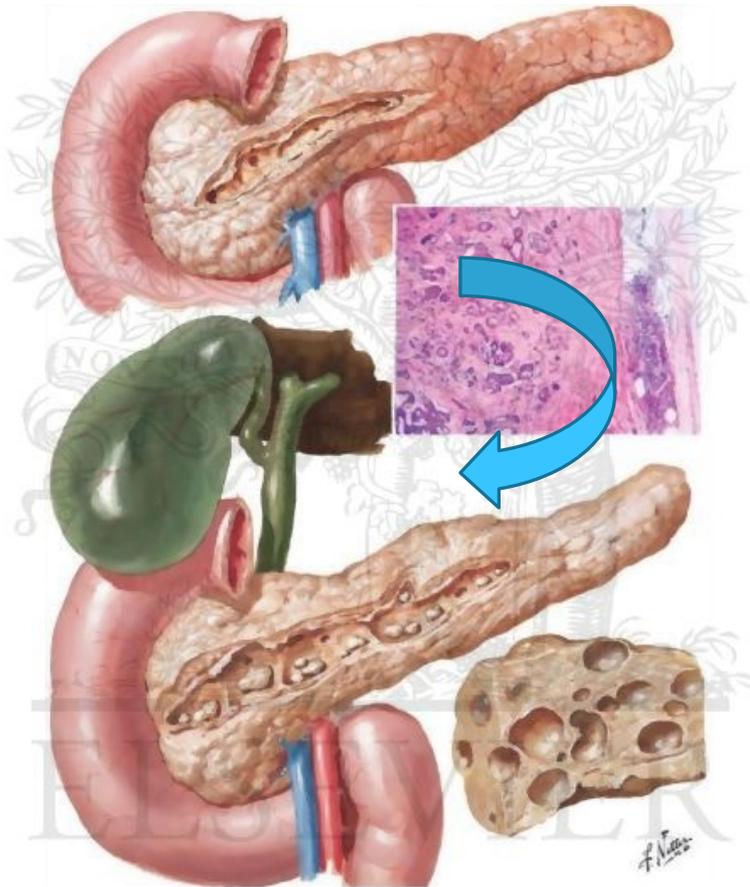


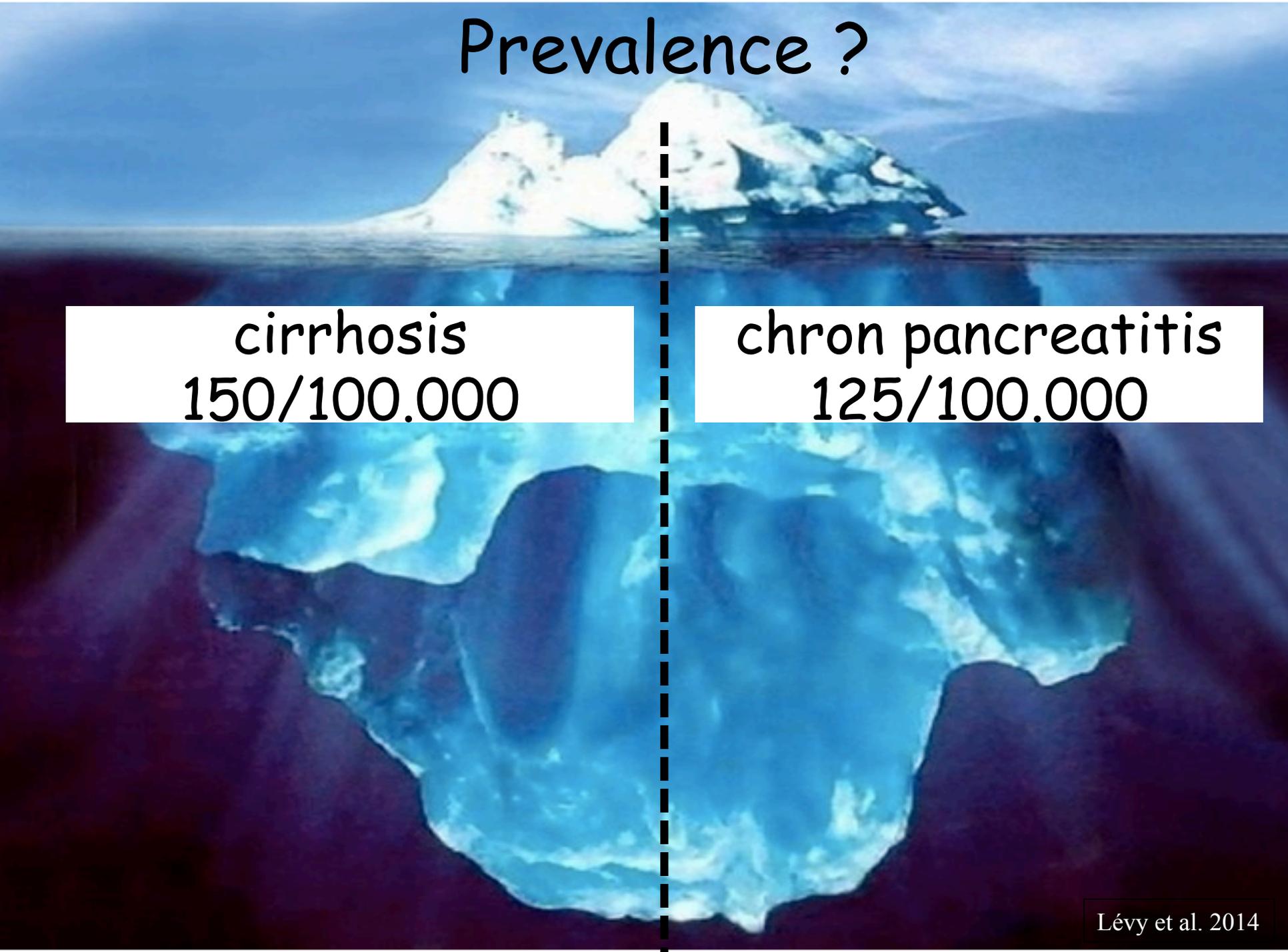
Pain treatment in chronic pancreatitis



Asbjørn Mohr Drewes
Aalborg University Hospital
Denmark



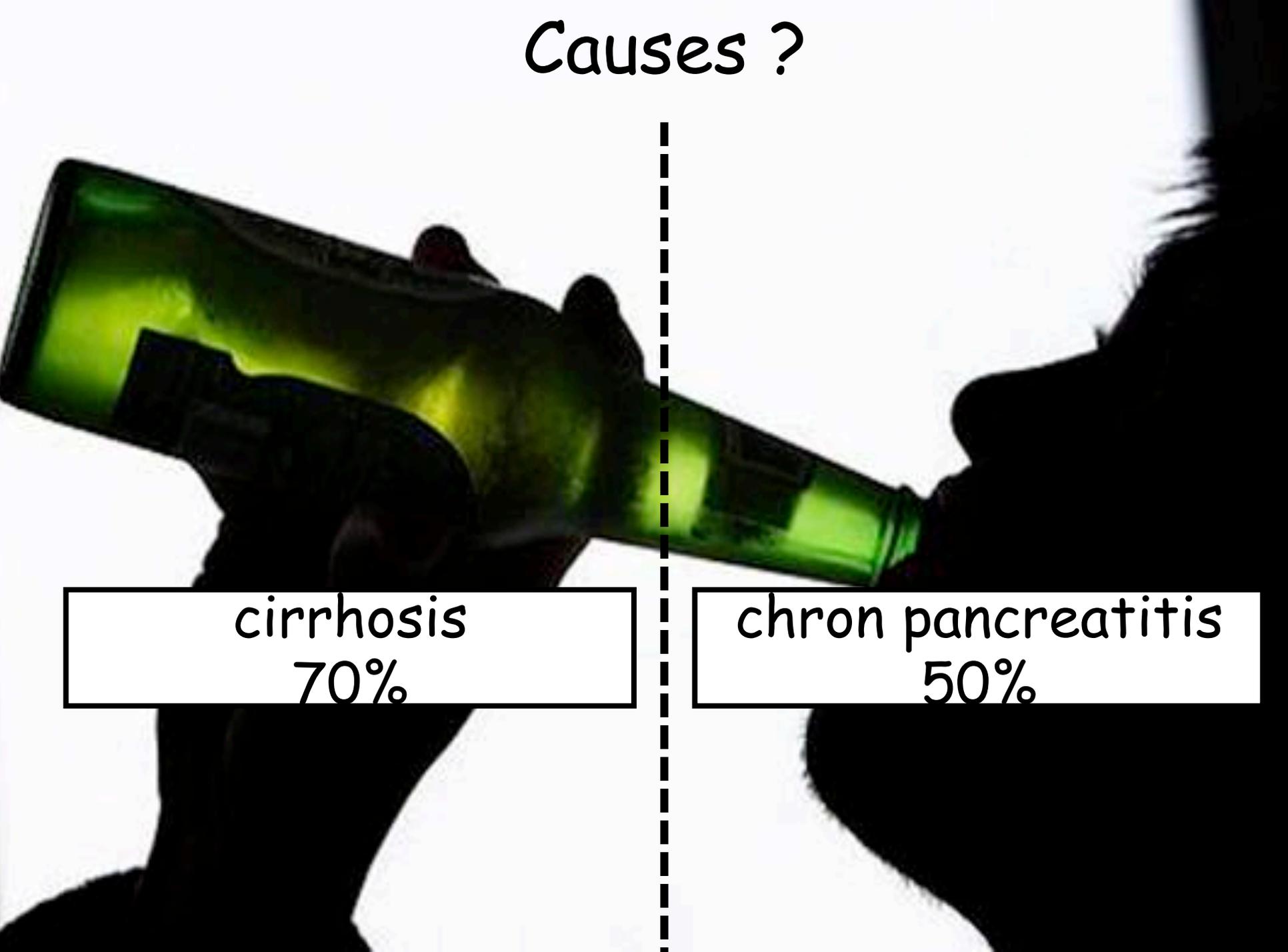
Prevalence ?

An iceberg floating in the ocean. The tip of the iceberg is above the water surface, while the much larger part of the iceberg is submerged below the surface. A vertical dashed line separates the two parts. The background is a blue sky and ocean.

cirrhosis
150/100.000

chron pancreatitis
125/100.000

Causes ?

