Opioid Bowel Dysfunction: Diagnosis & Treatment

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Disclosures

• No speaker’s bureaus
• Investigator initiated funding for analysis of IBS variations in healthcare (Takeda)
• Scientific advisory boards: Actavis, Ironwood, Prometheus, Salix, Takeda
Opioids: An Historical Perspective

• Opium - from the poppy *Papaver somniferum*
• 3000 BC – Medicinal/recreational use
• 1804 - Dr. Friedrich Serturner isolated the active ingredient of opium (morphine)
  • Named after Morpheus, the Greek god of sleep

Opioids: An Historical Perspective

• Widely Prescribed in the 1800’s and early 1900’s
• Civil War – “Soldier’s Disease”
• Opium Dens
**Historical Perspective**

- Banned from non-medical products in 1924
- Heroin labeled as a schedule 1 – 1970
- 259 million US Rx (2012 data)
- 3% of US population on long-term opioids
- 46 OD deaths/day

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**Opioids: The Good and the Bad**

- Non-gastrointestinal
- Gastrointestinal
  - Dry mouth
  - Dysphagia
  - Reflux
  - Dyspepsia
  - Nausea and vomiting
  - Constipation
Physiology of Opioids & Opioid Receptors

- Opioid receptors in the gut
  - Transmembrane; G-protein coupled
    - Mu (μ)
    - Kappa (K)
    - Delta (δ)
- Opioid peptides in the gut
  - Met-enkephalin
  - Leu-enkephalin
  - Beta-endorphin
  - Dynorphin

Physiology of Opioid Receptor Activation in the GI Tract

- Inhibit enteric nerve cell activity
  - Suppress enteric nerve excitability
  - Inhibit secretomotor activity
  - Inhibit motor neurotransmission
- Inhibit propulsive activity
  - Inhibition of peristalsis
  - Increase in non-propulsive contractions
  - Disturbs MMC
  - Elevation of muscle tone
  - Overall delay in GI transit
Key Definitions

• Narcotic Bowel Syndrome (NBS)
  – A progressive and paradoxical increase in the severity of chronic abdominal pain despite the use of continuous or increasing doses of opioids prescribed to relieve abdominal pain
  – A central process

• Opioid Bowel Dysfunction (OBD)
  – A spectrum of disorders that develop as a direct result of opioids on a specific segment of the gastrointestinal tract
  – A peripheral process

Etiology of NBS

• **Bimodal opioid dysregulation.** Preferential activation of excitatory pathways, mediated by G\textsubscript{s} receptor activation at the dorsal root ganglion, leads to opiate tolerance and pain augmentation.

• **Up-regulation of dynorphin.** Chronic opiate use up-regulates dynorphin release, sensitizing excitatory pathways, inducing hyperalgesia.

• **Glial cell activation.** Spinal dorsal horn glia release pro-inflammatory cytokines (chemokines) further accelerating hyperalgesia.
Gs receptor activation at the dorsal root ganglion leads to tolerance and pain augmentation

Drossman & Szigethy, Am J Gastroenterol 2014: Suppl 2

Activation of spinal cord glial cells leads to hyperalgesia

Drossman & Szigethy, Am J Gastroenterol 2014: Suppl 2
Development of NBS: Clinical Perspective

Diagnostic Criteria for NBS

- Abdominal pain worsens or incompletely resolves with continued or escalating doses of narcotics;
- A marked worsening of pain when the narcotic dose wanes and improvement when narcotics are reinstituted;
- There is a progression of the frequency, duration and intensity of pain episodes;
- The nature of the pain is not explained by a current or previous GI diagnosis.
NBS: Treatment

- Hospital admission required
- Team approach is vital: Coordinate with psychiatry, medicine, anesthesia
  - iv morphine or dilaudid based on out-patient dose
  - reduce by 15-30% each day
- Treat anxiety (benzodiazepines)
- Treat depression (SSRIs, SNRIs)
- Treat chronic pain (TCAs)
- Use clonidine
- Behavioral modification
- Treat constipation, if present

Opioi Bowel Dysfunction (OBD): Not just one disease

- Oropharynx
- Esophagus
- Stomach
- Small intestine
- Colon
Development of OBD

- μ-opioid receptors are the primary receptor for opioid analgesia
- Mostly localized to myenteric and submucosal neurons
- Higher concentration in stomach and colon
- Suppress propulsive motor and secretory activity

