Chronic Pancreatitis:
*Expert Tips and Tricks*

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Columbus, Ohio

Chronic Pancreatitis

- A  Computed tomography
- B  Endoscopic retrograde pancreatography
- C  Endoscopic ultrasound
- D  Histology
Outline Chronic Pancreatitis

- **Background**
  - Pathogenesis
  - Natural History of Chronic Pancreatitis

- **Case 1: Exocrine Insufficiency**
  - Targeted Enzyme therapy

- **Case 2: Pancreas Mass vs. “Pseudotumor”**
  - Observation versus Surgery

- **Case 3: Abdominal pain - Plumbing versus wiring?**
  - Neurobiology of Pain
  - Multi-modality + Multi-disciplinary Treatment
  - Treatment Options
    - Endoscopic
    - Surgical
    - New developments

- **Future directions**
  - Mechanism specific treatment
  - Neuropathic based treatment
  - Molecular biology: Gene therapy

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SAPE Hypothesis

- **Step A**: Acinar cell stimulation
  - Alcohol, gallstone, TG, oxidative stress

- **Step B**: Sentinel Event
  - Early: pro-inflammatory response
  - Late: Stellate cells, pro-fibrotic response

- **Step C**: Removal of stimulus
  - Abstinence
  - cholecystectomy
  - lipid lowering agents

- **Step D**: Recurrent stimulation
  - Stellate cell mediated periacinar fibrosis

Stellate Cells Mediate Fibrosis in CP

The natural history of hereditary pancreatitis: a national series

Exocrine Insufficiency by Age 30


Endocrine Insufficiency by Age 40

Increased Risk of Pancreatic Cancer in Hereditary Pancreatitis

- A pancreatic adenocarcinoma was diagnosed in ten patients (5%) six males and four females, in eight families.
- The median age at diagnosis of cancer was 55 years (range 39–78).
- The cumulative risks at age 50, 60 and 75 years were
  - 10.0% (95% confidence interval (CI) 1% to 18%)
  - 18.7% (95% CI, 3% to 32%)
  - 53.5% (95% CI, 7% to 76%), respectively


Natural History of (Hereditary) Chronic Pancreatitits

CP Case 1: Change in Bowel Habits

• RD  53 year old male
• Calcific chronic pancreatitis
• Intractable pain 9/10 constant
• Amman type B pain
• Recent Pancreaticojejunostomy
  – Successful, pain decreased markedly
• Three months after surgery referred for loose stools
  – Oily, malodorous, difficult to flush!

Indirect Tests for Exocrine Function

• Sudan stain
  – Qualitative fecal fat
  – Fat droplets
• Pancreatic elastase 1
  >201  Normal
  100-200  Mild
  <100  Severe

Digestion/Absorption

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Result</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic Elastase 1</td>
<td>80 mcg/g</td>
<td>&gt;251 mcg/g</td>
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</tbody>
</table>

Positive  Negative
CP Case 1: Change in Bowel Habits

- Lab: Sudan stain ++
- Pancreatic elastase-1 of 80 mcg/g
- What is the diagnosis?

DX: Pancreas Exocrine Insufficiency

- How do I treat pancreatic steatorrhea?
- Why is this important?
- Long term sequelae?
- Questions?
  - Coated pancreas enzyme
  - Uncoated pancreas enzyme
  - Proton pump inhibitor
  - Medium chain triglyceride (MCT) oil
Pancreas Exocrine Insufficiency: 
Physiology Based Therapy

- Researchers reported the accuracy of the 13C-mixed triglyceride breath test (MTG) as a tool for:
  - evaluating the effect of enzyme therapy on fat digestion in CP
  - analyze the impact of modifying the therapy according to the breath test on patients' nutritional status
- The MTG is equivalent to coefficient of fat absorption (CFA) at detecting steatorrhea and can be used to target enzyme therapy to improve nutritional parameters and fat maldigestion.