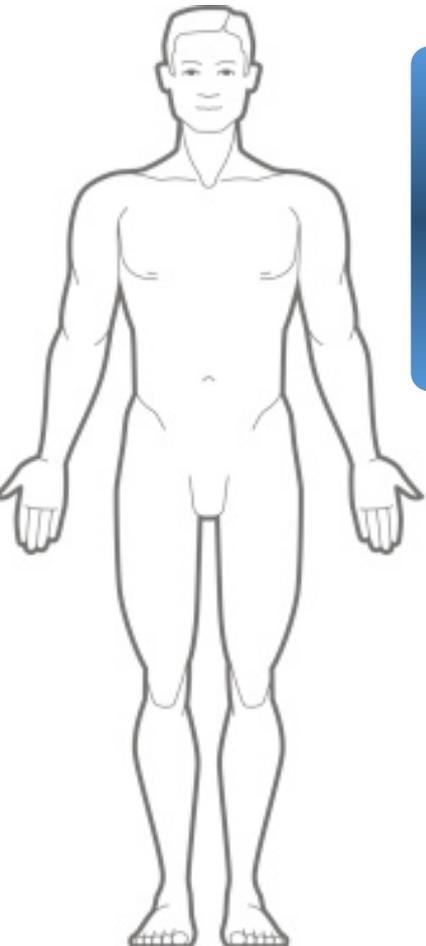


cirrhosis
70%

chron pancreatitis
50%

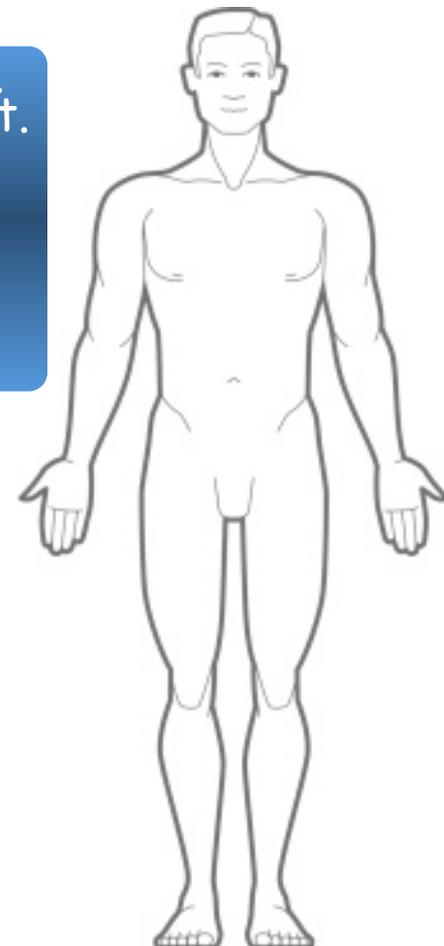
Complications

cirrhosis



encephalopathy
cardiomyopathy
hepatopulmonary
portal hypertension
hepato-renal
neuropathy
HCC
etc.

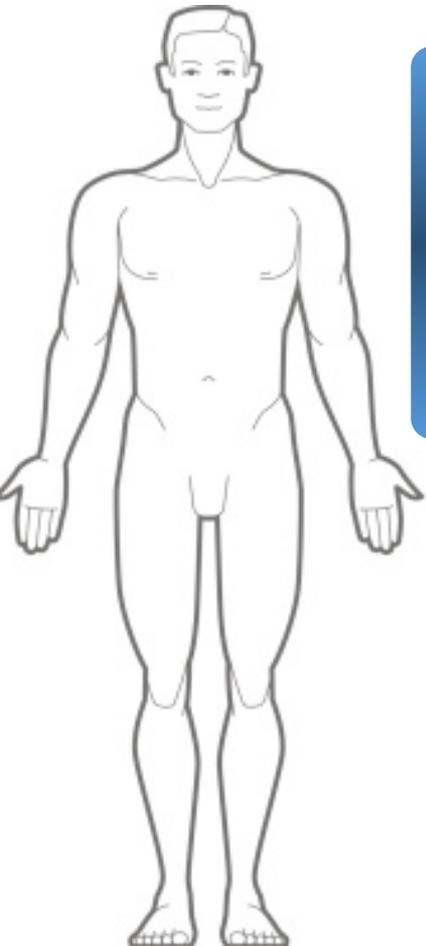
chron pancreatitis



exocrine dysfunct.
endocrine dysfunct.
pain
local (cysts etc.)
venous thrombosis
malnutrition
c. pancreatis
etc.

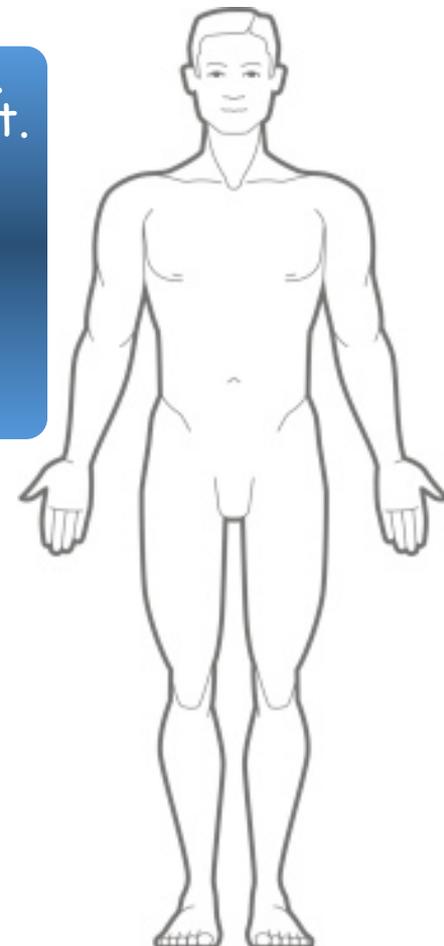
Complications

cirrhosis



encephalopathy
cardiomyopathy
hepatopulmonary
portal hypertension
hepato-renal
neuropathy
HCC
etc.

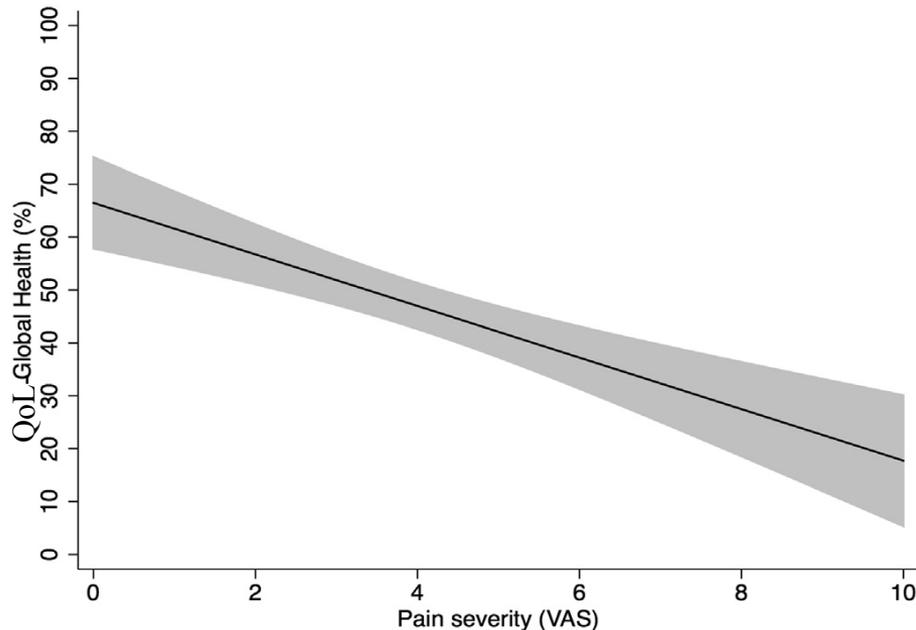
chron pancreatitis



exocrine dysfunct.
endocrine dysfunct.
pain
local (cysts etc.)
venous thrombosis
malnutrition
c. pancreatis
etc.

Epidemiology of complications in chronic pancreatitis

1. Pain is foremost problem in patients with chronic pancreatitis
2. Pain exacerbations and intensity are the most frequent causes for hospitalizations in patients with chronic pancreatitis
3. Pain is the strongest predictor of poor QoL among complications to chronic pancreatitis



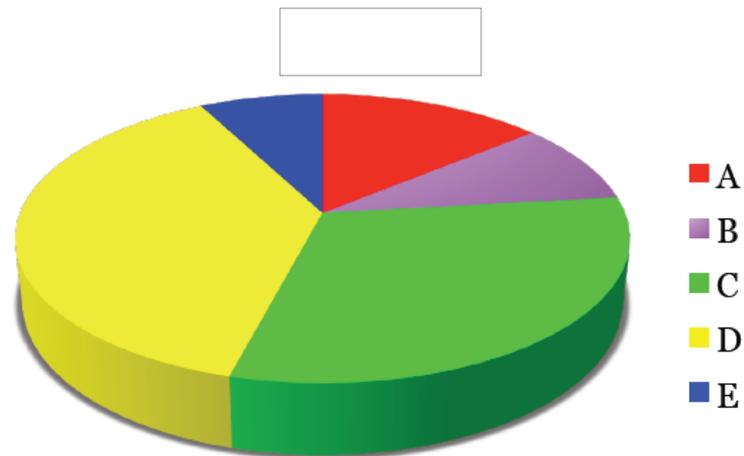
Mulladi et al. GUT 2011
Olesen et al. Pancreatol 2014
Olesen et al. Submitted 2015

Epidemiology of pain in chronic pancreatitis

Pain Patterns: NAPS2 study (n=540)

Table 1 Pain patterns

Pattern	Definition
A	Episodes of mild to moderate pain, usually controlled by medication
B	Constant mild to 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



Pain in “burnt-out” pancreas: controversy resolved?

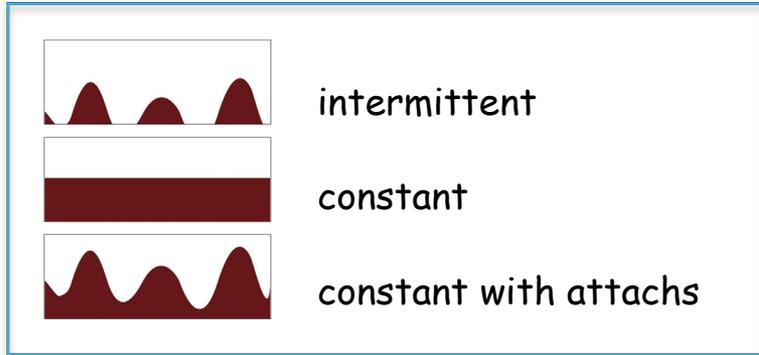
Old studies

- Majority of 245 patients with alcoholic pancreatitis achieved pain relief after a median time of 10 years, coinciding with onset of exocrine and endocrine pancreatic insufficiency¹
- Majority of 335 patients with painful CP followed for >10 years^{2,3}
 - Did not experience spontaneous pain relief with progressive pancreatic insufficiency.
 - Majority of patients with both alcoholic and non-alcoholic CP continued to have pain at a mean follow-up of 10 years
- Duration of the disease did not correlate with either the frequency (intermittent vs constant) or the severity of the pain⁴

New studies

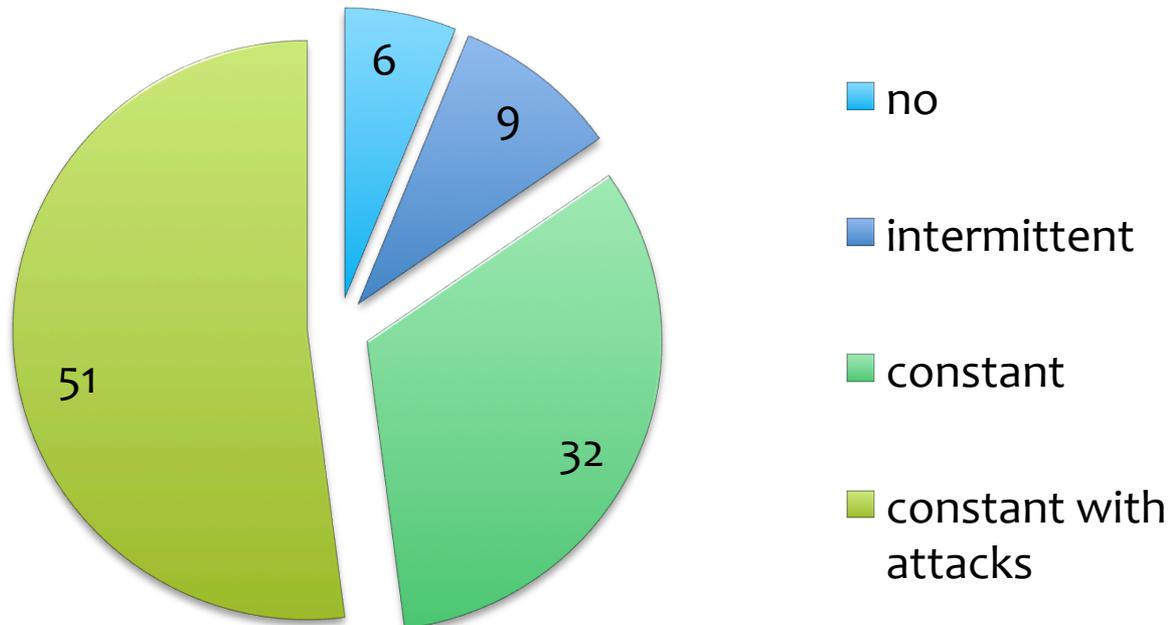
1. Amman et al *Gastroenterology* 1984
2. Lankisch et al *Digestion* 1993
3. Lankisch et al *Pancreas* 1995