The Impact of OBD

- Quality of Life
- Costs
  - Office visits
  - Testing
  - Medications
- Side effects
  - Constipation (OIC)
- Stigmatization

Opioid-induced Esophageal Dysmotility

- HREM in patients on and off opioids
- 66 studied on opioids
- 55 studied off opioids
- EGJ outflow obstruction more prevalent
- IRP higher in opioid users
- Type III achalasia Dx

Treatment of non-OIC opioid-induced bowel dysfunction

• Stop the opioids

OIC: Opioid-induced Constipation

• Definition:
  A change, when initiating opioid therapy, from baseline bowel habits and defecation patterns, that is characterized by any of the following:
  a) reduced bowel frequency;
  b) development or worsening of straining;
  c) a sense of incomplete evacuation; or
  d) a patients’ perception of distress related to bowel habits

• Epidemiology:
  – 15-90% of those treated with opioids
OIC Treatment Options

- Diet
- Fiber
- Laxatives
- Osmotic agents
- Secretagogues
- PAMORAs – Peripherally Acting μ-Opioid Receptor Antagonists

OIC: Lubiprostone

- Multi-center, international study, R, DB, PC
- 424 Pts with OIC (mean age = 51; 63% women)
- 24 ug b.i.d. or placebo x 12 wks
- Primary end point met:
  - Increase in SBM (3.2 vs. 2.4)
- Improved stool consistency
- Less straining
- Constipation severity reduced
- Approved for OIC in 2013

μ-Opioid Receptor Antagonists for OIC

Centrally Acting Antagonists
- Naloxone
- Naltrexone
- Nalmefene

Peripherally Acting Antagonists
- Methylnaltrexone
- Alvimopan

OIC: Methylnaltrexone

- DB,R, PC study
- 133 Pts with advanced illness
  - 62 Methylnaltrexone; 71 Placebo
- 0.15 mg/kg QOD x 2 weeks
- Decreased time to first SBM (4 hr)
  - 48% vs. 15%
- Fewer patients on methyl-naltrexone required rescue med.
- No evidence of withdrawal

Thomas J, et al. NEJM 2008; 358: 2332-2343
SQ MethylNaltrexone for OIC

4 week R, DB, PC Trial
N = 460 patients (61% women; 90% Caucasian)

% RFBM within 4 hours of 1st dose
MNT QD 33%
MNT QOD 35%
Placebo 10%

% Injections/patient resulting in RFBRM within 4 hours
MNT QD 29%
MNT QOD 30%
Placebo 9%

P<0.001 for all MNT comparisons to placebo


OIC: Naloxegol

- Oral, peripherally acting μ-opioid receptor antagonist
- PEGylated derivative of naloxone, which markedly limits its ability to cross the blood-brain barrier
- FDA approved for non-cancer Pts with OIC (9-2014)

Naloxone

Naloxegol

Naloxegol for Opioid-Induced Constipation in Patients with Noncancer Pain

- Two, large, R, DB, PC trials (n = 1352)
- Naloxegol q.d. –
  - 12.5 mg vs. 25 vs. placebo x 12 wks
- Primary end point - > 3 SBM/week and an increase from baseline > 1 SBM/week for 9/12 weeks, and for > 3 of last 4 weeks.
- Back pain – most common reason (56%)
- Mean duration of opioid use – 3.6 yrs.

OIC: Alvimopan

- Peripherally acting, oral antagonist (PAMORA)
- Used for post-op ileus
- Multicenter, R, DB, PC
- 168 Pts randomized
- Placebo (54) vs. 0.5 mg (56) vs. 1.0 mg (56)
- Primary outcome = BM within 8 hrs of study medication
- Weekly BMs and patient satisfaction improved
- No evidence of opioid withdrawal


OIC: Drugs in Development/Testing

- Prucalopride
- Bevenopran (TD-1211)
- N-aldemedine (S-297995)
OBD: Summary

• Common
• Challenging
• A peripheral process, not central
• Not just limited to the colon
• Specific agents now available
Rumination Syndrome Versus Cyclical vomiting

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Chairman, Division of Gastroenterology and Hepatology
Director, Esophageal and Swallowing Center
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Rumination - Definition

- Rumination is defined as the effortless regurgitation of recently ingested food into the mouth, followed by either re-chewing and re-swallowing or expulsion of the regurgitate

Ronnie Fass, MD, FACG

Rumination in Animals

The cud is regurgitated and chewed to completely mix it with saliva and to break it down to particle size.