Targeted Pancreas Enzyme Supplementation Normalizes Nutrition Parameters in CP

Improved Nutritional Parameters: Body Weight, RBP and pre-albumin
Enteric coated preparation dosed to normalize C13 MTG BT (60-80,000/meal)
Acid suppression (PPI) needed in some cases.
FDA Approved Pancreatic Enzyme Preparations

<table>
<thead>
<tr>
<th>Product</th>
<th>Enzyme Content/Unit Dose (United States Pharmacopeia units)</th>
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<tbody>
<tr>
<td></td>
<td>Lipase</td>
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<tr>
<td>Immediate Release Capsule</td>
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<tr>
<td>Non Enteric-Coated</td>
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<tr>
<td>Viokace 10,440</td>
<td>10,440</td>
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<tr>
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<td>Enteric-Coated Minimicrospheres</td>
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<td>6,000</td>
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<td>12,000</td>
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<tr>
<td>Creon 24,000</td>
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<td>Enteric-Coated Minitablets</td>
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<td>13,800</td>
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<tr>
<td>Ultresa 20,700</td>
<td>20,700</td>
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<td>Ultresa 23,000</td>
<td>23,000</td>
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<tr>
<td>Enteric-Coated Beads</td>
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<td>Zenpep 3,000</td>
<td>3,000</td>
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<td>Zenpep 5,000</td>
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<tr>
<td>Pancreaze 21,000</td>
<td>21,000</td>
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</tbody>
</table>


Measuring Exocrine Function In Adults: Why?

- **Recognition of exocrine insufficiency**
  - Maldigestion associated morbidity / mortality

- **Malabsorption of fat-soluble vitamin**
  - *Pancreatology* 2008; 8:583-6
    - Vitamin D
    - Osteopathy associated
    - Bone fractures associated with low fecal elastase-1

    - Vitamin A - Night blindness, visual impairment
    - Vitamin E - Neurologic symptoms
    - Vitamin K - Coagulopathy

ACG Midwest Regional Postgraduate Course - Indianapolis, IN
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**Inflammation Induces an Imbalance between Osteoclast and Osteoblast Activity**


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**Is There a High Prevalence of Low-Trauma Fracture in Chronic Pancreatitis?**

- **Hypothesis:** Chronic Pancreatitis is a risk factor for metabolic bone disease

- **Aim 1:** Compare prevalence of fracture
  - Controls
  - Chronic Pancreatitis
  - “High Risk” GI Illness

- **Aim 2:** Compare prevalence of fracture in each “high risk” group to controls and Chronic Pancreatitis
  - Odds Ratio, [95% CI]
High Prevalence of Low-Trauma Fracture in Chronic Pancreatitis

April S. Tignor, MD, MPH, Bechien U. Wu, MD, MPH, Tom L. Whitlock, MD, MPH, Rocio Lopez, Kathryn Repas, Peter A. Banks, MD and Darwin Conwell, MD

OBJECTIVES: Chronic pancreatitis (CP) is associated with risk factors that may negatively impact bone and mineral metabolism. The important clinical end point of osteoporosis is “low-trauma” fracture. The purpose of this study was to examine the prevalence of “low-trauma” fracture in patients with CP, compared with fracture rates in “high-risk” gastrointestinal (GI) illnesses, for which metabolic bone disease screening guidelines are in place.

METHODS: This is a retrospective cohort database study examining patients with CP and “high-risk” GI illnesses seen at a single tertiary care center. Time points ranged between 31 July 1996 and 31 July 2008. The main outcome measure was “low-trauma” fracture prevalence using specific International Classification of Diseases, Ninth Revision, Clinical Modification fracture codes.

RESULTS: A total of 3,192 CP patients and 1,461,207 non-CP patients were included in the study. The fracture prevalence (patients with fracture per total patients) was as follows: controls, 1.1% (16,208/1,436,699); Crohn’s disease, 3.0% (182/6057); CP, 4.8% (154/3192); celiac, 4.8% (90/1484); cirrhosis, 2.7% (174/6312); and postgastrectomy, 6.4% (17/263). Prevalence for each group was statistically greater than controls (P<0.001). CP fracture prevalence was greater than controls (P<0.001) and Crohn’s disease (P<0.001), and comparable with the remaining “high-risk” GI illness groups (P>0.05). The odds of fracture (odds ratio 0.8, 95% confidence interval CI) compared with controls, adjusted for age, gender, and race was CP 2.4 (2.1, 2.9); Crohn’s disease 1.7 (1.5, 2.0); gastrectomy 2.3 (1.5, 4.1); celiac 2.6 (2.4, 2.7); and celiac disease 2.7 (2.1, 3.4). The odds of fracture for each disease group were statistically greater than controls (P<0.0001).

