Chronic Pancreatitis

Michelle A. Anderson, MD, MSc

HEALTH SYSTEM
UNIVERSITY OF MICHIGAN

> More than 100,000 people in the U.S. suffer from chronic pancreatitis – 80% have debilitating pain

> Almost 1 million outpatient visits with a dx of CP/year

>Financial Burden ~ $638 million dollars annually

Everhart JE, Ruhl CE. Burden of digestive diseases in the United States Part III: Liver, biliary tract, and pancreas. Gastroenterology. 2009 Apr;136(4):1134-44. Epub 2009 Feb 24. Review. PubMed PMID: 19245868.

Goals

- Understand the pathophysiology of pain in CP: Why this isn't "one-size-fits-all"
- Identify best treatment options: medical and endoscopic
- Recognize risks of opioid Rx and optimize use

- 540 patients with CP
- 414 (77%) designated pain pattern
- Association of pain patterns with various outcomes
  - Missed work/school
  - Disability
  - Narcotic use
  - QoL

Pattern	Definition
A	Episodes of Mild-Moderate Pain, usually controlled by medication
B	Constant Mild-Moderate Pain, usually controlled by medication
C	Usually pain free with episodes of severe pain
D	Constant Mild pain plus episodes of severe pain
E	Constant severe pain that does not change

Pattern	Definition
A	Episodes of Mild-Moderate Pain, usually controlled by medication
B	Constant Mild-Moderate Pain, usually controlled by medication

Mild to Moderate

Pattern	Definition
	Severe
C	Usually pain free with episodes of severe pain
D	Constant Mild pain plus episodes of severe pain
E	Constant severe pain that does not change

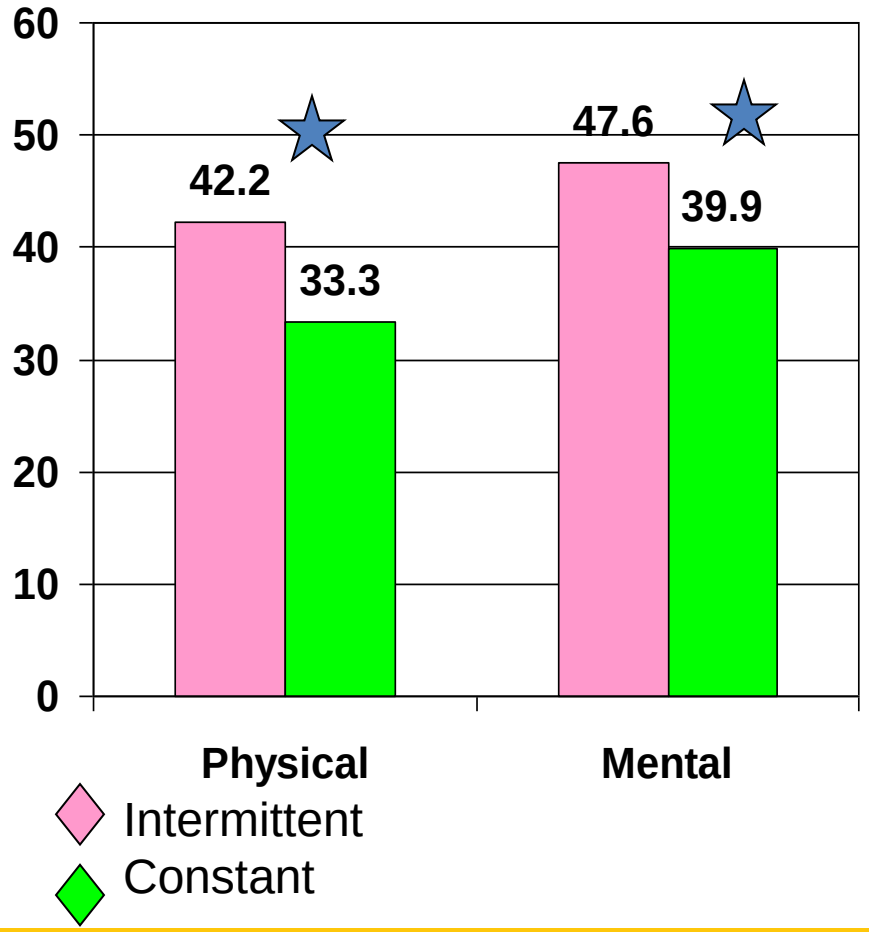
Pattern	Definition
A	Episodes of Mild-Moderate Pain, usually controlled by medication
	Intermittent
C	Usually pain free with episodes of severe pain