Rome III - Functional Gastroduodenal Disorders

- **Functional Dyspepsia**
  - Postprandial distress syndrome
  - Epigastric pain syndrome
- **Belching Disorders**
  - Aerophagia
  - Unspecified excessive belching
- **Nausea and vomiting disorders**
  - Chronic idiopathic nausea
  - Functional vomiting
  - Cyclic vomiting syndrome
- **Rumination syndrome**
Diagnostic Criteria for Rumination Syndrome

- Must include the following:
  - Persistent or recurrent regurgitation of recently ingested food into the mouth with subsequent spitting or remastication and swallowing
  - Regurgitation is not preceded by retching

Supportive Criteria
- Regurgitation events are usually not preceded by nausea
- Cessation of the process when the regurgitated material becomes acidic
- Regurgitant contains recognizable food with a pleasant taste

Rome III, 2006

Typical Presentations

<table>
<thead>
<tr>
<th>Rumination</th>
<th>Vomiting</th>
<th>Reflux</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effortless</td>
<td>Forceful</td>
<td>Effortless</td>
</tr>
<tr>
<td>No retching</td>
<td>Retching</td>
<td>No retching</td>
</tr>
<tr>
<td>No nausea</td>
<td>Nausea</td>
<td>No nausea</td>
</tr>
<tr>
<td>Recognizable food</td>
<td>Recognizable food</td>
<td>Acidic material</td>
</tr>
<tr>
<td>Postprandial and during meals</td>
<td>During entire day</td>
<td>During entire day, mostly postprandial</td>
</tr>
<tr>
<td>Not during nighttime</td>
<td>May occur during nighttime</td>
<td>During nighttime</td>
</tr>
<tr>
<td>Episodic and repetitive</td>
<td>May be episodic</td>
<td>Isolated events</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Weight loss</td>
<td>No weight loss</td>
</tr>
</tbody>
</table>

Epidemiology

- Young adults and females
- Prevalence – Unknown
- Bulimia nervosa – 17% of patients
- 25% with depression
- Poor quality of life
- Significant absenteeism from work or school
- Frequent emergency room visits and hospitalizations
- Significant delay in diagnosis
- Highly motivated to seek treatment

Rumination in Mentally Handicapped Adult Patients

- 10% of retarded adults
- Voluntary, repetitive and associated with sucking, belching and tongue movements
- Frequent cleaning of patient, changes of clothing and bedding
- Differential diagnosis – GERD and vomiting disorder
- Treatment – Dietary manipulations (peanut butter, lemon, tabasco etc.) and behavioral intervention
Pathophysiology – Types of Rumination

- Primary – unclear trigger
- Secondary – triggered by,
  - Reflux episode
  - Supragastric belch
- “Conditional” Vomiting

“Conditional” Vomiting Or Dyspeptic Rumination

- Patients with gastroparesis, dyspepsia or nausea/vomiting
- Rumination is developed to ameliorate symptoms
- Epigastric discomfort/pain
  - Bloating
  - Belching
  - Regurgitation
  - Nausea
- Weight loss

Sajwaj T et al, J Appl Behav Anal 1974;7:557-63
Primary Rumination

Secondary Rumination - Supragastric Belch

Comparison of Gastric Accommodation to Standard Meal

X = lowest mean change in bag volume postprandially in controls


How not to diagnose Rumination
Diagnosis

Primarily – high suspicion

* 5 physicians on average
* An average 2.8 years delay in diagnosis
* Rumination occurs after most meals and on average 20 times after one meal


Diagnosis

- Diagnostic tools:
  - Upper endoscopy
  - pH and Impedance
  - High Resolution Esophageal Manometry (HREM)
  - Gastric emptying studies
  - Antro-duodenal manometry
The different Phases of Rumination

1. Gastric strain
2. Common Cavity Phenomenon
3. Retrograde flow

Rumination Episode During HREM-Impedance
Treatment

- Non aversive behavioral therapy
  - Assurance/education
  - Biofeedback
  - An eating habit regulation program
  - Relaxation techniques
  - Psychotherapy
  - Diaphragmatic breathing
- Aversive behavioral therapy (mentally handicapped)
  - Alkalis
  - Acids
  - Bitter liquids/food

Diaphragmatic Breathing for Rumination

Chitkara DK et al. Am J Gastroenterol 2006;101:2449 – 52
Treatment (cont.)