CONCLUSIONS: The prevalence of low-trauma fracture in CP patients is comparable with or higher than that of “high-risk” GI illnesses, for which osteoporosis screening guidelines exist.

Fracture prevalence in CP was 4.8%

Fracture Prevalence in GI Illness

CP versus Crohn's p<0.001
CP versus Controls p<0.001

Odds Ratio of Fracture Among CP was comparable to other “High Risk” GI Disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Pancreatitis</td>
<td>4.4</td>
<td>(3.7, 5.2)</td>
</tr>
<tr>
<td>Crohn’s Disease **</td>
<td>2.6</td>
<td>(2.2, 3.0)</td>
</tr>
<tr>
<td>Celiac Disease</td>
<td>4.4</td>
<td>(3.4, 5.6)</td>
</tr>
<tr>
<td>Postgastrectomy</td>
<td>4.7</td>
<td>(2.8, 8.0)</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>4.4</td>
<td>(4.1, 4.7)</td>
</tr>
</tbody>
</table>


Algorithm Exocrine Insufficiency

- Dose adjustment
  - LARGE DOSES
- MCT oil
  - Not usually
- Enteric coated
  - Protects enzymes
- Acid suppression
  - Lipase protection
- New Data
  - Synthetic enzymes
  - NDA and FDA
  - Standardization
  - Breath Test needed!!

Stevens T, Conwell DL., www.clevelandclinicmeded.com
CP Case 2: Increased pain, anorexia, weight loss

- MP 56 year old Hispanic male
- Alcohol induced Chronic Calcific Pancreatitis
- 5 year follow-up in BWH Center for Pancreatic Disease (CPD)
- Elevated Ca 19-9 of peak 437….nadir 173
- Serial imaging no change in morphology
- **PCP call:** increased pain, decreased appetite, fatigue
- CT Scan recommended and follow-up in CPD

CT Scan: Pancreas Adenocarcinoma

**CT Report 2007**
- The pancreatic duct is diffusely dilated up to 13mm in the head to the level of coarse calcifications in the head.
- There are additional coarse calcifications within the pancreas and within the pancreatic duct in the upstream pancreas.
- **IMPRESSION:** 1. Findings consistent with chronic pancreatitis with no evidence of acute pancreatitis.

CT 1/15/2009: Mass, malignant ascites, Metastases, biliary dilation
Pancreatitis and Pancreas Cancer: Meta-analysis

Roles of Pancreatic Stellate Cells in Carcinogenesis

PDGF, TGF-β, FGF-2

MMPs and TIMPs

Proliferation

ECM deposition (collagen, fibronectin, laminin)

Other cells in the tumor and/or pancreas

PsSC

Tumor cells

Tumor desmoplasia, angiogenesis, and tumor invasion


Fig. 4: Forest plot of the included studies showing the association between pancreatitis and pancreas cancer risk.
Cumulative Incidence of Pancreatic Cancer is elevated in Chronic Pancreatitis

- **Approx 1% every 5 years**
  - 4-5% at 20 years

- No screening guidelines

- Better methods needed

- Modifiable Factors: inflammation, alcohol, diabetes, obesity, SMOKING


Algorithm Pancreas Mass vs. “Pseudotumor”

- Pancreas CT scan?
  - Repeat if not
  - Ancillary data:
    - CA 19-9? Jaundice?
    - Duct morphology
    - Abdominal pain

- Outside film review with radiology staff
  - Ask: “Would MRI help?”