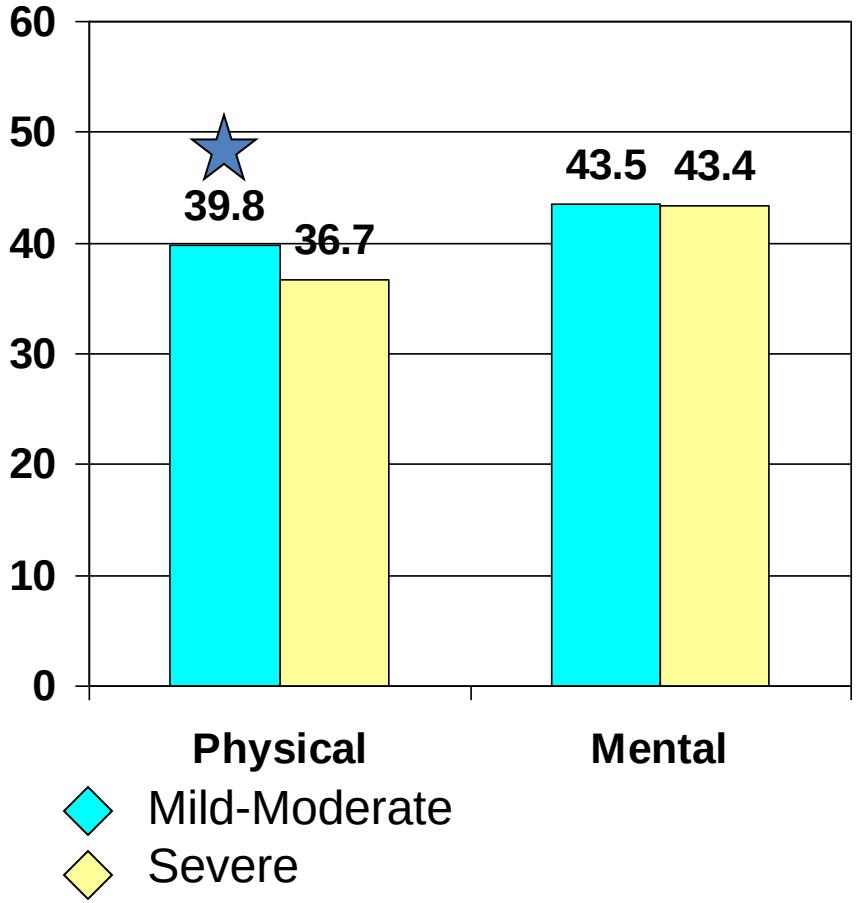
Pattern	Definition
	Constant
B	Constant Mild-Moderate Pain, usually controlled by medication
D	Constant Mild pain plus episodes of severe pain
E	Constant severe pain that does not change

Variable	Intermittent	Constant	P-value
Number (%)	**186 (45)**	**228 (55)**	
Age	**50.6±17.1**	**47.6±13.8**	**0.05**
Drinking Category			
Abstainer	**48 (26)**	**47 (21)**	**0.01**
Light	**38 (20)**	**41 (18)**	
Moderate	**43 (23)**	**41 (18)**	
Heavy	**20 (11)**	**28 (12)**	
Very Heavy	**36 (20)**	**71 (31)**	
Smoking			
Never	**65 (35)**	**55 (25)**	**0.02**
Past	**45 (25)**	**52 (23)**	
Current	**75 (41)**	**121 (53)**	
Reg Use Pain Meds			
Yes	**37 (22)**	**119 (73)**	**<0.001**
No	**129 (78)**	**45 (27)**	
Disability			**<0.001**
Yes	**32 (18)**	**91 (42)**	
No	**151 (82)**	**125 (58)**	

Variable	Mild-Moderate	Severe	P-value
Number(%)	96 (23)	318 (77)	
Age	50.1±14.6	48.6±15.7	0.38
Drinking Category			
Abstainer	16 (17)	79 (25)	0.50
Light	24 (25)	55 (17)	
Moderate	20 (21)	64 (20)	
Heavy	9 (9)	39 (12)	
Very Heavy	27 (28)	80 (25)	
Smoking			
Never	24 (25)	96 (30)	0.25
Past	28 (30)	68 (22)	
Current	43 (45)	153 (48)	
Reg Use Pain Meds			
Yes	36 (45)	120 (48)	0.73
No	44 (55)	130 (52)	
Disability			
Yes	23 (25)	100 (33)	0.21
No	69 (75)	207 (67)	