Epidemiology of pancreatitis pain in Northern Europe

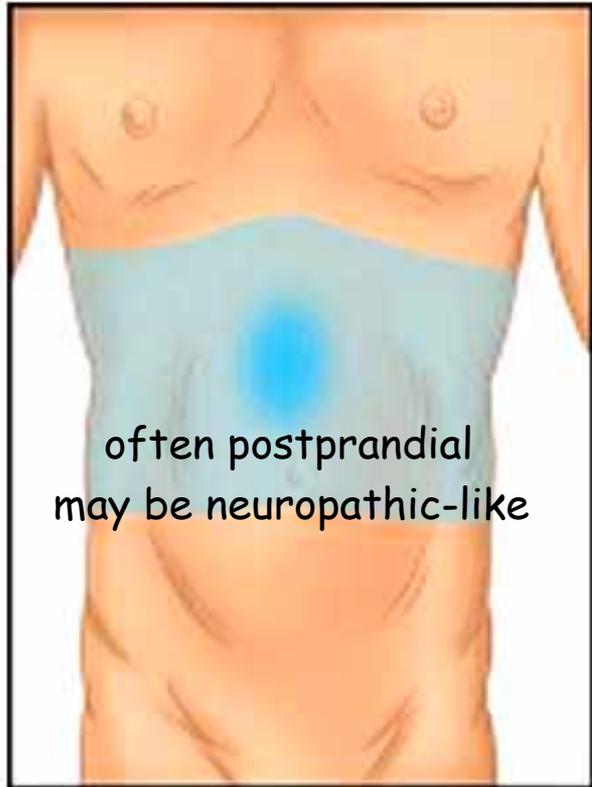


N=106 from Holland and Denmark

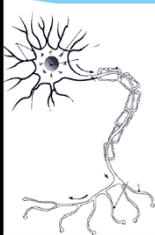
Pain pattern (%)



Characteristics of pain

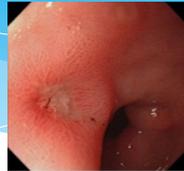


Pain mechanisms - the "Aalborg classification"



Wiring problem

1. peripheral sensitization
2. neuropathy
3. CNS changes



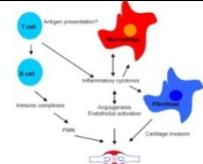
Extrapancreatic complications



Local: inflammatory mass, pseudocysts etc.



Plumbing problem: duct stenosis and stones



Inflammation ~ e.g. cytokines

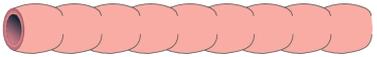


Tissue hypertension

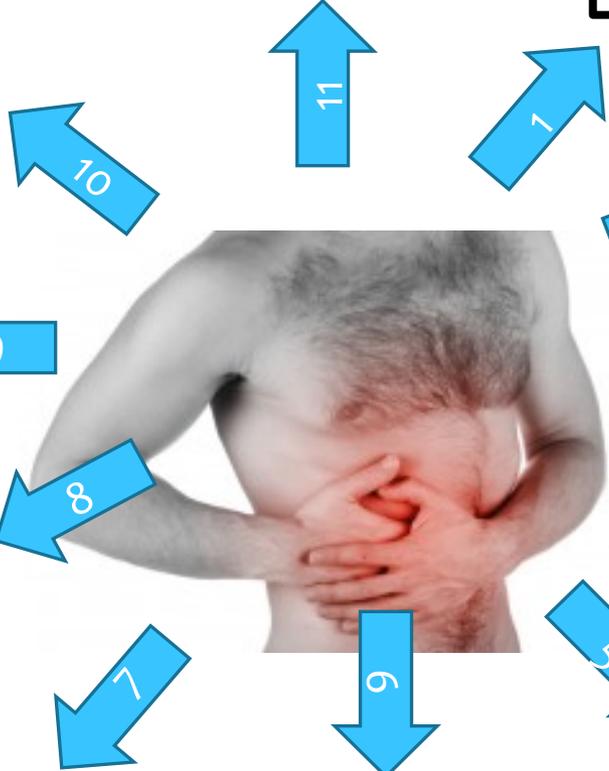
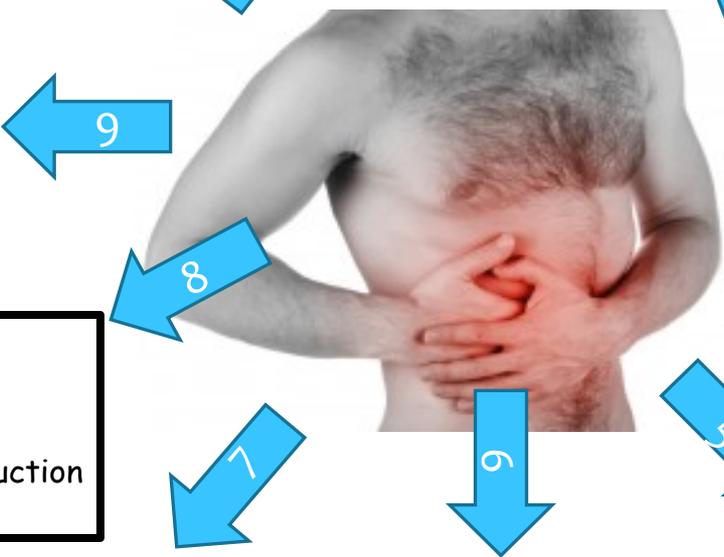
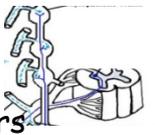
Drewes et al. Pancreatodedia 2015



Surgical/endoscopic complications

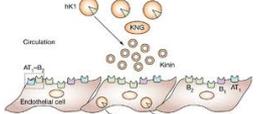


Drug induced bowel dysfunction

Others

1. increased sympathetic activity
2. enteric nervous system changes
3. mesenteric ischaemia
4. opioid induced hyperalgesia
5. other concomitant diseases
6. smoking/alcohol, nutrition



bacterial overgrowth
Lack of hormones
~ diabetic neuropathy



Increased CCK production
(stimulate pancreas & brain)

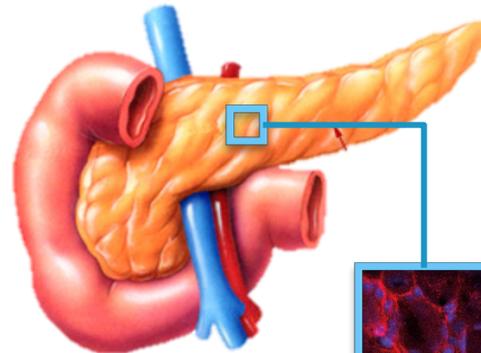
Plumbing vs. wiring ?

Endoscopy
or surgery

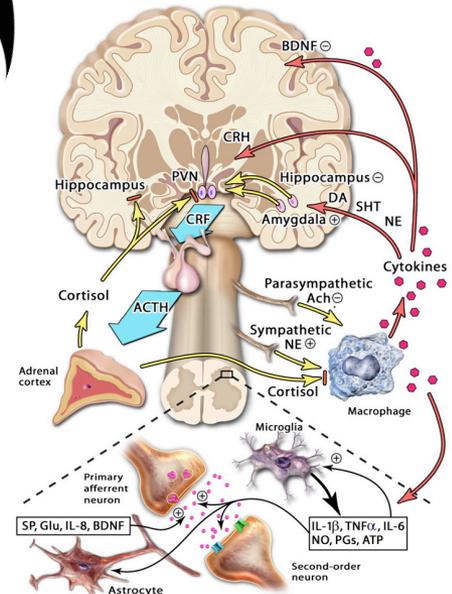
Medical
treatment



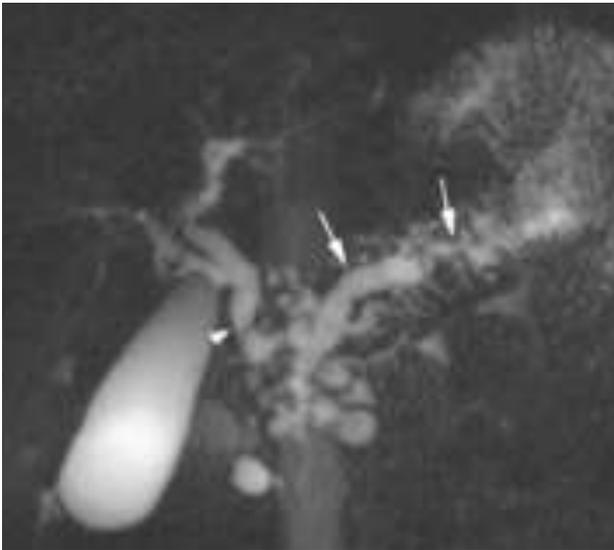
plumbing



wiring



The "usual suspects": Strictures, stones and duct dilatation - what to do?