- EUS with FNA
  - Cytology on site?
  - AMPULLARY BIOPSY (IgG4 stain)
  - 5+ passes

- Surgical versus Oncology Referral

- 2 week steroid trial – suspected AUTOIMMUNE

- When in doubt: SURGICAL RESECTION

Stevens T, Conwell DL., www.clevelandcliniemeded.com
CP Case 3: Pain Management

- NM 19 year old male with chronic calcific pancreatitis
- SPINK 1 mutation
- Intractable pain 9/10 in severity
  - Fentanyl lollipops 800-1600 mcg every 6h
  - Methadone 10-20 mg every 8 h
- Diabetes mellitus, steatorrhea

CP Pain: Introductory Comments

- Pain and chronic pancreatitis: is it the plumbing or the wiring?

- Cerebral excitability is abnormal in patients with painful chronic pancreatitis.
  - Eur J Pain 2012 Apr 16.

- Pancreatic nociception - Revisiting the physiology and pathophysiology.

- Pain in chronic pancreatitis: the role of neuropathic pain mechanisms.
  - Gut 2008 Nov;57(11):1616-27

- Meta-analysis: The Placebo Rate of Abdominal Pain Remission in Clinical Trials of Chronic Pancreatitis.
  - Pancreas 2012 ..........................20%
**Chronic pancreatic pain**

*Neuropathic pain syndrome*

- Intrapancreatic (Level 1)
  - Neuropathic mechanisms

- Extrapancreatic (Level 2)
  - DRG and spinal cord hypersensitivity

- Cerebral cortex adaptation (Level 3)

Demir et al., Langenbecks Arch Surg 2011; 396: 151-160

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19 year old male abdominal pain: *I need a Plumber!*

NM 19 year old male with chronic calcific pancreatitis
SPINK 1 mutation
Fentanyl lollipops 800-1600 mcg every 6h
Methadone 10-20 mg every 8 h
Diabetes mellitus
Exocrine Insufficiency: steatorrhea
Chronic Pancreatic Pain Management

Plumbing Problem

• What are my options?
  – Call a plumber!!

• Endoscopic Therapy
  – ESWL / Sphincterotomy / Stent

• Surgical Therapy
  – Drainage
  – Total Pancreatectomy

• Observation
  – Not acceptable to patients
  – Pancreatic Burnout
  – Doctor I need your help!

• Radiation Therapy?
  – Need RCT

Be careful in your selection of a plumber………..you may get Joe!

Ductal and Mechanical: Plumbing Problem

• Duodenal obstruction
• Pseudocyst
• Main pancreatic duct obstruction
• Parenchymal hypertension
  – No relationship between parenchymal pressure and pain

  – No correlation between pain and endoscopic intervention or pressure reduction

  – No clear relationship in duct anatomy (dilated or blocked) and pain
Chronic Pancreatitis: CT Scan

Endoscopic therapy
*Chronic Pancreatitis*

*Courtesy of David Leslie Carr-Locke, MD*
Surgical Therapy
Frey procedure

140 eligible patients
72 randomized to surgical vs. endoscopic therapy
Surgery 80% resection / 20% drainage
Endotherapy 100% Sphincterotomy/Stent 23% with stone removal

Conclusion:
Endotherapy > Surgery short term relief (1 year) 51.6 versus 42.1% complete relief
Surgery > Endotherapy for long term pain relief (5 year) 36.9 versus 14.3% complete relief

Surgical was Superior to Endotherapy

Endoscopy

• Improved QOL
• Improved Pain Score
• Less Procedures
• More Technical Success

What do we learn from these RCT “Plumbing” studies?

