

# Medical Management of Pain in Children with Chronic Pancreatitis *(for gastroenterologists)*

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July 22, 2019

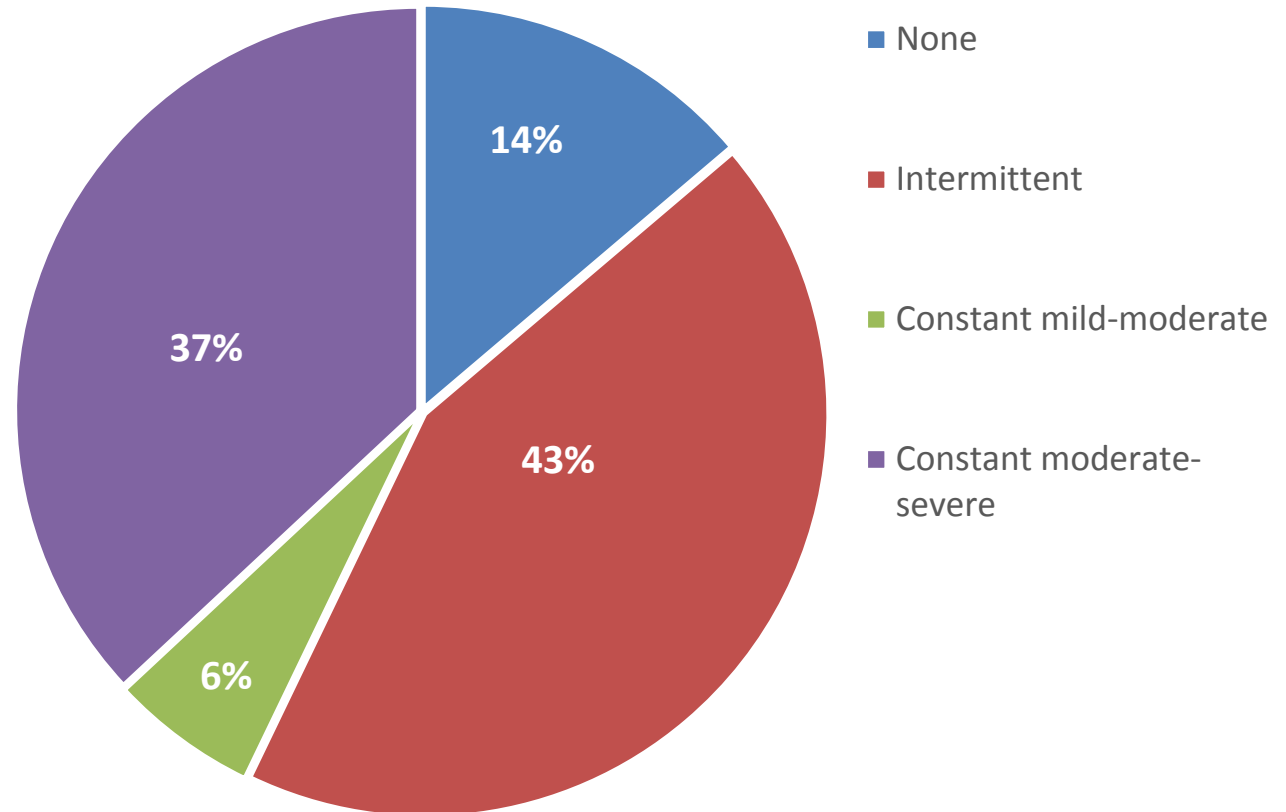
# Disclosures

- Pain management providers continue to teach me everything I know about managing pain
  - Al Clavel, MD
  - Stefan J. Friedrichsdorf, MD
  - Molly Hagen, PNP
  - Matt Armfield, MD
- I consult for the Cystic Fibrosis Foundation
- I will be discussing unapproved or investigative uses of medications (“off-label”)

# Outline

- Focus on outpatient management of chronic pain
- Impact of pain on children with CP
- Evaluation of pain in CP
- Management of pain in CP