SF-12 scores by Temporal Experience versus Intensity

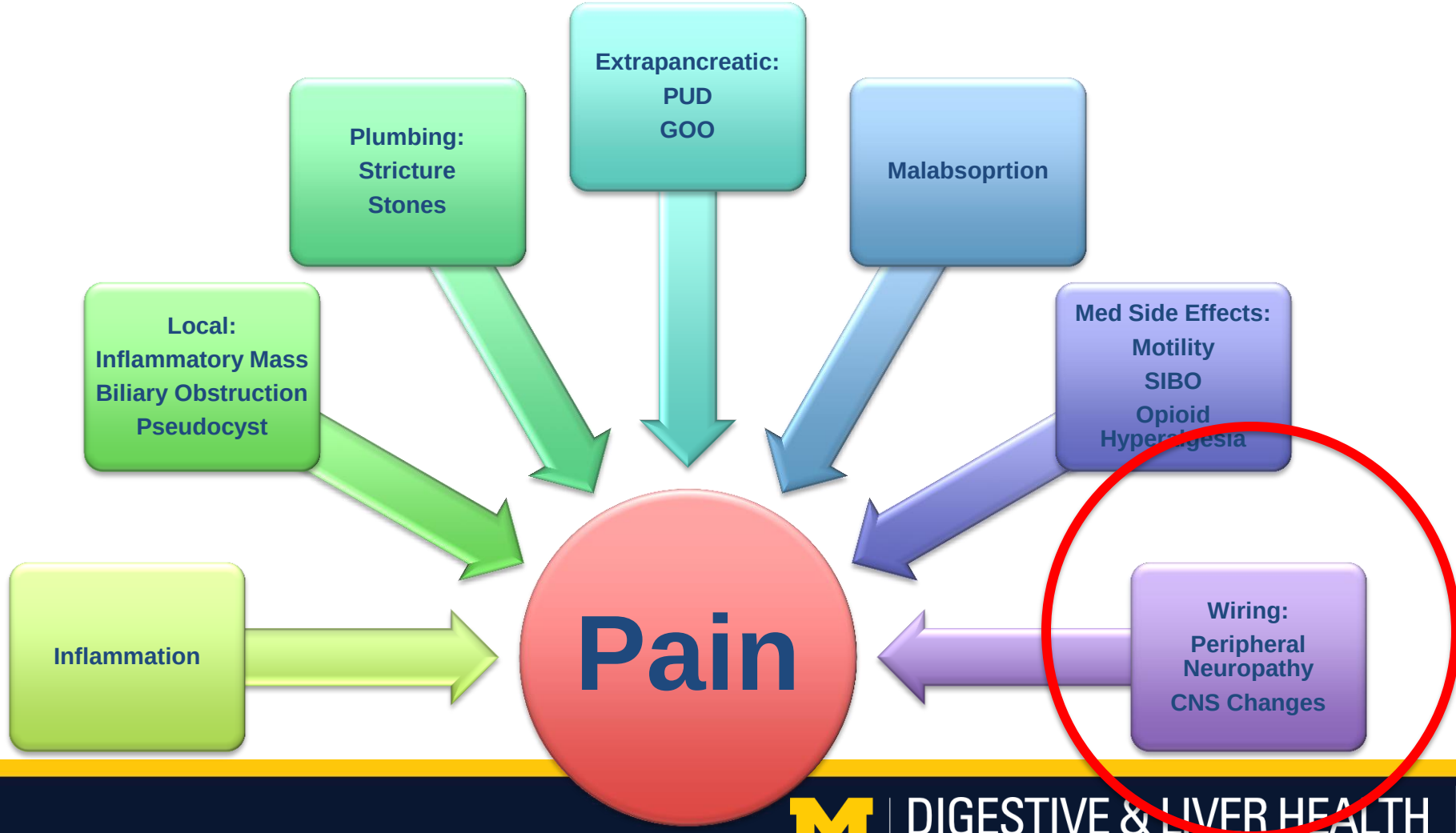




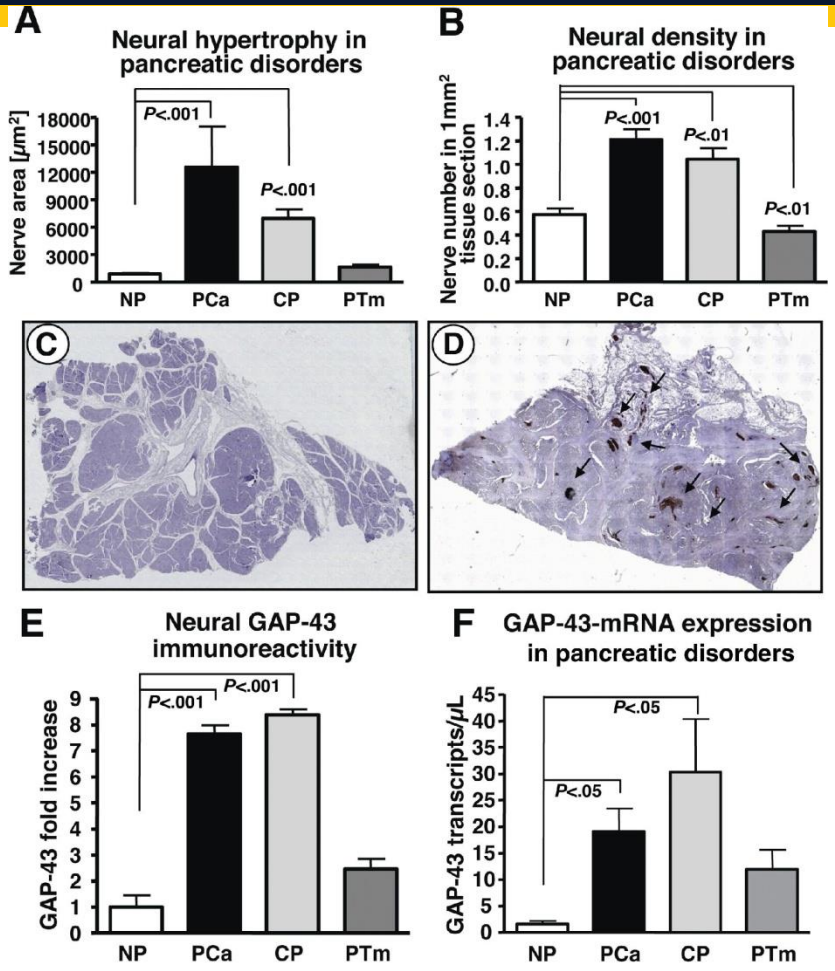
What we learned

- Pain in CP is a continuum – even 5 categories did not “capture” all experiences
- Temporal nature of pain (frequency) may be more influential on endpoints than severity
- Pain pattern was NOT influenced by duration of disease – i.e. we did not observe a “burnout” phenomenon

Mechanisms of Pain in CP

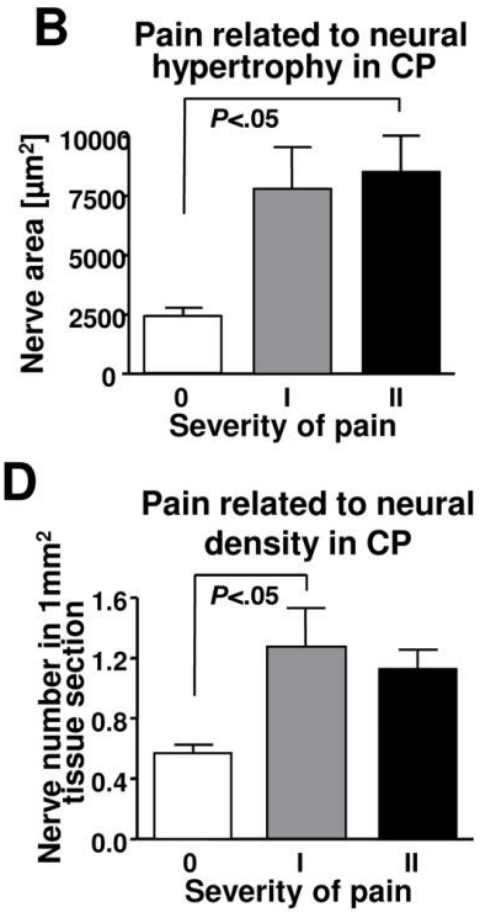


Neuropathy in pancreatic tissue from 546 subjects



Ceyhan, et al Gastro 2009

Neural Remodeling Associated with Pain and is Unique to Pancreatic Adeno & CP



- Constant Pain = Greater Neural Changes
- Not seen with:
  - Serous adenomas
  - Mucinous adenomas
  - IPMT
  - Ampullary Tumors
  - Neuroendocrine tumors