- Anti-reflux medications (H2RA, PPI's) – Short term
- Prokinetics and antiemetics – dyspepsia rumination
- Low dose tricyclic antidepressants
  start 10mg qhs, increase by 10mg increments weekly to 50mg
- Baclofen – 10mg tid
- Nutritional support for weight loss
- Anti-reflux surgery – Controversial

Cyclic Vomiting Syndrome - Definition

- A chronic functional disorder characterized by episodes of severe nausea and vomiting that alternate with symptoms free intervals
  
  - Originally described by Dr. Samuel Gee (19th century) in a series of 9 children

Rome III - Functional Gastroduodenal Disorders

- Functional Dyspepsia
  - Postprandial distress syndrome
  - Epigastric pain syndrome
- Belching Disorders
  - Aerophagia
  - Unspecified excessive belching
- Nausea and vomiting disorders
  - Chronic idiopathic nausea
  - Functional vomiting
  - Cyclic vomiting syndrome
- Rumination syndrome
Diagnostic Rome Criteria for Cyclic Vomiting Syndrome

- Must include the following:
  - Stereotypical episodes of vomiting regarding onset (acute) and duration (less than one week)
  - Three or more discrete episodes in the prior year
  - Absence of nausea and vomiting between episodes

Supportive Criteria
- History or family history of migraine headaches

Rome III, 2006

Epidemiology

- The prevalence of CVS in children – 0.3% - 2.2%
- The prevalence of CVS in adults - unknown
- In the U.S.
  - Caucasians
  - Mean age in adults - 35 years
  - Mean age in children - 5 years
  - No gender predilection
Phases of Cyclic Vomiting Syndrome

Thurler AH et al. Gastroenterol Nurs 2013;36;407-13

Precipitating Factors for CVS

1. Stress
   a. Physical: infections, sleep deprivation, exercise, trauma
   b. Emotional: holidays, birthdays, family vacations, festivals, school camps, examinations, familial conflicts, anxiety
2. Menstruation
3. Pregnancy
4. Food allergies

Comorbid Conditions

- Irritable bowel syndrome – 28%
- Anxiety – 47%
- Depression – 44%
- Migraine – 48%
- Syncope – 36%
- Photophobia – 29%
- Headache – 52%
- Motion sickness – 46%
- Seizure disorder – 5.6%

- Rapid gastric emptying – 57%

“Abdominal Migraine”

- Whitney 1898 – first described
- Association with migraine headache or family history of migraine
  - Adults – 24% - 48%
  - Children – 39%
- Common symptoms – nausea, fatigue and aura

Pathophysiology

- Mitochondrial DNA polymorphism
- Autonomic nervous system dysfunction
- Neuroendocrine dysfunction involving the hypophyseal – pituitary-adrenal axis
- Psychological comorbidity and stressors

Hyperemesis Cannabis Syndrome

- Associated with long term of at least weekly cannabis use
- Cyclic nausea and vomiting
- Compulsive hot showers and baths
- Abdominal pain
- Negative laboratory, radiographic and endoscopic tests results
- Often confused with CVS
- Resolves with marijuana cessation

Diagnosis

- Clinical criteria (Rome criteria)
- No specific test or biomarker
- Optimal workup – unknown
  - Upper endoscopy
  - CT enterography
  - Gastric emptying
  - Colonoscopy (?)