→ decompression with endoscopy or surgery

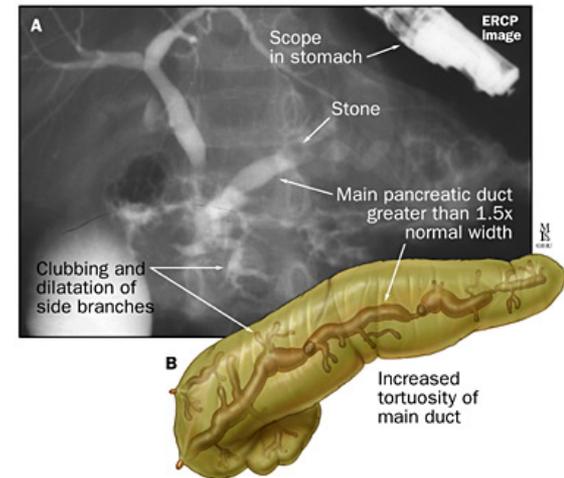
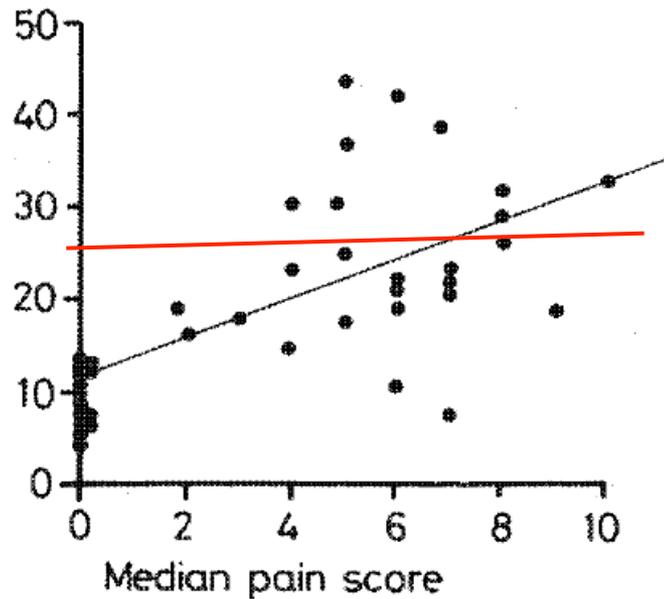
Drawbacks with existing studies



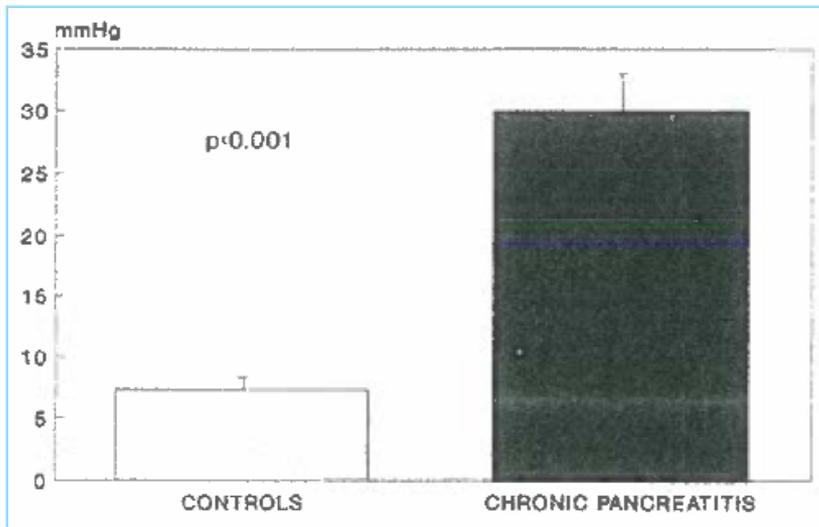
1. Studies are not blinded, historic data as controls
2. Insufficient follow-up
3. No physiological evidence for effect!!!

Tissue pressure and pain?

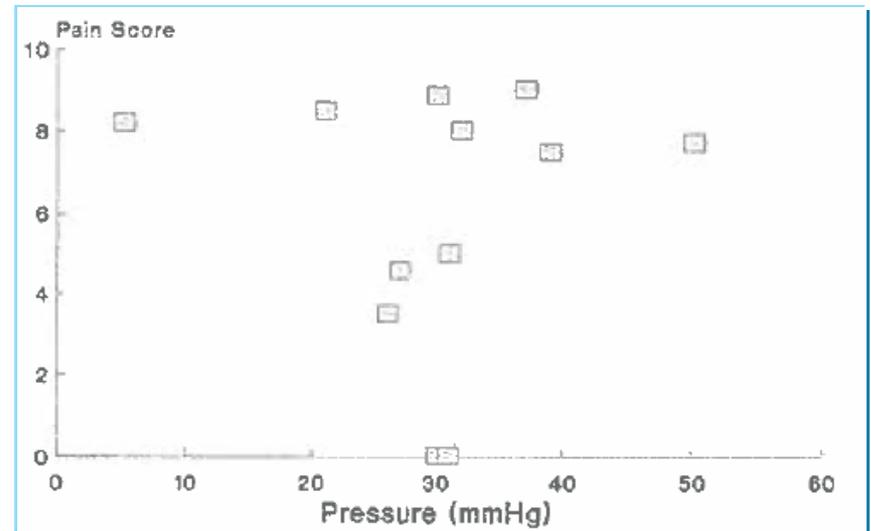
Pressure
mmHg



Tissue pressure and pain?

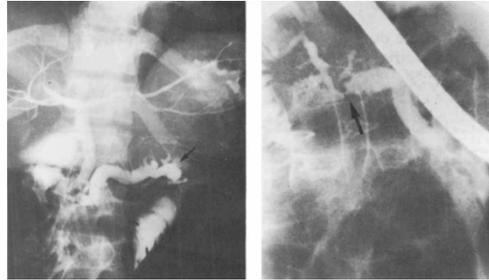


Pancreatic parenchymal pressures increased
- and correlated to ERC findings

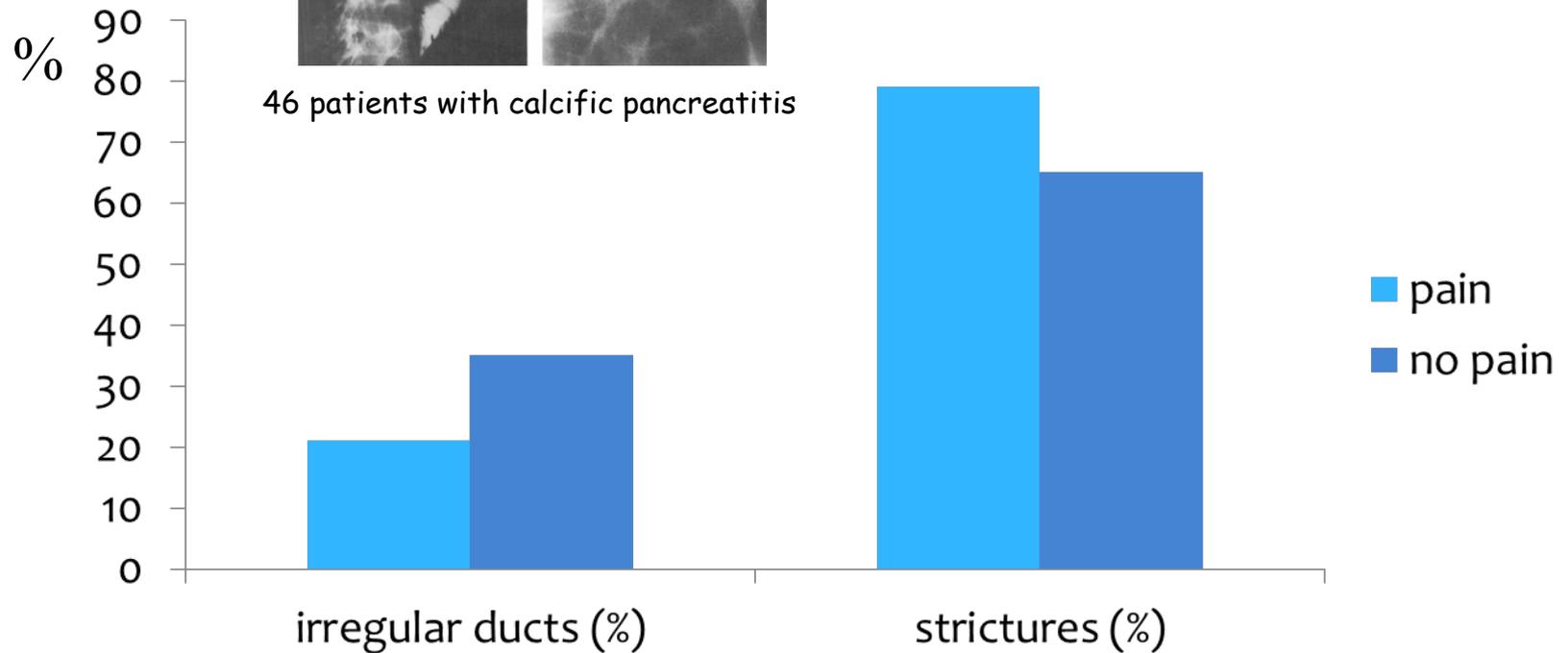


No correlation between parenchymal pressure and pain

Morphology and pain?

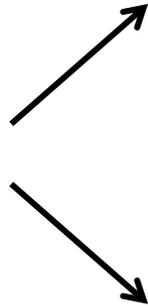


46 patients with calcific pancreatitis

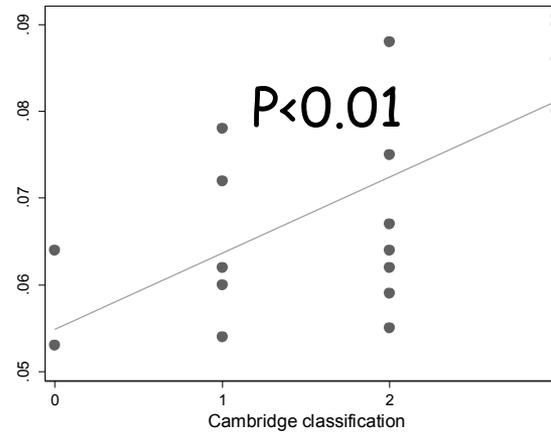


Pathophysiological changes vs. exocrine/endocrine function

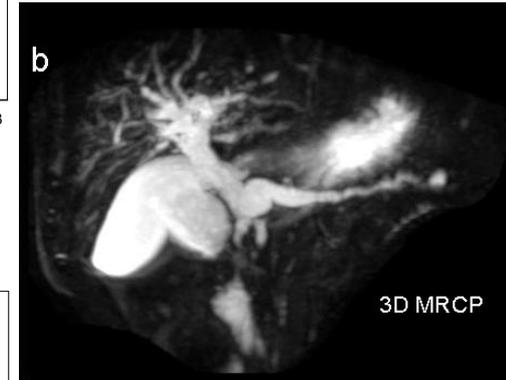
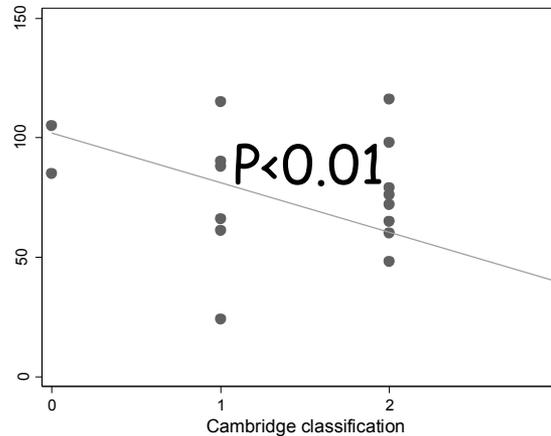
Fibrosis (DWI)
Cambridge class.
Atrophy
Etc.