  - Normal Pancreas

Ceyhan, et al Gastro 2009

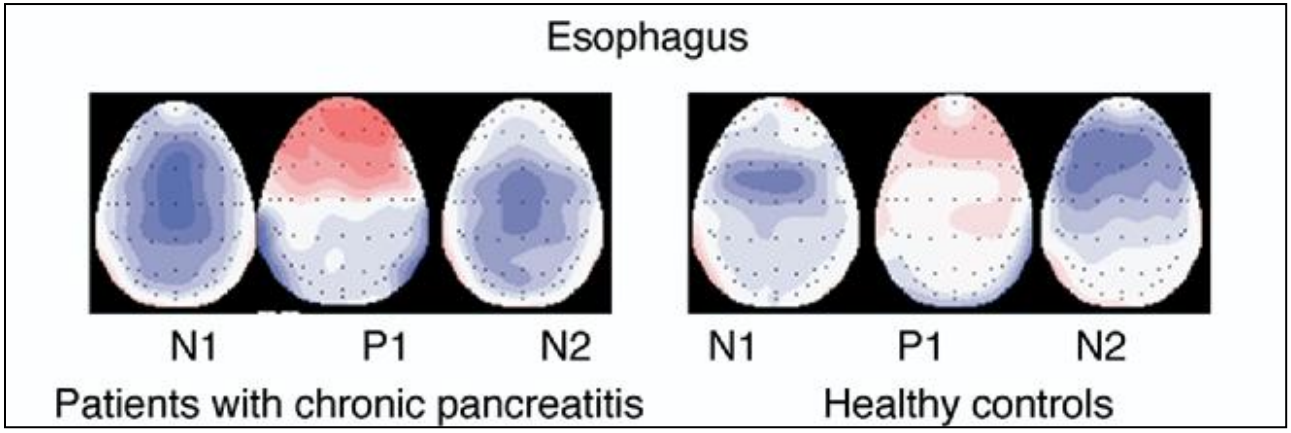
Evidence for CNS changes in CP

- Partial or complete pancreatectomy ≠ pain relief in 100%
- Relative Failure of Celiac Plexus Block
- Patients with CP have slowed EEG rhythms → Hallmark of neuropathic pain*

Sarnthein et al 2006

CNS Changes in Painful Chronic Pancreatitis

- 12 controls/ 10 CP
- 64-lead EEG
- Painful electrical stim to esophagus/stom/duoden
- Saw changes in pattern c/w other neuropathic syndromes e.g. early EP slowing



Dimcevski *2007 Gastro*

Clinical assessment of pain in patients with chronic pancreatitis

- Why do it?
  - Understand patient status in depth
  - Select right Rx at right Time
  - Improve health and function
  - Decrease healthcare utilization and costs
- How often?
- Using what?