# Pain patterns in children with CP



Schwarzenberg SJ, JPGN 68:566, 2019

# Risks of chronic pain

- Depression and anxiety
- Loss of school time, social structure
- Neuropathic changes that may reduce effectiveness of future surgery
- Opioid dependence and opioid hyperalgesia
- Cognitive decline resulting from reorganization and structural brain changes

# Presentation of pain in CP

- Pattern of pain
  - Highly variable-may be episodic or continuous, with or without pain-free intervals
  - Usually epigastric with radiation to the back, often made worse by eating
- Both hyperalgesia and allodynia may be present
- Imaging findings do not correlate with pattern of pain or intensity of pain

# Evaluating pain in CP

- Confirm diagnosis of CP
- Evaluate and treat CP-related pain
  - Constipation
  - Pancreatic insufficiency
  - Gastroparesis
  - Small bowel overgrowth
- Evaluate for factors amenable to ERCP management
  - Large pseudocysts, ductal stones, biliary obstruction
  - MRCP, perhaps CT

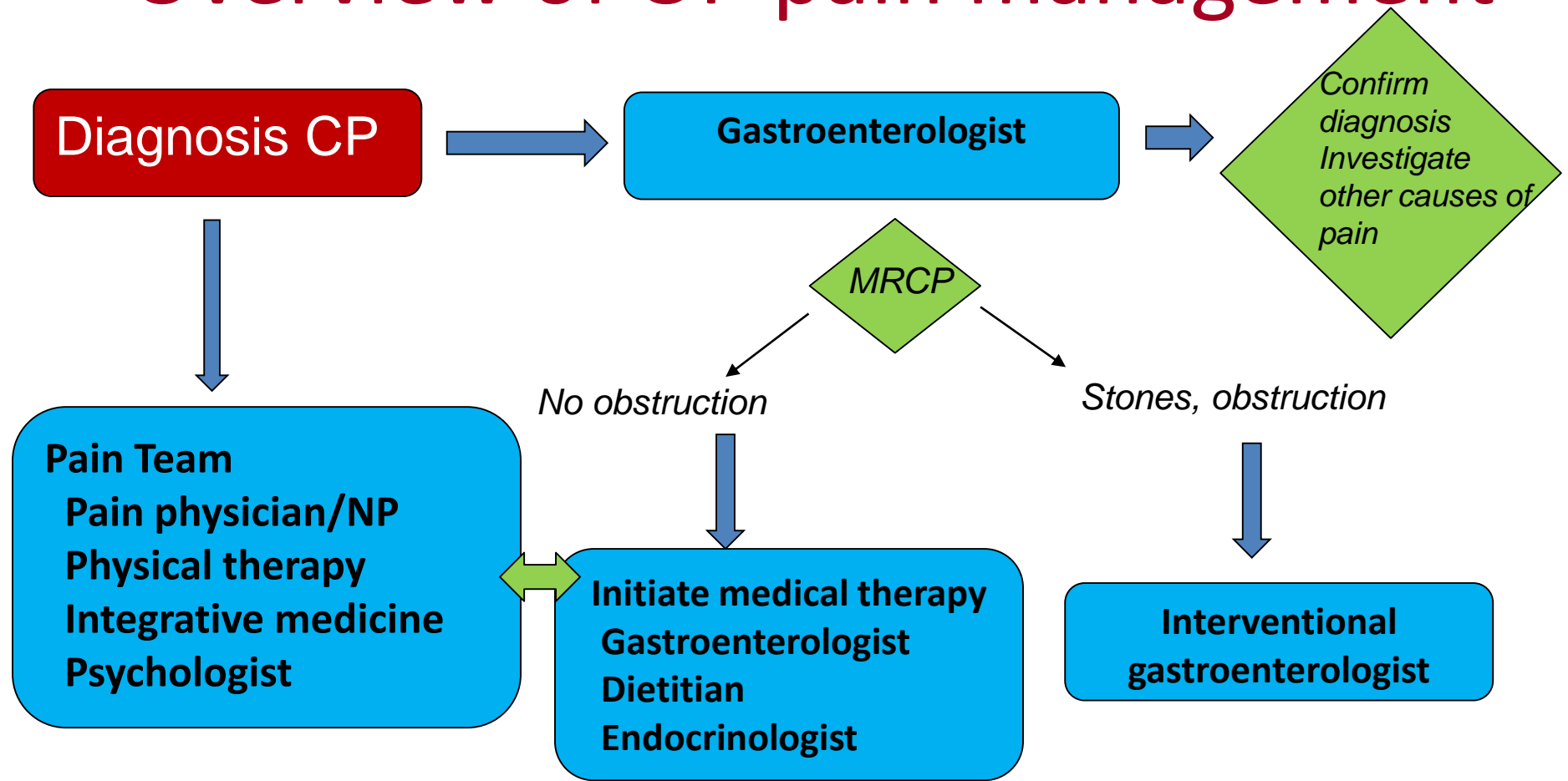
# Measuring pain in children

- Multitude of measuring tools
- Function is best single measure for the non-pain management provider
- Simple framework for function
  - School
  - Sports
  - Social
  - Sleep

From a much longer email from Matt Armfield MD



# Overview of OP pain management



**PRODUCT**

**Immediate management protocol  
Emergency management protocol  
Daily practice to self-regulate**

# Proposed medical therapies for pain in CP

- Stop alcohol and tobacco
- Detect and treat pancreatic insufficiency
- Low-fat diet (<20 g/day)
- Pancreatic enzymes
- Antioxidants
- CFTR modulators
- Progesterone
- Gabapentin

# Low fat diet, open label observational

| Study        | N   | Length LFD | Diet                                 | Outcome                              |
|--------------|-----|------------|--------------------------------------|--------------------------------------|
| Maruki 2013  | 14  | 4 weeks    | <20 g fat                            | Improvement in pain 14/14            |
| Ikeura 2014  | 17  | 8 weeks    | “restricted fat” + elemental formula | Improvement 15/17                    |
| Kataoka 2014 | 594 | 12 weeks   | Regular meals + elemental formula    | Decrease in mean visual analog scale |

