBS, drug efficacy was similar but constipation was a significant complication of therapy with TCA and alosetron resulting in negative net value of these two products
- Rifaximin normalized bowel function without opposite functional effects (FNV=Benefit)

# Results

## Functional Net Values of Selected Drugs for IBS

| | Drug | Benefit (%) | Diarrhea side effect (%) | Constipation side effect (%) | FNV (%) |
|---|---|---|---|---|---|
| C-IBS | Tegaserod | 10.0 | 4.7 | - | +5.3 |
| | Lubiprostone | 7.8 | 2.0 | - | +5.8 |
| | Linaclotide | 19.8 | 15.1 | - | +4.7 |
| | SSRI | The quality of studies precluded meaningful analysis | | | |
| D-IBS | Tricyclics | 12.5 | - | 16.4 | -3.9 |
| | Alosetron | 13.3 | - | 16.8 | -3.5 |
| | Rifaximin | 10.6 | - | 0 | +10.6 |

# Conclusions

- In evaluating the benefits of IBS drugs it is important to recognize that using improvement in D- or C-IBS as an endpoint should also incorporate a means of evaluating a negative functional bowel outcome
- It is not sufficient to say that D-IBS is improved if the therapy simply produces C-IBS
- An outcome measure such as FNV may be a better way to evaluate the effect of a drug on normalizing bowel function