Recommendations from Multidiscipline Expert Consensus Meeting

- Assess pain @ every visit:
  - Character
  - Frequency
  - Intensity
- Assess QOL and Psychological Co-morbidities
- Use validated instrument

PEG Pain Assessment Tool

Krebs EE, Lorenz KA, Bair MJ, Damush TM, Wu J, Sutherland JM, Asch SM, Kroenke K. Development and initial validation of the PEG, a three-item scale assessing pain intensity and interference. J Gen Intern Med. 2009 Jun;24(6):733-8.

1. What number best describes your pain on average in the past week:

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

2. What number best describes how, during the past week, pain has interfered with your enjoyment of life?

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

3. What number best describes how, during the past week, pain has interfered with your general activity?

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

Recommendations from Multidiscipline Expert Consensus Meeting

- Imaging may guide therapy but does not correlate with pain pattern or severity
- Medical management should be first line
- Smoking & alcohol cessation
- Use invasive therapies sparingly
  - Endoscopic Rx only when target α symptoms
  - Avoid resection & drainage if candidate for TPIAT

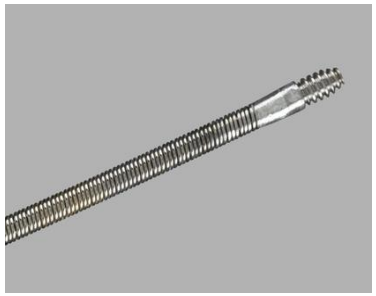
Pancreatic Endotherapy for Chronic Pancreatitis

- Duct disruptions, pancreatic ascites
- Pseudocyst drainage
- Treatment of chronic pain: strictures & stones
  - MPD obstruction*:
    - Due to strictures in 47%
    - Due to stones in 18%
    - Due to combination stricture and stones in 32%
  - MPD obstruction can cause pain although pain is multifactorial & treatment of obstruction only relieves pain in about 80%

* Rosch Endoscopy 2002

Endotherapy for MPD Strictures

- Dominant strictures may lead to pain or superimposed AP on CP
- Strictures are tight, need dilation plus stenting, dilation alone not recommended
  - Graduated dilators or balloons
  - Soehendra stent retrieval device if refractory
- Pancreatic sphincterotomy
  - No need for concomitant BES*



*Kim Endoscopy 1998

Pancreatic Stricture Endotherapy

- Large caliber (8.5 or 10 F) vs. multiple small stents, no comparative trials
  - Single small caliber stents: higher risk for hospital admission for pain (likely due to early occlusion)*
  - Multiple small caliber favored by some experts- ? less obstruction of side branches**
- Ideal duration of stenting unknown
  - Stent change q 2-4 months or leave in place if asymptomatic for up to 1-2 yr
  - q 2 months until stricture gone

*Sauer Pancreas 2009 ** Costamagna Endoscopy 2006

Pancreatic Endotherapy for MPD Stones

- MPD stones <5mm may be removed successfully w/o ESWL
- MPD stones>5 mm require ESWL or intra-ductal lithotripsy
- ESWL successful fragmentation: 85-93%
  - Average # of ESWL sessions: 1.5
  - Lower success rates reported in US - ? Due to low volume centers vs. different stones

Endotherapy vs. Surgery

- RCT surg vs endotherapy in 72 pts*
  - Initial pain relief similar
  - 5 yr f/u: Pain relief 86% w. surgery vs 61% endo RX
  - Problems: no ESWL in this study, efficacy non-blind

- RCT surg vs endotherapy in 39 pts**
  - 2 yr f/u: Pain relief 75% surgery vs 32% endotherapy
  - 5 yr f/u: Pain relief 80% surgery vs. 30%***
  - Problems: small study with low technical success w endotherapy (53%)