Diabetes regulation

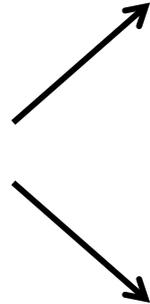


Vitamin D

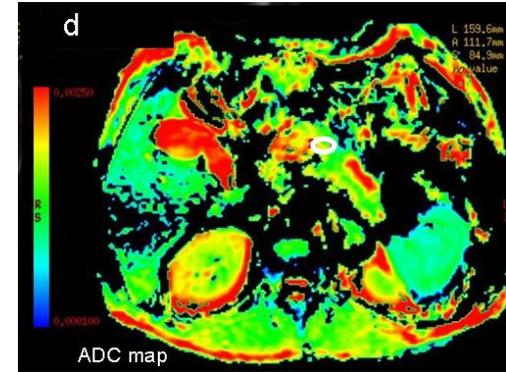
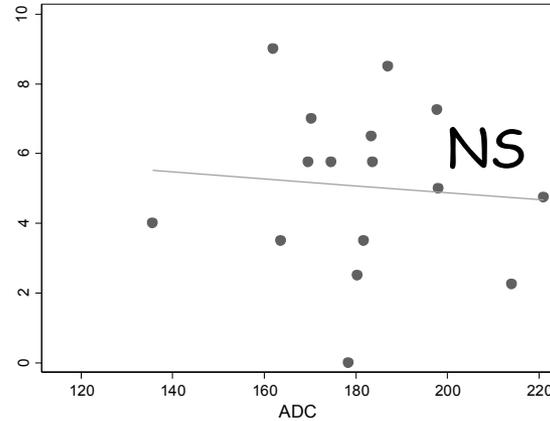


NO correlations to pain

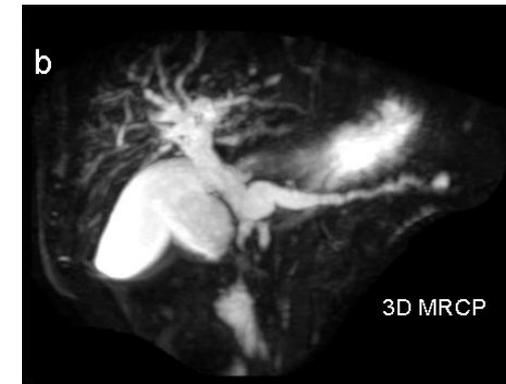
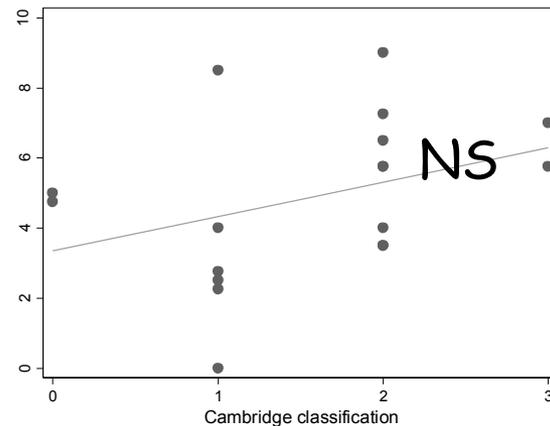
Fibrosis (DWI)
Cambridge class
Atrophy
Etc.



Microstructure



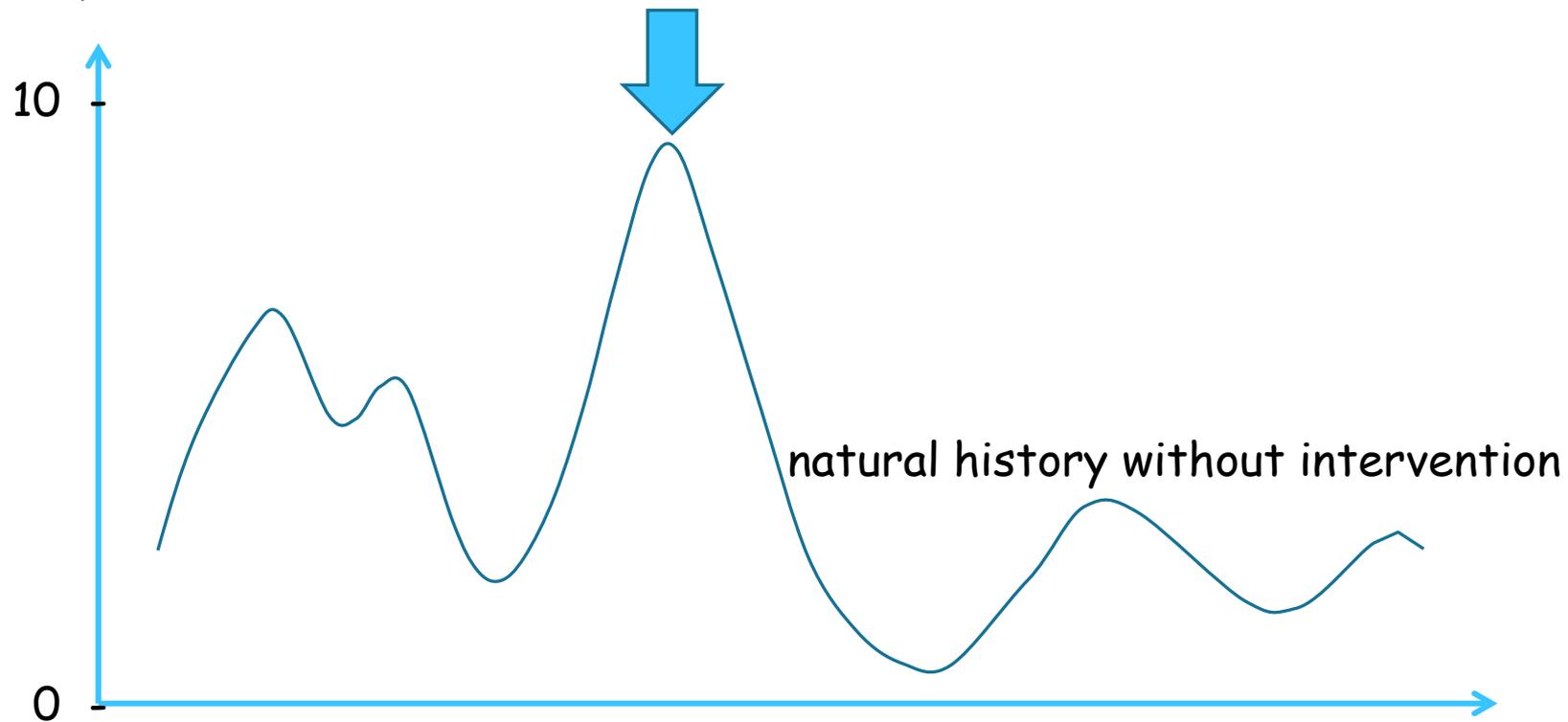
Macrostructure



Selection bias of treatment

Pain intensity (0-10)

visit & treatment (when patients are desperate)

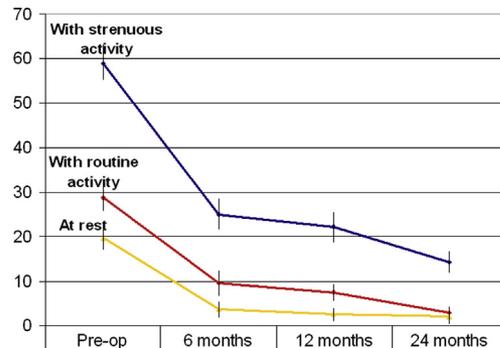


Sham controlled studies - what to learn from ortopedics ?

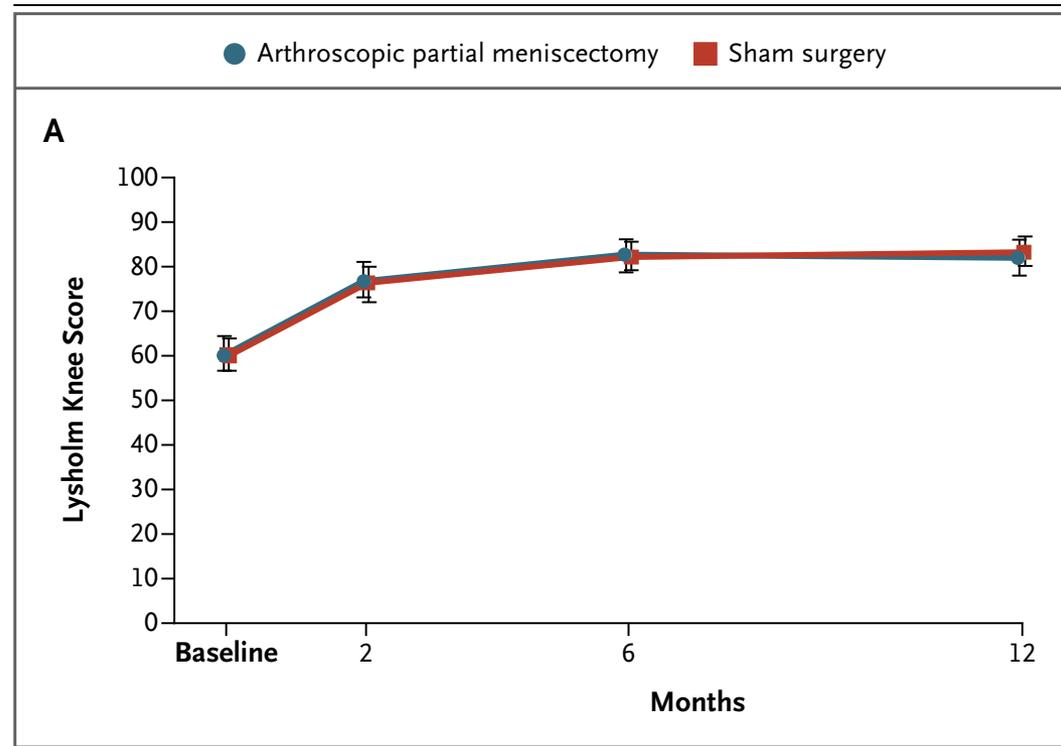


Medial meniscus tear

Pain Scale (0-100)

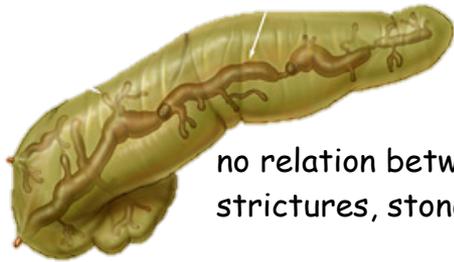


With strenuous activity	59	25	22	14
With routine activity	29	10	7	3
At rest	20	4	3	2



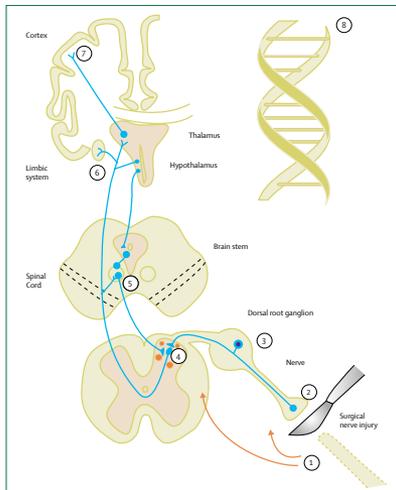
Sihvonen et al. NEJM 2013
Brophy. J Bone Joint Surg Am 2014