Maruki J, Pancreas 42:48, 2013

Ikeura T, Int J Chronic Dis 2014, Article ID 862091

Kataoka K, Pancreas 43:451, 2014

# PERT and pain in CP

| Study         | N                        | Enzyme             | Study type                                 | Outcome                    |
|---------------|--------------------------|--------------------|--|----------------------------|
| Malesci 1995  |                          | Enteric coated     | 4 months randomized double-blind crossover |                            |
| Mossner 1992  | 47                       | Enteric coated     | 2 wk randomized double-blind crossover     | No difference from placebo |
| Halgreen 1986 | 20 (20 with steatorrhea) | Enteric coated     | 4 wk randomized double-blind crossover     | No different from placebo  |
| Slaff 1984    | 20 (8 with steatorrhea)  | Not enteric coated | 4 wk randomized double-blind crossover     | 11/20 had pain relief      |
| Isaksson 1982 | 19 (9 with steatorrhea)  | Not enteric coated | 2 wk randomized double-blind crossover     | 15/19 pain relief          |

Mossner J, Digestion 53:54, 1992; Halgreen H, Scand J Gastro 21:104, 1986; Slaff J, Gastro 87:44, 1984; Isaksson G, Dig Dis Sciences 28:97, 1982; Malesci A, Scan J Gastro 30:392, 1995

# Antioxidants and pain in CP

- 12 distinct studies found in Cochrane review
- High dropout rate because of adverse events associated with antioxidants (16%)
- Pain measured on visual analogue scale was less after 1-6 months antioxidants (mean difference - 0.33, 95% confidence interval -0.64 to -0.02, p value 0.04)
- No difference in number who were pain-free

# Ivacaftor and pain in CP

- Multicenter retrospective study in cystic fibrosis
- 6 patients, all F508 del + class III or IV mutation
- 12 months before ivacaftor, median 2 episodes of pancreatitis (range 2-5)
- 12 months after ivacaftor, only 1 episode of pancreatitis in entire group

Carrion A, JPGN 66:451, 2018

# Progesterone and pain in CP

- 13 women with acute recurrent pancreatitis and at least one CFTR mutation
- 3/13 started depo-medroxyprogesterone
- Those on depo-medroxyprogesterone had no episodes of acute pancreatitis for 6 months
- Further studies ongoing