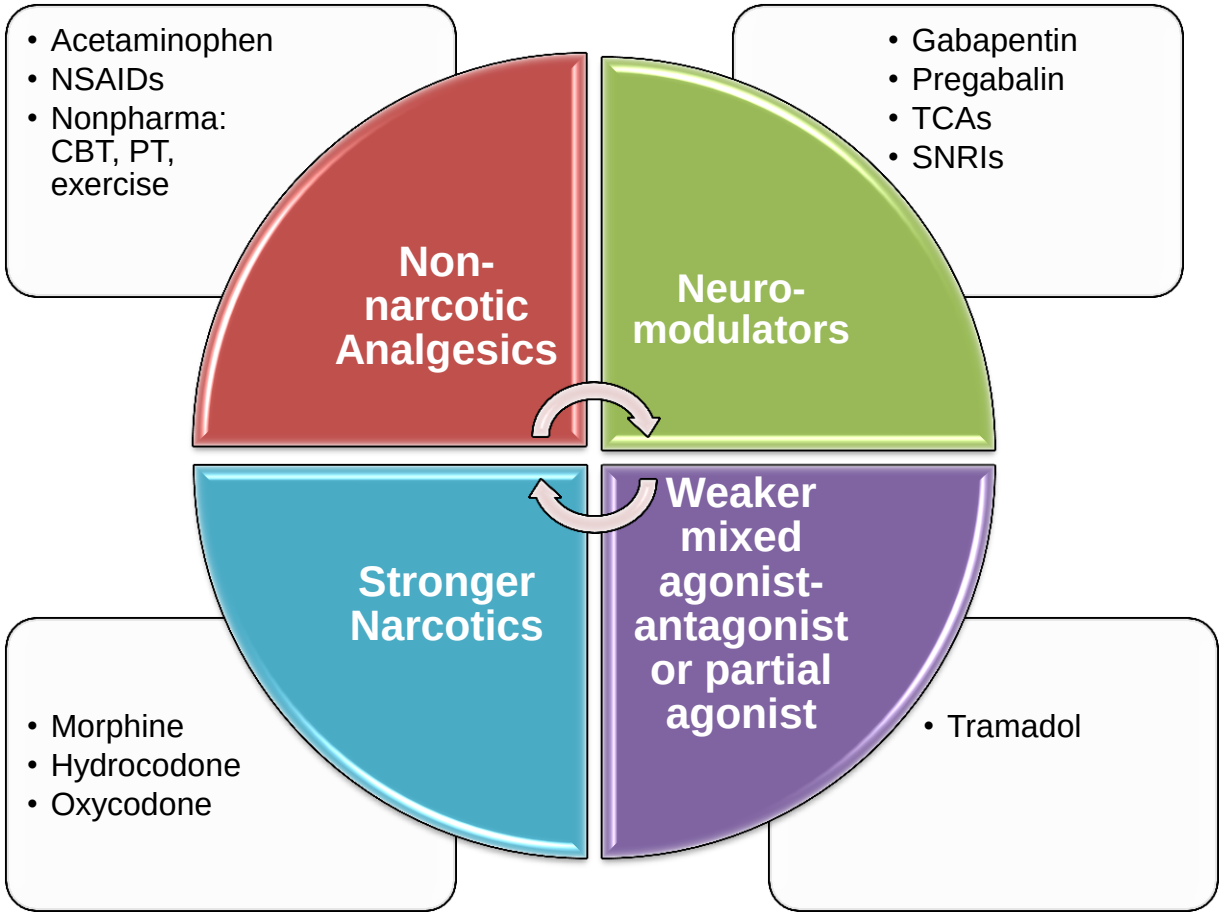
*Dite Endoscopy 2003 **Cahen NEJM 2007 ***Cahen Gastro 2011

Endotherapy vs. Surgery

- Complications of endotherapy lower:
  - Morbidity: Surgery 6-30% vs. endo RX 3-9%
    - Some complications require repeat surgery
  - Mortality: Surgery 0-4% vs. endo <1%
- Endotherapy doesn't preclude subsequent surgery if it fails
  - Subsequent surgery required in 1-26%
  - Pain relief w surgery after failed endo RX only 50%*