Neurogenic pain and surgery

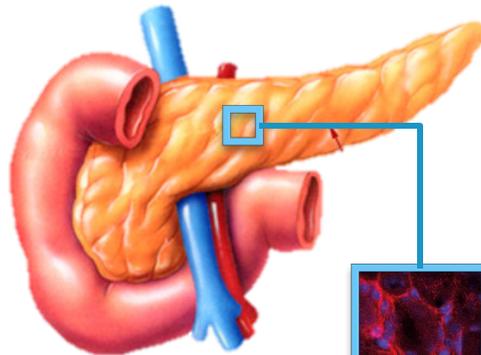


no relation between pain vs.
strictures, stones or pressure

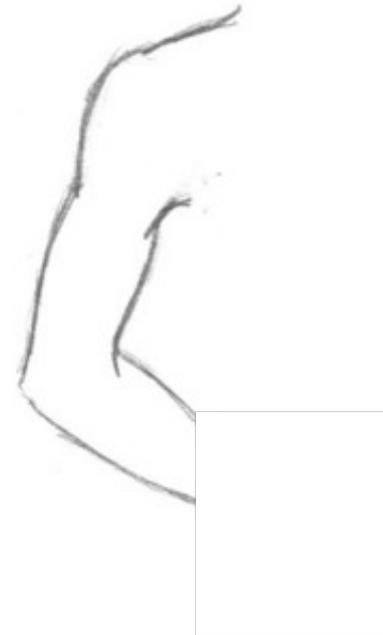
plumbing



Kehlet et al. Lancet 2006



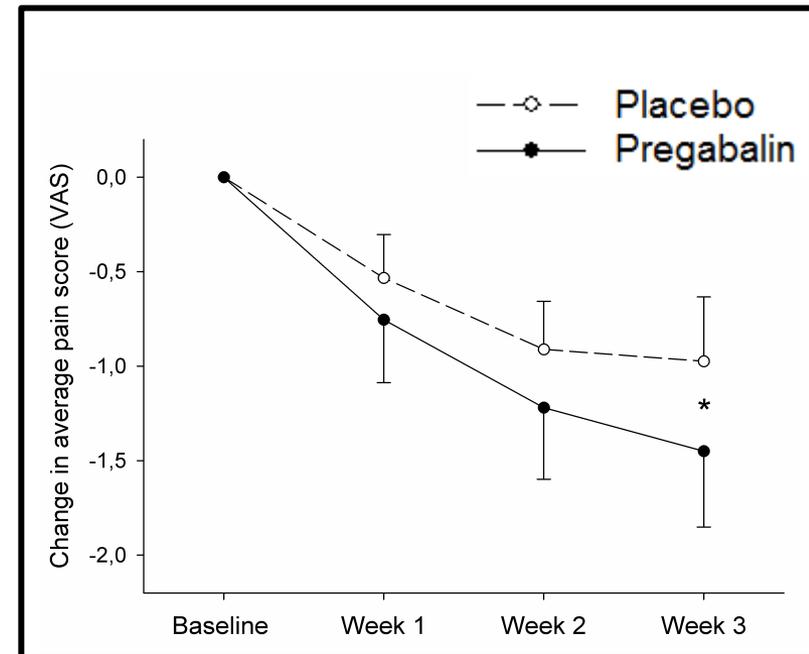
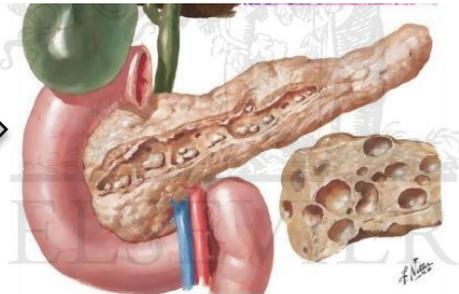
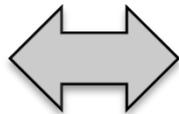
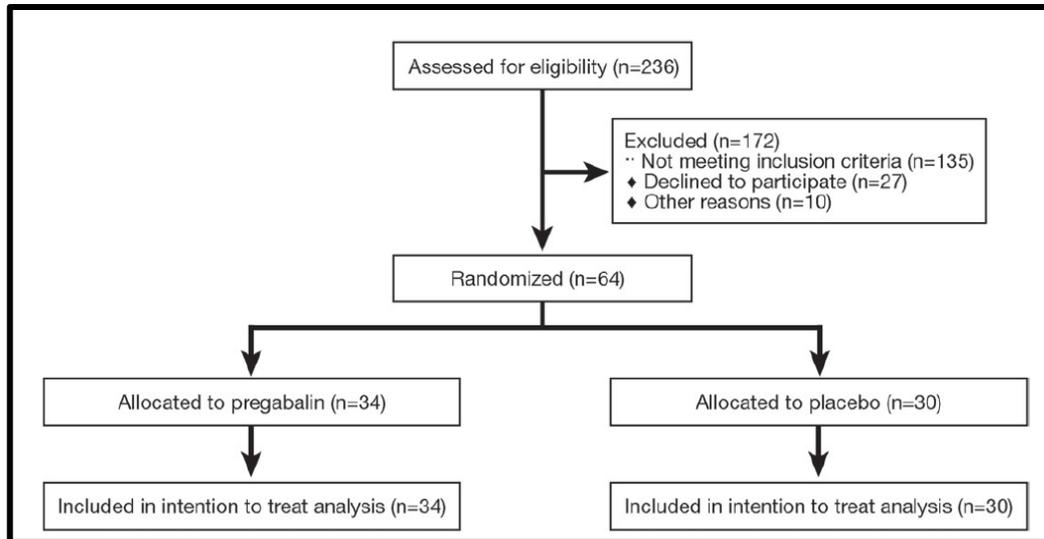
wiring



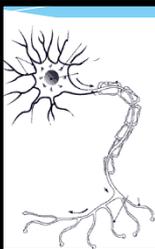
Neurogenic pain in chronic pancreatitis

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Pregabalin in chronic pancreatitis

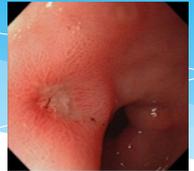


Remember - the extrapancreatic causes for pain



Wiring problem

1. peripheral sensitization
2. neuropathy
3. CNS changes



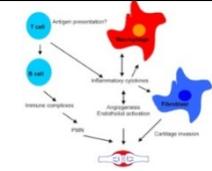
Extrapancreatic complications



Local: inflammatory mass, pseudocysts etc.



Plumbing problem: duct stenosis and stones



Inflammation ~ e.g. cytokines

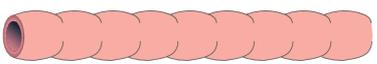


Tissue hypertension

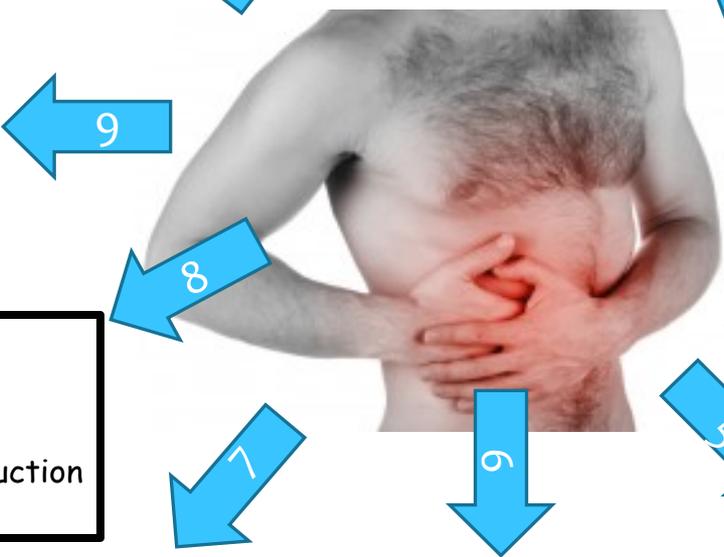
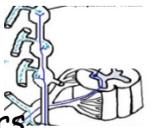
Drewes et al. Pancreatodedia 2015



Surgical/endoscopic complications

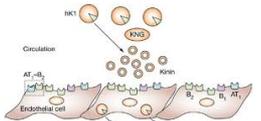


Drug induced bowel dysfunction

Others

1. increased sympathetic activity
2. enteric nervous system changes
3. mesenteric ischaemia
4. opioid induced hyperalgesia
5. other concomitant diseases
6. smoking/alcohol, nutrition



bacterial overgrowth

Lack of hormones

~ diabetic neuropathy



Increased CCK production

(stimulate pancreas & brain)

Postprandial pain - the patient cannot eat



Pain due to duodenal obstructions - the patient cannot eat

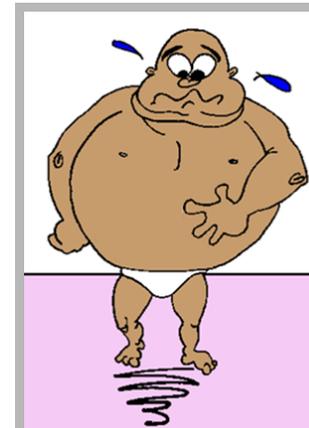
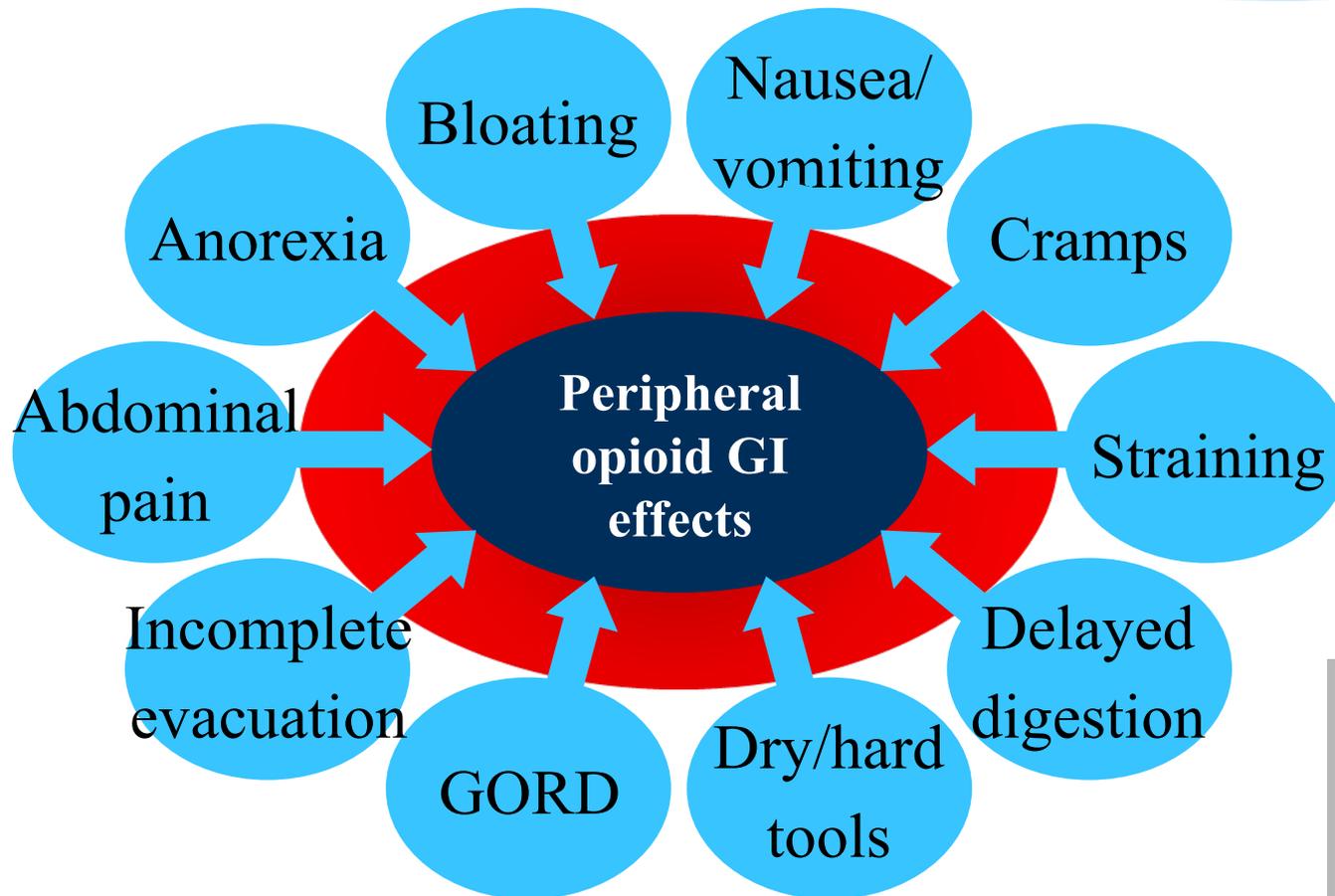