Figure 1 One possible management algorithm for cyclic vomiting syndrome

- **Interepisodic phase**
  - Avoid triggers (e.g., drugs, psychosocial stressors)
  - Help the patient to recognize and control anxiety
  - Medical therapy:
    - Antimigraine therapy (e.g., a triptan, dihydroergotamine, prochlorperazine, cyproheptadine)
    - Antipsychotic therapy (e.g., zonisamide, lamotrigine)

- **Prodromal phase**
  - Make the patient comfortable
  - Medical therapy:
    - Benzodiazepine (e.g., lorazepam 1–2 mg given 1–2 h)

- **Emetic phase**
  - Ensure the patient is comfortable
  - Minimize sensory stimulation
  - Medical therapy:
    - Benzodiazepine (e.g., lorazepam 1–2 mg given 1–2 h)

- **Antimigraine therapy**
  - Antihistamines
  - Anticonvulsants
  - Alpha-2 agonists

- **Analgesics**
  - Nonsteroidal anti-inflammatory drugs
  - Opioids

*Supplements: L-carnitine, Coenzyme Q-10*

Olden KW et al. 2006 Nat Clin Pract Gastroenterol Hepatol doi:10.1038/ncpgasthep1094
The End
Functional Biliary Syndromes

PJ Pasricha, MD

Acknowledgements

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• Rome Committee Colleagues
  – Peter Cotton
  – Grace Elta
  – Ross Carter
  – Enrico Corraziari
Outline

- General concepts
- Controversies in functional biliary pain syndromes
  - Biliary dyskinesia
  - Sphincter of Oddi Dysfunction
- Understanding the nature of biliary pain
- Unifying concepts

Functional Biliary Syndromes

GENERAL CONCEPTS
“Chronic right upper quadrant pain allows greater scope for diagnostic and therapeutic mismanagement than perhaps any other abdominal symptom”

Kingham and Dawson 1985

Functional Biliary Syndromes according to ROME

- Functional gallbladder syndrome (gallbladder dyskinesia)
- Sphincter of Oddi Dysfunction (sphincter of Oddi dysfunction)
Rome Criteria for Biliary Pain

Pain located in the epigastrium and/or right upper quadrant and all of the following:

1. Episodes lasting 30 minutes or longer
2. Recurrent symptoms occurring at different intervals (not daily)
3. The pain builds up to a steady level
4. The pain is moderate to severe enough to interrupt the patient's daily activities or lead to an emergency department visit
5. The pain is not relieved by bowel movements
6. The pain is not relieved by postural change
7. The pain is not relieved by antacids

Patterns of Visceral Pain
Where Does biliary Pain Localize?

- 56 post-cholecystectomy patients
- T-tube in place
- Foley inserted into bile duct and distended
- Pain location mapped

Br J Surg 1967;54:599-605

Functional Biliary Syndromes

GALLBLADDER DYSKINESIA
GBD is a major clinical problem

- About 1 million new cases of gallbladder disorder per year in the USA
  - 700,000 cholecystectomies
  - Most common gastrointestinal disorder requiring hospitalization
  - Cost estimated to be about $5 billion per year
- 10-20% of the cholecystectomies for Gallbladder Dyskinesia and rising

Studying function and dysfunction

- Image gallbladder: scintigraphy (or ultrasound)
- Give contractile stimulus: CCK or CCK-analog (meal)
- Measure difference in volume (before-after)
- “Normal” ejection fractions: 37-81%
CCK-HIDA scan: How specific is it?

- Low ejection fractions in 15-25% of normal volunteers
- EF can be affected by
  - Hormone replacement therapy
  - Exercise
  - Hyperglycemia
  - PPIs!

Trial Design: General Principles

Suspected Pathology

Normal Test

Sham Rx → Rx → 1

Abnormal Test

Sham ES → Rx → 1

1 = Does intervention relieve pain?
2 = Does diagnostic test select patients who benefit from intervention?
Randomized Clinical Trial of Cholecystectomy in GBD

Suspected Gallbladder Pain

<table>
<thead>
<tr>
<th>Normal GBEF (&gt;40%)</th>
<th>Abnormal Test (&lt;40%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No CCx</td>
<td>60</td>
</tr>
<tr>
<td>1</td>
<td>103</td>
</tr>
<tr>
<td>CCx</td>
<td>14</td>
</tr>
<tr>
<td>57%</td>
<td>21</td>
</tr>
</tbody>
</table>

Don’t know

1 = Does CCx relieve pain?
2 = Does GBEF select patients who benefit from CCx?

CCK-HIDA scan: Does it predict response to cholecystectomy?

Abnormal EF

Does GBEF predict gallbladder pathology?