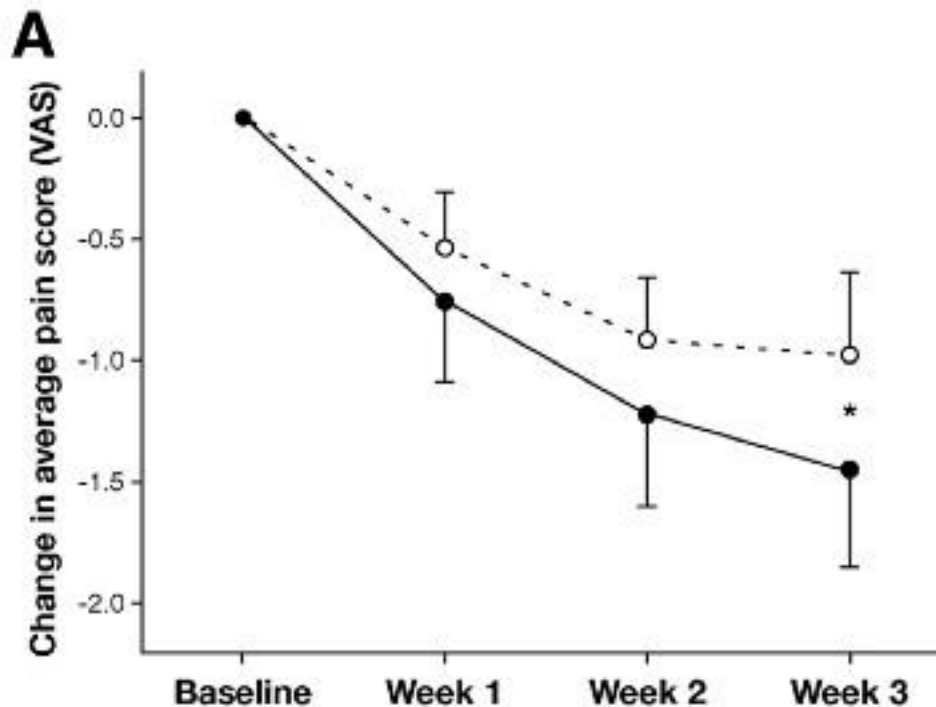
# Treat the central sensitization

- Gabapentinoids Gabapentin, Pregabalin (Neurontin, Lyrica)
- Ketamine (experimental)
- Antidepressants
  - No direct data
  - Depressive symptoms correlated with increased pain and decreased quality of life in non-alcoholic CP in an adult study



# Pregabalin and CP

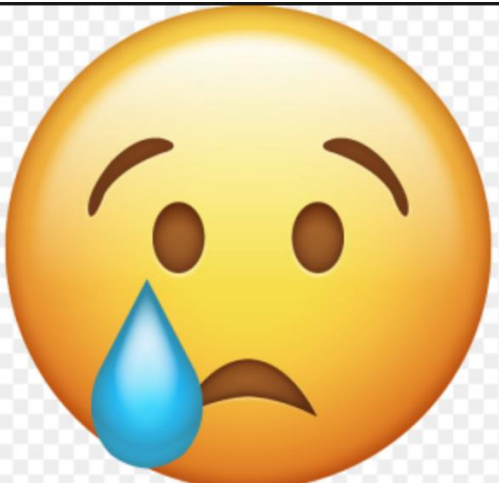
- Double-blind study of increasing doses of pregabalin over 3 weeks vs. placebo in 64 adults with CP