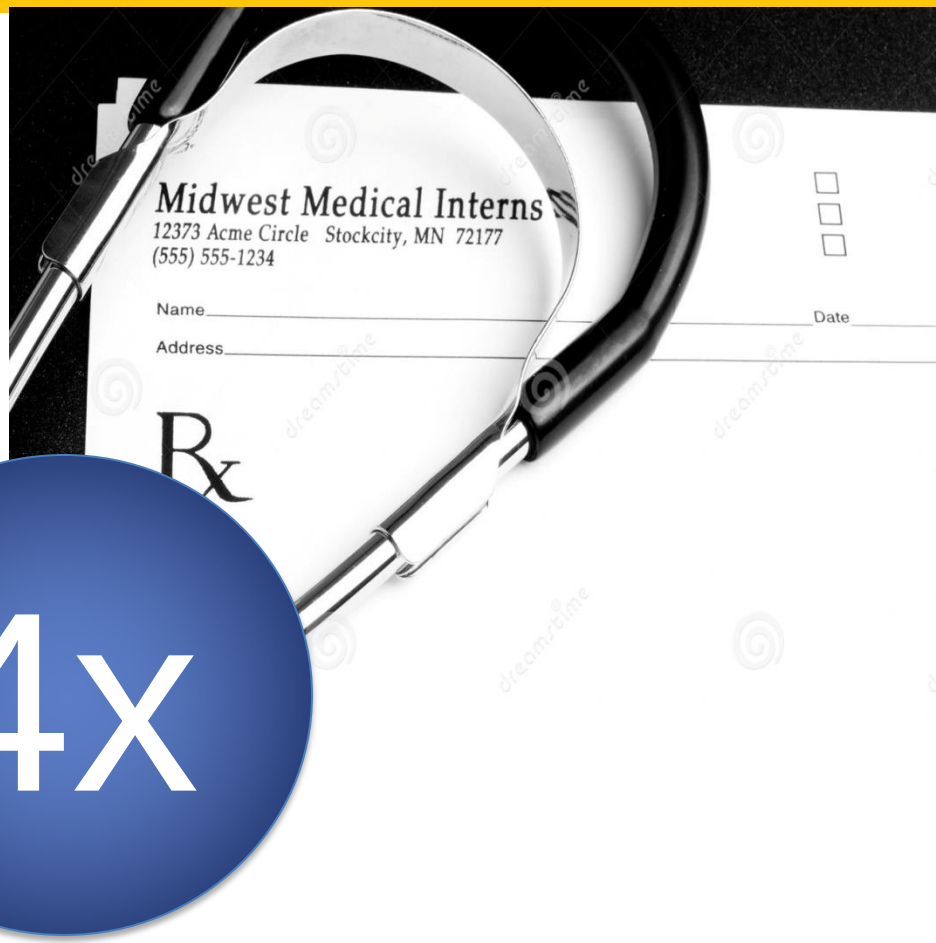
*Clarke Clin Gastro Hep 2012

Medical Therapy for Painful CP



Narcotic Prescriptions

Since 1999, prescription opioid sales have **quadrupuled** in the United States



Narcotic Use in Painful CP

Drug	# Prescriptions	Prescription Cost
Hydrocodone/Acetaminophen	171,121	6,524,330
Oxycodone/Acetaminophen	76,199	3,970,182
Oxycodone	25,097	2,629,763
Promethazine	20,846	184,599
Codeine/Acetaminophen	8,808	89,625
Acetyl Salicylic Acid/Oxycodone	964	30,971
Meperidine	1,139	21,709

More than 300,000 Rxs in 2004→ $13, 451, 179

The Effect

Prescription Opioid Overdoses Claim more than 15,000 Lives Annually

46 PER DAY!!!

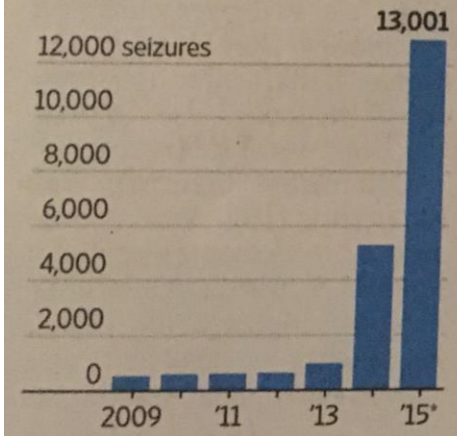
Front page of Wall Street Journal 06/23/2016

CHINA'S ROLE IN U.S. OPIOID CRISIS

Global network delivers chemicals used to make fentanyl, up to 50 times as powerful as heroin

Deadly Drug

Fentanyl seizures reported by forensic labs in the U.S.



*2015 subject to further updates as labs continue to process and report evidence.
Source: Drug Enforcement Administration

By Jeanne Whalen and Brian Spegele

Last spring, Chinese customs agents seized 70 kilograms of the narcotics fentanyl and acetyl fentanyl hidden in a cargo container bound for Mexico.

The synthetic opium-like drugs were so potent that six of the agents became ill after handling them. One fell into a coma.

The cargo had traveled through five freight forwarders before reaching customs, obscuring its exact origins, according to an internal U.S. Drug Enforcement Administration intelligence briefing reviewed by The Wall Street Journal.

One thing is clear: The shipment and a host of others, detailed in the DEA briefing, court documents and interviews with government officials in multiple countries, are part of a vast drug-distribution network beginning in China by trading not only in finished fentanyl but related products subject to little or no regulation in China or internationally. These include some copies of fentanyl known as analogs, as well as the chemical ingredients and pill presses used to produce the drug, according to the documents and interviews.

The China Food and Drug Administration declined to comment on the sale and production of fentanyl and referred questions to the Ministry of Public Security, which didn't respond.