• ENDOTHERAPY: Endoscopists are better
  – Short term relief; “bridge”
  – Urgent; temporizing measure
  – Non-surgical candidates

• SURGICAL THERAPY: Surgeons are better
  – Long term relief
  – Elective

25 y female chronic abdominal pain: *I need an Electrician*

- Recurrent abdominal pain as teenager
- Fluctuating pancreas enzymes
- Chronic Abdominal pain as adult

Courtesy of Koenraad Mortele, BWH Radiology
Pancreas Neurobiology

Results of Differential Neuroaxial Blockade in Chronic Pancreatitis (n = 23)

<table>
<thead>
<tr>
<th>Pain Type</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visceral</td>
<td>5 (22%)</td>
</tr>
<tr>
<td>Nonvisceral</td>
<td>18 (78%)</td>
</tr>
<tr>
<td>Central</td>
<td>11</td>
</tr>
<tr>
<td>Somatosensory</td>
<td>4</td>
</tr>
<tr>
<td>Mixed</td>
<td>3</td>
</tr>
</tbody>
</table>


Descending Inhibitory Pain Modulation is Impaired in patients with Chronic Pancreatitis

- 25 CP; 15 HS
- Descending pain modulation assessment
  - Noxious inhibitory control
  - Multimodal central processing
  - Evoked brain potentials after rectosigmoid stimulation

- Conclusion: CP impairments in pain modulation and central sensitization

- Treatment of pain should include pancreas and descending pain modulation from supraspinal structures and central nervous system sensitization

Olesen SS, et al., Clin Gastro Hep 2010
Pain-Associated Adaptive Cortical Reorganisation in Chronic Pancreatitis

Søren Schou Olsen, Jens Brendum Frøkjær, Dina Lelic, Maximilian Valeriano, Ashjarn Mørk Druhwek.
Mech-Sense, Department of Gastroenterology, and Department of Radiology, Aalborg Hospital, Aarhus University Hospital, and Center for Sensori-Motor Interactions (SMI), Department of Health Science and Technology, Aalborg University, Aalborg, Denmark; Division of Neurology, Ospedale Pediatrico Bambino Gesù, Rome, Italy.


A Safe, Effective, and Cheap Method of Achieving Pancreatic Rest in Patients With Chronic Pancreatitis With Refractory Symptoms and Malnutrition

Jeffrey T. Lordan, MRCS, Mary Phillips, BSc, An Vinh Chung, MRCS, Tim R. Willingham, FRCS, Neville S. Menezes, FRCS, Robin Lighthiowad, FRCS, Faisal Hussain, FRCS, Christopher Tibbs, FRCP, and Navin D. Kanania, FRCS

Rest the Pancreatic Nerves

FIGURE 1. Flocare benchmark Nt tube.
EUS Guided Celiac Plexus Block:

**Block the Pancreatic Nerves**

50% response; short term benefit

### TABLE 1. Meta-analysis of the Studies With Right Open 95% CI and Heterogeneity Assessment (EUS-guided Celiac Plexus Block for Chronic Pancreatitis)

<table>
<thead>
<tr>
<th>Study</th>
<th>Pain Relief Reported Out of Total Patient</th>
<th>Observed Proportion</th>
<th>Analysis for Proportion</th>
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<tr>
<td></td>
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<tr>
<td>Grass et al14</td>
<td>5/10</td>
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<tr>
<td>Gross et al15</td>
<td>59/90</td>
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<tr>
<td>Levy et al16</td>
<td>5/13</td>
<td>0.39</td>
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<tr>
<td>O’Toole et al17</td>
<td>20/31</td>
<td>0.65</td>
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<td>LeBlanc et al18</td>
<td>21/51</td>
<td>0.53</td>
<td></td>
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<tr>
<td>Stevens et al19</td>
<td>16/26</td>
<td>0.62</td>
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<td>Over All Studies</td>
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<td>Estimates         SE  95% CI</td>
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<tr>
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<td>0.5029           0.1322 (0.2836-1)</td>
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<td>0.5534           0.0516 (0.4489-1)</td>
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<td>0.4112           0.1183 (0.2217-1)</td>
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<td>0.6312           0.0818 (0.4932-1)</td>
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<td>0.5004           0.0661 (0.4215-1)</td>
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<td>0.6033           0.0883 (0.4533-1)</td>
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<td>0.5146           0.1112 (0.3272-1)</td>
</tr>
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</table>

P value for heterogeneity = 0.6077.
CI indicates confidence interval; EUS, endoscopic ultrasound.