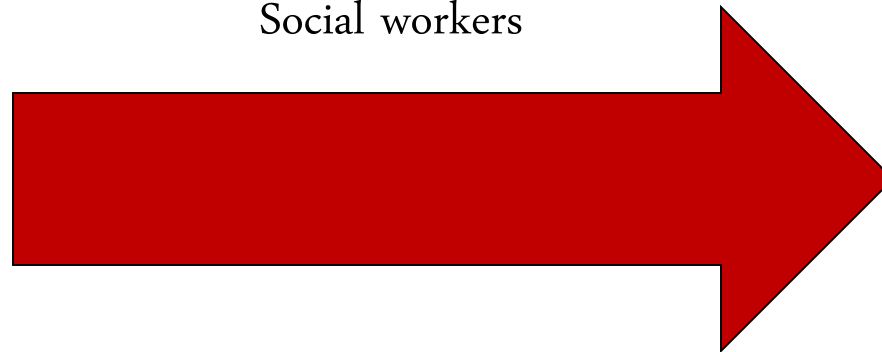
Olesen et al,  
Gastroenterology 141:536,  
2011

# Chronic pancreatitis in children requires multidisciplinary management by experts

**EVERY CHILD**



Dietitians  
Pain physicians  
Psychiatrists  
Endocrinologists  
Psychologists  
Physical Therapists  
Surgeons  
Social workers



Gastroenterologists

Interventional gastroenterologists

Nurses

Integrative medicine specialists



University of Minnesota  
Masonic Children's Hospital

# Sequential or concomitant trials of unproven therapies

- Pancreatic enzymes
  - Must use non-enteric coated enzymes
  - Viokase 20, 3 with meals and at night with acid reduction, for 6-8 weeks
- Antioxidant cocktail with methionine
- Low-fat diet with dietitian supervision

Any improvement could be placebo effect or favorable natural course of disease

# Interventions needing clinical trials

- Ivaftor
  - 2 CFTR mutations
  - 1 CFTR mutation
  - No CFTR mutation
- Depo-provera

# Conclusions

- Pain in CP is complex and multi-factorial in origin
  - Evaluate for sources of non-pancreatic pain
  - Consider overlapping sources
- Early effective treatment of pain may have beneficial long-term effects
- Current literature has severe limitations with respect to evidence-based medical pain management in CP

# A Modest Proposal

## *With apologies to Mark Twain*

- There are limited opportunities for well-powered randomized controlled clinical trials
  - Small pediatric populations
  - Variable population of CP
  - Increments of improvement likely small
- Some therapies will be used without evidence
- Pediatric pancreatologists have responsibility
  - To advocate for large multicenter studies of promising therapies, avoiding single center trials
  - To make non-pancreatologist-GI's aware of the management of pancreatic pain

# A scoping review of pain management in children with chronic pancreatitis

- Matt Armfield
- Addie Cuneo
- Maria Mascarenhas
- Emily Perito
- John Pohl
- Sarah Jane Schwarzenberg





# Language of pain

- Nociception-sensing of noxious stimuli; leads to pain
- Pain-complex psychological sensation with suffering and illness behavior
- Hyperalgesia (Sensitization)-increased nerve response to nociceptive trigger
- Allodynia-physiologic stimuli producing nociceptive trigger and sensation of pain

# CP pain is peripheral

- Nociceptive source
  - intrapancreatic ductal pressure/tissue ischemia
  - Inflammation of the pancreas
  - Complications (e.g., pseudocysts, strictures)
- Peripheral sensitization
  - Upregulation of nerve growth factors, brain-derived neurotrophic factors, cytokines
  - Nerves become hypertrophied and more excitable
- Result: *spontaneous pain without stimulation*

# CP pain and imaging

- 518 participants asked to identify pain and pain patterns
- Pancreatitis imaging features scored independently

# CP pain is central

- Spinal and supraspinal sensitization
  - Hyperalgesia and referred pain, commonly in upper GI organs, but also in distal sites
  - Decreased inhibitory pain modulation
- Central remodeling may occur
- Psychological/Social factors (loss of school and friends, debilitation) are both results and exacerbating factors
- Result: *pain in the “wrong place” and isolation*

# Complex pain management

- Early referral to plan current and future pain management
- May include
  - Medical evaluation discussed above
  - Physical methods (massage, heat, cold, TENS, yoga, stretching)
  - Cognitive behavioral techniques (guided imagery, hypnosis, distraction, abdominal breathing)
  - Acupuncture, acupressure, aromatherapy
  - Evaluation for depression, anxiety with appropriate treatment

**EVERY CHILD**