Fentanyl and its analogs are killing Americans at an alarming rate, marking a deadly new chapter in the nation's struggle with opioid addiction. Fentanyl is up to 50 times as potent as heroin but easier and cheaper to produce, made from chemicals instead of fields of poppies. Legal versions of fentanyl have been used as painkillers or anesthetics since the 1960

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Early Release / Vol. 65
March 15, 2016

CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

12 Key Recommendations

- Opioids are not first-line Rx
- Establish Goals for Pain and Function
- Discuss Risks and Benefits
- Use Immediate-Release Opioids initially
- Use Lowest Effective Dose
- Prescribe short duration for acute pain

CDC Recommendations continued

- Evaluate Benefits and Harms Frequently
- Use Strategies to Mitigate Risks
- Review PDMP Data
- Use Urine Drug Testing
- Avoid Concurrent Opioid and Benzos
- Offer Treatment for Opioid Use Disorder

Known Risk Factors for Misuse or Harm

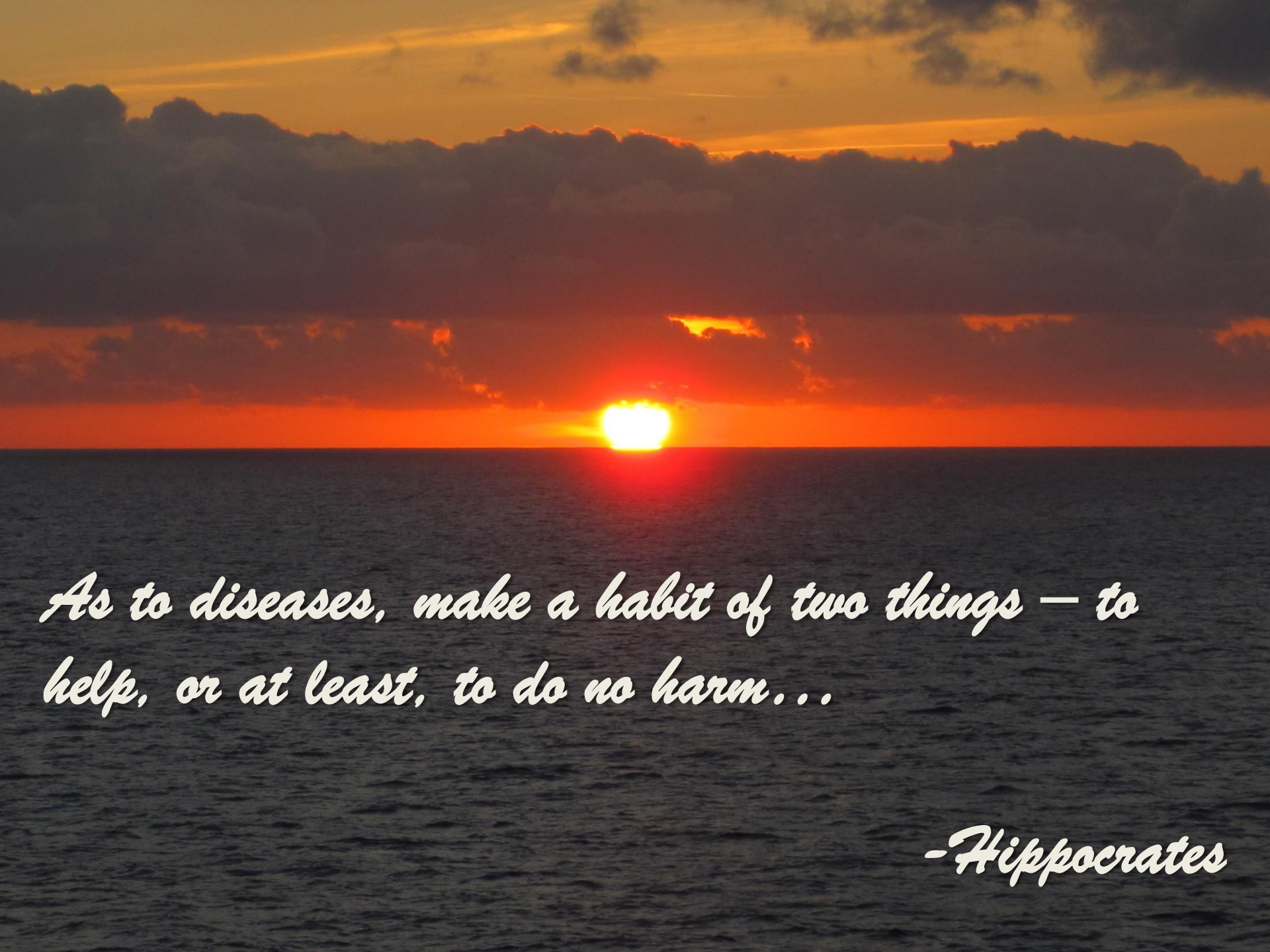
- Illegal Drug Use
- Prescription Drug Use for nonmedical reasons
- History of Substance Use Disorder
- Mental Health Conditions
- Sleep-disordered Breathing
- Concurrent Benzodiazepine Use

Resources from CDC

- Summary of recommendations
- Checklist for prescribing opioids for pain
- Calculating daily dose inc. MME conversion
- PDMP Fact Sheet
- Assessing benefits and harms info sheet
- Non-opioid treatment recommendations

Summary

- Pain in chronic pancreatitis is complex → Measure it and Understand it!
- Endoscopic therapy has a limited but useful role
- Medical therapy should start with and include non-narcotic treatments


As to diseases, make a habit of two things – to help, or at least, to do no harm...
-Hippocrates