GBEF <40%
- Normal: 93%
- Chronic cholecystitis: 7%

GBEF >40%
- Normal: 64%
- Chronic cholecystitis: 36%

Yapp et al

Functional Biliary Syndromes

SPHINCTER OF ODDI DYSFUNCTION
Sphincter of Oddi Dysfunction

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>Incidence of SOD</th>
<th>Response to ES SOM+</th>
<th>Response to ES SOM-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>75-95%</td>
<td>90-95%</td>
<td>90-95%</td>
</tr>
<tr>
<td>Type II</td>
<td>55-65%</td>
<td>85%</td>
<td>35%</td>
</tr>
<tr>
<td>Type III</td>
<td>25-55%</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

Lehman and Sherman 2000

Randomized Clinical Trial of Sphincterotomy for SOD

Cotton et al. JAMA 2014;311(20):2101-2109

1 = Does sphincterotomy relieve pain in general?

Treatment success:
- < 6 days of lost productivity at months 9 and 12
- No second intervention
- No narcotics for abdominal pain during months 10, 11, and 12

NO, may be worse off!
Randomized Clinical Trial of Sphincterotomy for SOD

Subgroup Analysis

Normal SOM
Sham ES 48% 1 ES 20%

Abnormal SOM
Sham ES 33% 1 ES 24%

2 = Does SOM select patients in whom sphincterotomy relieves pain?

Cotton et al. JAMA 2014;311(20):2101-2109

Randomized Clinical Trial of Sphincterotomy for SOD

Subgroup Analysis

Normal SOM
Sham ES 48% 1 ES 20%

Abnormal SOM
Sham ES 33% 1 ES 24%

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Cotton et al. JAMA 2014;311(20):2101-2109

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Functional Biliary Syndromes

UNDERSTANDING (BILIARY) PAIN

“Pain is real when you get other people to believe in it. If no one believes in it but you, your pain is madness or hysteria.”

Naomi Wolfe
Understanding pain signaling…

Visceral organs are difficult to distinguish as sensorineural units

Dorsal Root Ganglion

1. Signal Transduction
2. Conduction
3. Neurotransmitter Release

Li…Pasricha. Am J Physiol Gastrointest Liver Physiol; 2013 304:G490-500.
Knowles and Aziz. PAIN; 2009: 191–209
Clinical Implications

- 22 consecutive patients with severe chronic RUQ pain
- Average work-up:
  - 3.5 consultations
  - 7.3 procedures
  - 1.7 operations
  - >20 blood tests

Kingham and Dawson Gut 1985;26:783-788

Nociceptive Sensitization and Pain

- Esophagus 0
- Duodenum 6
- Jejunum 15
- Ileum 12
- Right colon 9
- Left colon 0

Pasricha, Yamada Textbook of Gastroenterology
Evidence for a sensory disorder

Response to duodenal distension

Response to rectal distension

“Pain is real when you get other people to believe in it. If no one believes in it but you, your pain is madness or hysteria.”

Naomi Wolfe

Functional Biliary Syndromes

UNIFYING CONCEPTS
GBD and inflammation

Pathogenesis of Pain in Biliary Dyskinesia

- Stasis
  - Decreased activity of motor neurons

- Inflammation
  - PGE2
    - Increased sphincter contractility
  - Increased activity of sensory neurons (sensitization)

- Distention
  - Pain
Pathogenesis of Post-Cholecystectomy Pain

Biliary dyskinesia

Inflammation

Nociceptive sensitization of the duodenobiliary-pancreatic region

Post-cholecystectomy

Sensitization persists

Persistent pain

Sensitization resolves

Pain-free

Changes in SO pressure and dynamics

“SO Dysfunction”

Interruption of neural reflexes

Summary

• GBD
  – Possibly an inflammatory disorder
  – CCx is probably beneficial
  – The value of scintigraphy over clinical judgment in recommending CCx remains to be proven
Summary

• SOD
  – No evidence base to support utility of SOM or sphincterotomy in patients presenting with pain only
  – High complication rate and degree of difficulty makes it unacceptable for widespread use
  – Obsession with implicating sphincter has distracted us from looking at other contributing factors and therapies

Summary and Conclusions

• Visceral including biliary pain is a complex clinical and pathophysiological phenomenon
• Clinical criteria do not reliably indicate the true site of origin of pain because of overlapping neuroanatomical paths
• Sensitization of nociceptive nerves is a key factor in the generation of pain
So, so you think you can tell
Heaven from Hell,
blue skies from pain