Total Pancreatectomy With and Without Islet Cell Transplantation for Chronic Pancreatitis

**A Series of 85 Consecutive Patients**

Giuseppe Garcea, MD, MRCS, James Weaver, MBChB, John Phillips, MBChB, Cristina A. Pollard, BA, Severine C. Ionac, PhD, M Bala A. Webb, BSc, David P. Berry, MD, FRCS, and Ashley R. Dennison, MD, FRCS

**Remove the Pancreatic Nerves**

Narcotic Use:

- **90% initial**
- **40% 1 year**
- **15% 5 year**

FIGURE 4. Percentage of patients on regular opiate analgesia before and after total pancreatectomy. Numbers of patients in the following period indicated at the top of the bars. (Pancreas 2009;38: 1Y7)
Pregabalin reduces pain in patients with chronic pancreatitis in a randomized, controlled trial

Modify nerve transmission

• CP pain processing by the central nervous system is abnormal and resembles that observed in patients with neuropathic pain disorders. We investigated whether agents used to treat patients with neuropathic pain are effective in CP.

• METHODS:
  RCT, 64 patients
  Pregabalin or placebo (control) for 3 consecutive weeks.
  The primary end point was pain relief, based on a visual analogue scale documented by a pain diary. Secondary end points included Patients’ Global Impression of Change (PGIC) score, changes in physical and functional scales, patient character, quality of life, and tolerability.

• RESULTS:
  Pregabalin, compared with placebo
  Pain relief after 3 weeks of treatment (36% vs 24%; mean difference, 12%; 95% confidence interval, 22%-2%; P = .02).
  Improved health status (PGIC score) at the end of the study was higher in the pregabalin than the control group (44% vs 21%; P = .048).

• CONCLUSIONS:
  In a placebo-controlled trial, pregabalin is an effective adjuvant therapy for pain in patients with CP.

**CP Pain Management**

- Unraveling the mystery of pain in chronic pancreatitis
  - Associated with a severe burden of disease.
  - Pathogenesis is poorly understood
  - Treatment has been largely empirical, often consisting of surgical or other invasive methods, with an outcome that is variable and frequently unsatisfactory.
  - Human and experimental studies have indicated a critical role for neuronal mechanisms that result in peripheral and central sensitization.
  - The pancreatic nociceptor seems to be significantly affected in this condition, with increased excitability associated with downregulation of potassium currents.
  - Some of the specific molecules implicated in this process include the vanilloid receptor, TRPV1, nerve growth factor, and the protease activated receptor 2

Algorithm Pain Management

- Smoking, alcohol cessation
- Enzyme Therapy
  - Inhibits CCK-RF stimulation (trypsin)
- Pain Character (DNB or CPB)
- Duct morphology
- Surgical Therapy
  - Large duct
  - Total Pancreatectomy with Islet cell transplantation
    - Small duct
- Multi-modality approach
  - TCA, SSRIs
  - Pregabalin
- RCTs greatly needed!!
  - XRT, RFA

Future Management

- Synthetic pancreas enzymes
- Mast cell directed therapy
- Anti-nocioceptive therapy
- Nerve growth factors
- Anti-fibrogenesis therapy
- Treatment of “central” pain
- Radiofrequency ablation
- Radiation Therapy
- Gene Therapy

Stevens T, Conwell DL., www.clevelandclinicmeded.com
Gene Therapy for CP pain

- Efficacy of a replication defective Herpes (HSV-1, DPE) viral vector construct encoding the human preproenkephalin gene (HSV-Enk)
- Pain behavior patterns in two alcoholic pancreatitis animal models
  - Significant analgesia and protection of pancreatic tissue was provided for the duration of the transgene expression (4–6 weeks)
  - These studies establish a basis for use of HSV-based gene therapy for chronic visceral pain
  - Targeted enkephalin gene therapy approaches are providing clear promise for pain control