Pain treatment with opioids

- anorexia and the patient cannot eat



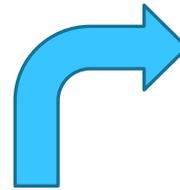
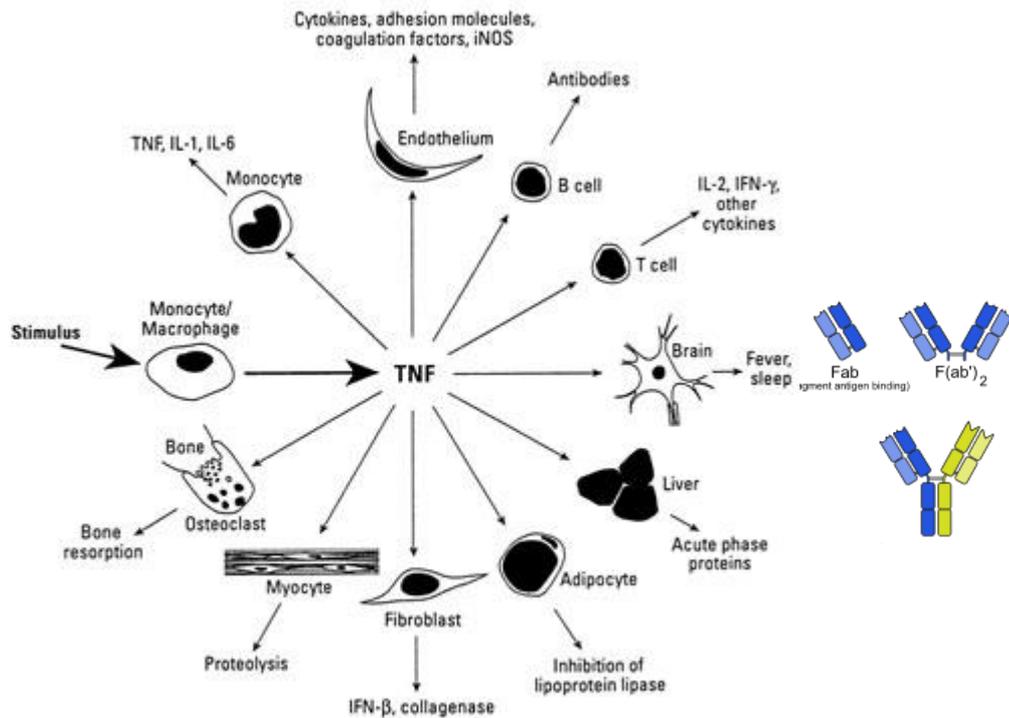
Opioid induced bowel dysfunction - the patient cannot eat



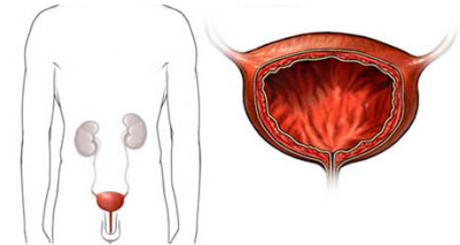
Alternative and supplementary treatments



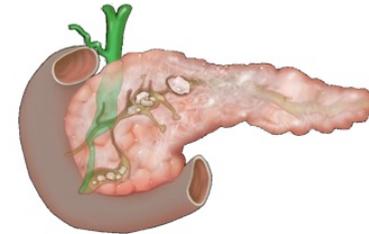
Biological therapies



Osteoarthritis/low back pain



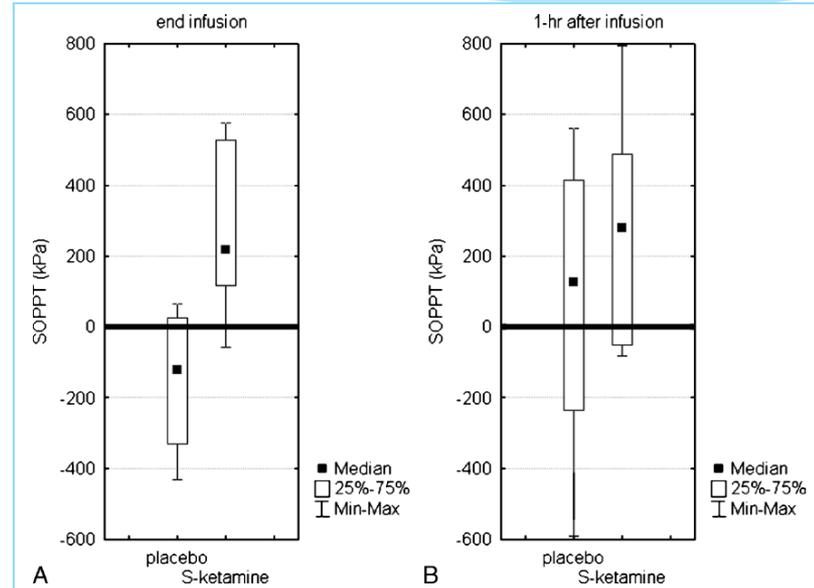
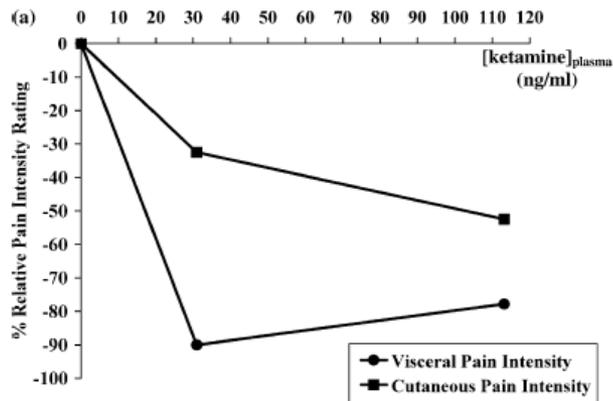
interstitial cystitis/pelvic pain



chronic pancreatitis ?

Antibodies against tumor necrosis factor - "Tanezumap"

Ketamine - resetting the pain system



Patients with chronic pancreatitis had an effect of S-ketamine on somatic pain pressures

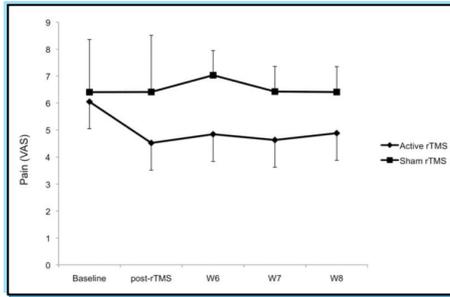
Ketamine attenuated unpleasantness to stimulation of oesophagus and skin

Strigo et al. Pain 2005

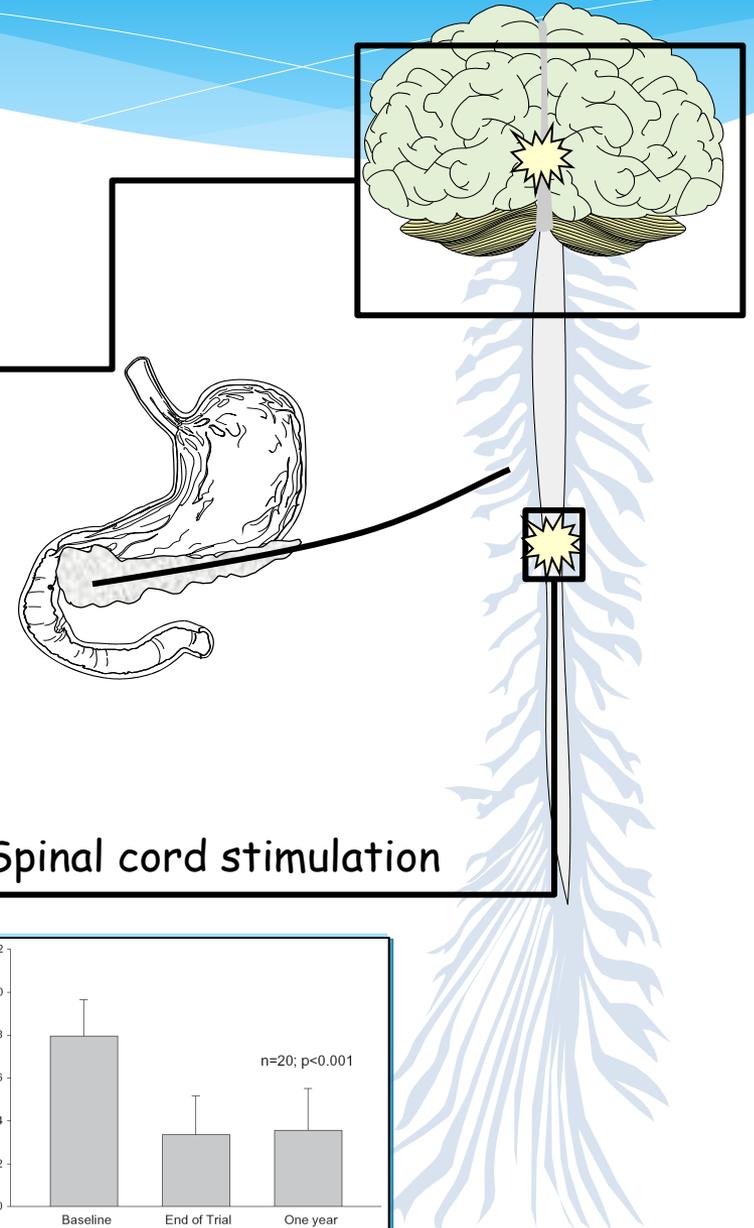
Bouwense et al. Reg Anesth Pain Med 2011

Juel et al. BMJ Open 2015

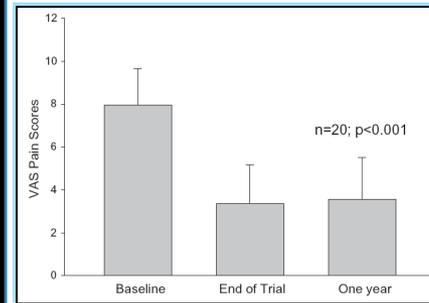
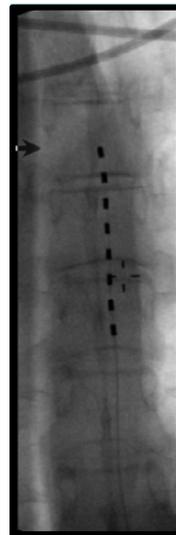
CNS stimulation and pancreatic pain



Transcranial magnetic stimulation

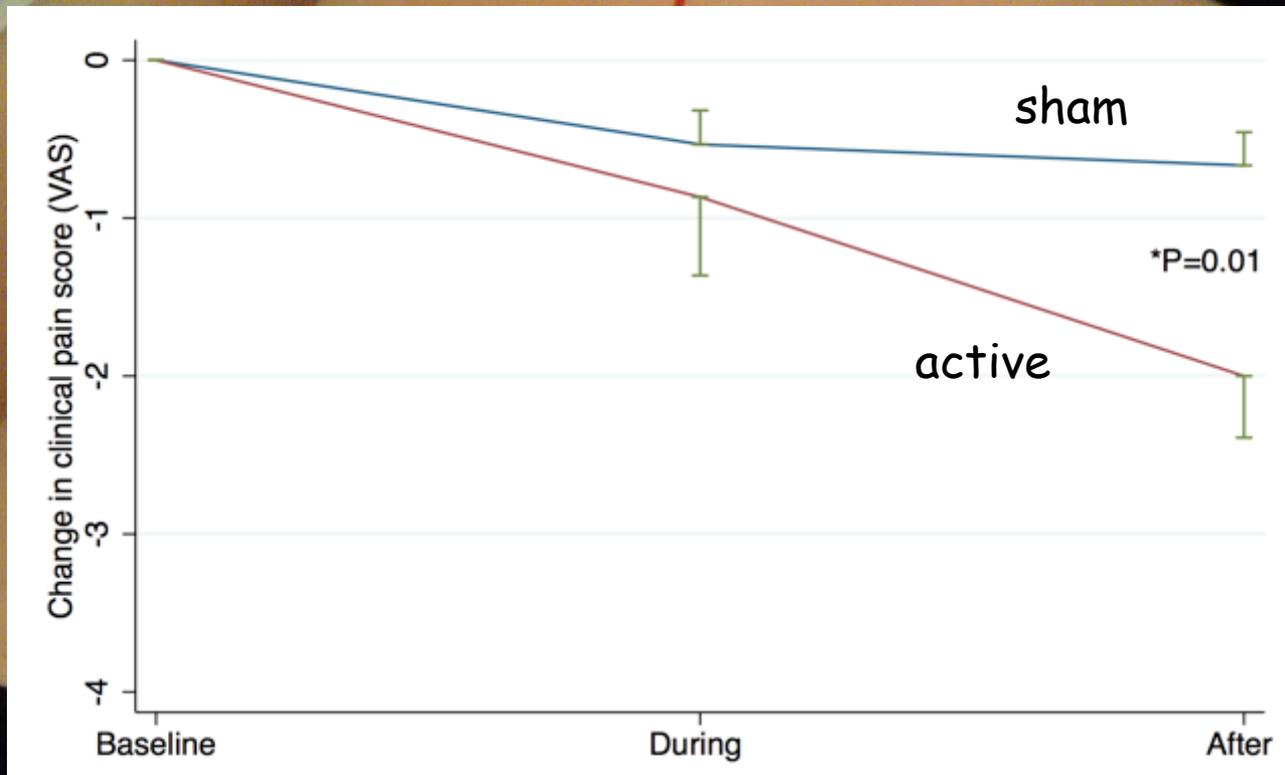


Spinal cord stimulation

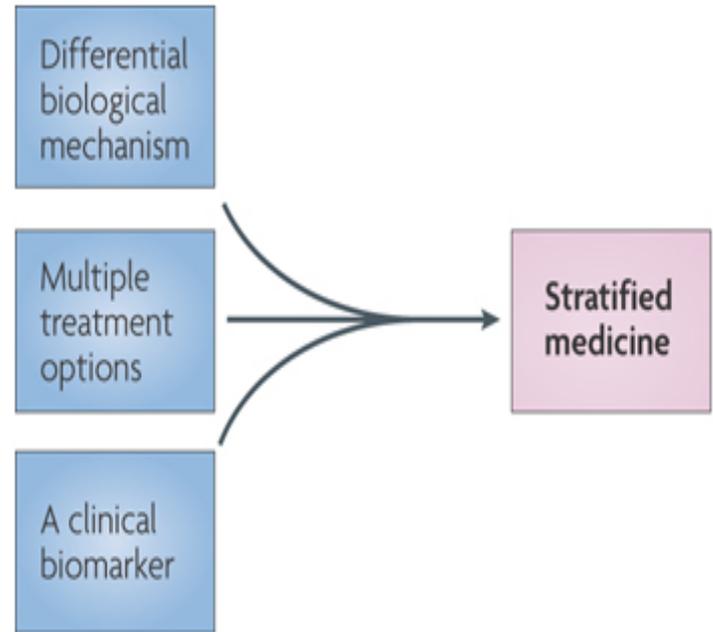


Kapural et al. Neuromodulation 2011
Fregni et al. Eur J Pain 2011

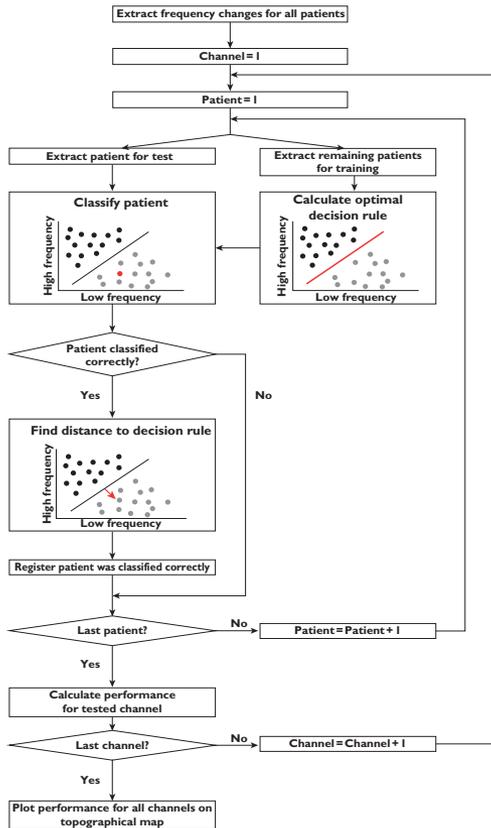
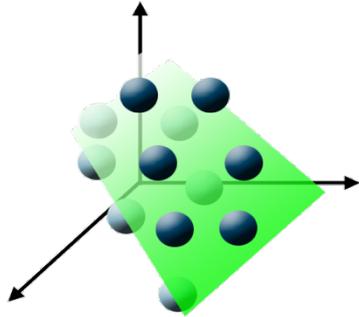
Acupuncture and pancreatic pain ?



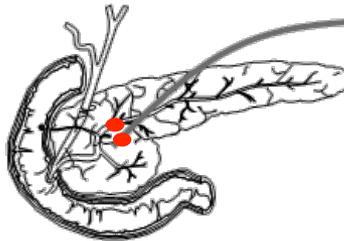
Selection of treatment - individualised medicine



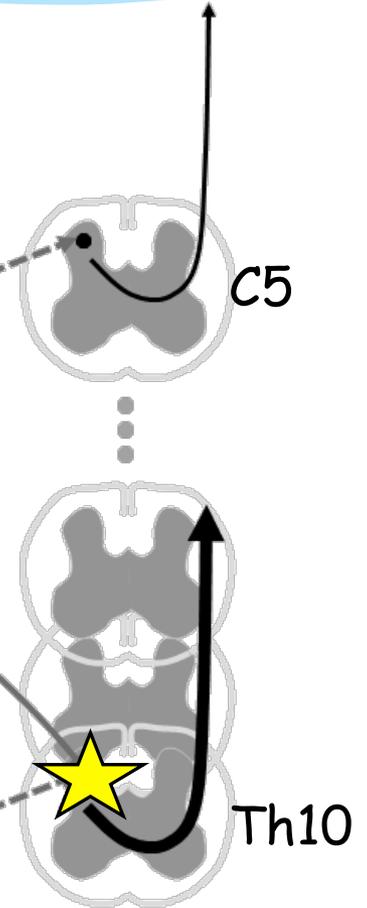
Individualized vs. group statistics



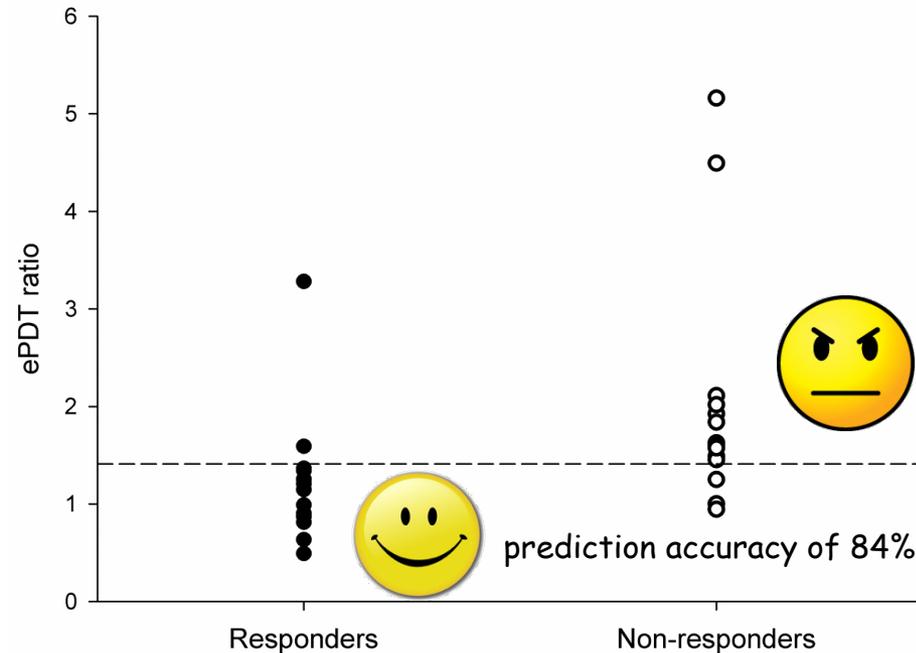
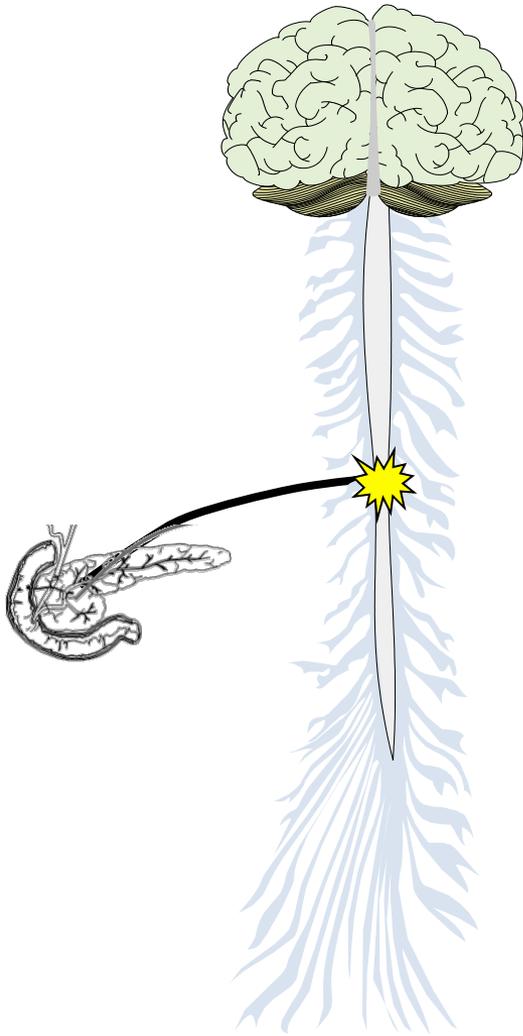
Skin C₅



Skin Th₁₀



Ratio "local vs. universal sensitization"



The more segmental hyperalgesia the better effect → individual tailored therapy