Increased HSV-ENK Expression in Dorsal Root Ganglia

Figure 3: Herpes simplex virus (HSV-1) and met-enkephalin immunohistochemical staining in dorsal root ganglia (DRG) (A) HSV-1. Photomicrographs of immunohistochemical staining for human HSV-1 protein at week 10. No stain is evident in DRG of (a) naïve animals or (b) vehicle-treated animals fed the alcohol and high-fat diet. Note the presence of staining for human HSV-1 protein in DRG of animals given the (c) HSV-β-gal and (d) HSV-Enk vector treatments. Cryptic localization is noted for HSV in DRG from vector-treated animals only in some dorsal ganglia. (e–l) Met-enkephalin immunohistochemical staining for met-enkephalin in DRG. (e–l) Staining is noted in the met-enkephalin positive dorsal root ganglia (DRG) of animals fed alcohol and high-fat diets and an associated induced pancreatitis at week 10. Met-enkephalin staining is noted in (e–l) dorsal root ganglia (DRG) of animals fed alcohol and high-fat diets and an associated induced pancreatitis at week 10.

Gene Therapy (2009) 16, 483–492
Pain Behavior and Tolerance are Improved with HSV-ENK

Figure 2. Nociceptive behavior measurements: Open-field and hot-plate response latencies were reduced by HSV-ENK. (A) Acute pancreatitis: Open-field exploratory behavior for rats with acute pancreatitis induced by CCK (60 min/ml). Pain behavior significantly reduced, tested in the San Diego open-field testing units, except in animals receiving the HSV-ENK corepression vector. (B) Chronic pancreatitis: Hot-plate response latency measurements were shown for naive animals and for the groups of animals fed chronically with the alcohol and high-fat diet. Hot-plate tests were conducted at 1 week before induction of pancreatitis and for 10 weeks subsequently. Note the significant shortening of hot-plate response latency in the rats on the high-fat and alcohol diet for week 3, indicating sensitization. The HSV-ENK treatment (given at 3 weeks) significantly elongated the shift in response latency for at least 4 weeks. Four weeks is also typical of HSV vector expression before latency at this time.

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TRPV1 and TRPA1 Antagonists Prevent the Transition of Acute to Chronic Inflammation and Pain in Chronic Pancreatitis


6wk CCK CP model
Treatment < 3 wk
*prevented AP-CP transition
*pain behavior

Treatment > 3 wk
*no effect
19 year old “small duct” CP: *I need a Plumber!*

- Chronic Pain; Borderline Diabetes mellitus
- Exocrine Insufficiency: steatorrhea
- Fentanyl lollipops 800-1600 mcg every 6h
- Methadone 10-20 mg every 8 h
- Frey Procedure
- Total Pancreatectomy with Islet Cell Transplant …..Pain continues; “brittle” diabetes

25 year old “small duct” CP: *I need an electrician*

- Celiac plexus block
- Deep Brain Stimulation Study
- Nasojejunal feeding x 3-4 mo
- Total Parenteral Nutrition x 3-4 mo
- Pain 6-8/10
- Chronic Narcotics
- SSRIs, TCAs

1st Pancreas Center: EUS – 4 criteria / 1 hour Dreiling tube PFT peak bicarbonate 50 meq/L……………….2 years later….
2nd Pancreas Center: EUS – 6 criteria / 1 hour ePFT peak bicarbonate 48 meq/L

Considering Total Pancreatectomy with Islet Cell Transplantation
Finale: Chronic Pancreatitis

• **Background**
  – Pathogenesis: Stellate Cells---CP----->CANCER
  – Natural History of Chronic Pancreatitis

• **Abdominal pain - Plumbing vs. wiring or Both?**
  – DIFFICULT !!!!!
  – Neurobiology of Pain
  – Multi-modality + Multi-disciplinary Treatment
  – Treatment Options – endoscopic, surgical, new developments

Finale: Chronic Pancreatitis

• **Exocrine Insufficiency**
  – Targeted Enzyme therapy; acid suppression
  – Long term – metabolic bone disease

• **Pancreas Mass vs. “Pseudotumor”**
  – Modify risk Factors: smoking, alcohol
  – Endoscopic Ultrasound with FNA
  – Surgical intervention

• **Future directions**
  – Mechanism specific treatment
  – Neuropathic based treatment
  – Molecular biology: Gene therapy