Canada Future Directions in IBD 2023

Treatment of Pain in the IBD Clinic

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Department of Medicine
Queen's University

Conflict of Interest Declaration

- Co-founder of pHarm Therapeutics Inc.

Targeting “acidic” inflammatory micro-environments with pH-sensitive analgesics

Patient and Health Care Provider Resources

- Lack of guidelines

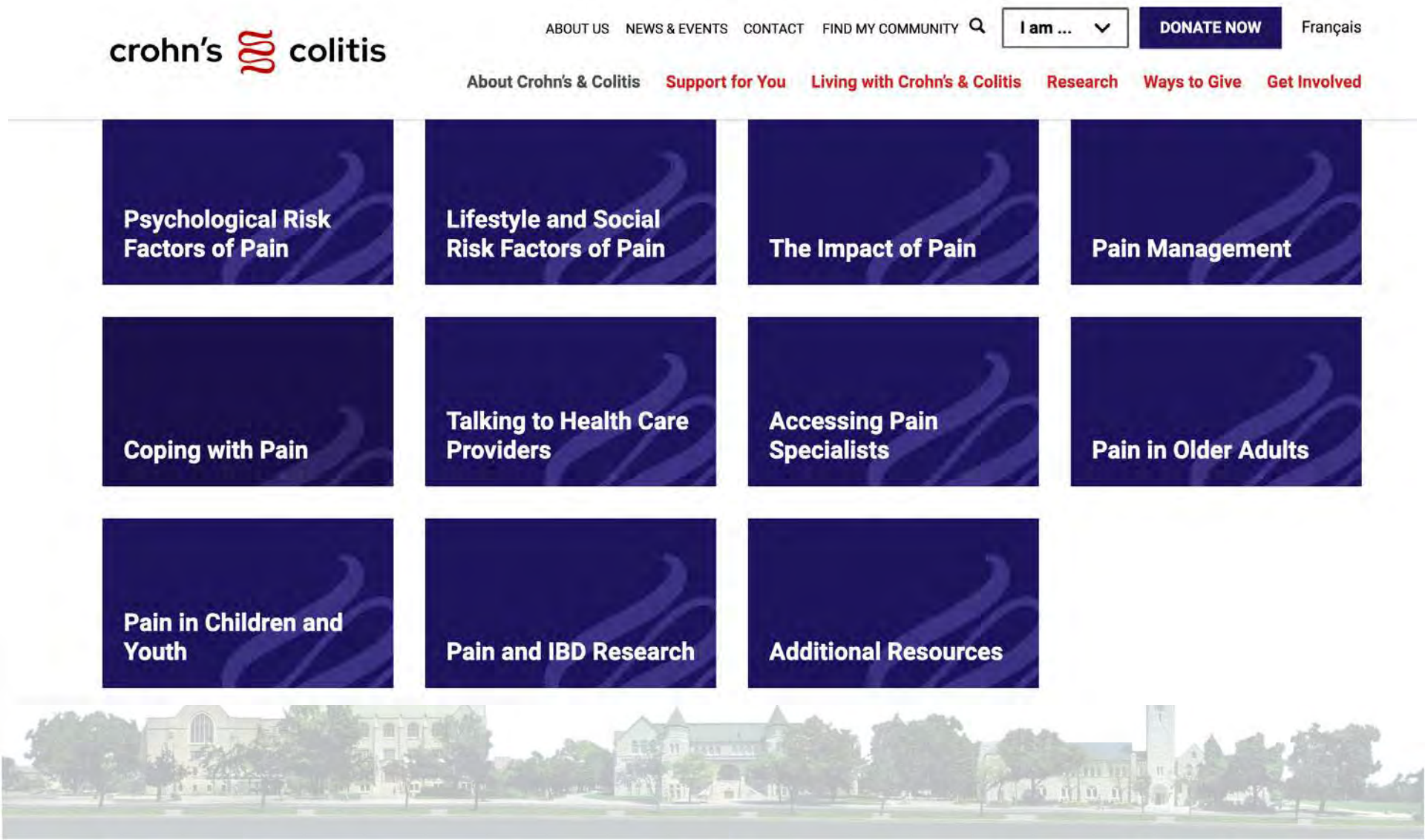
- Systematic reviews suggest little guidance from studies

Norton et al. APT 2016

- Excellent patient web resource from C&C

https://crohnsandcolitis.ca/About-Crohn-s-Colitis/IBD-Journey/Pain-in-IBD

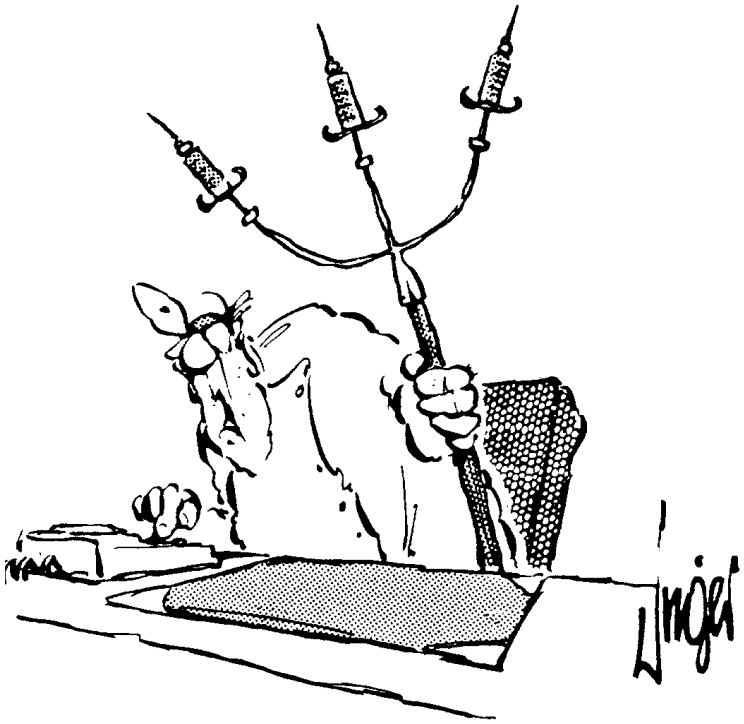
C&C website


crohn's colitis
ABOUT US
NEWS & EVENTS
CONTACT
FIND MY COMMUNITY
I am ...
DONATE NOW
Français
About Crohn's & Colitis
Support for You
Living with Crohn's & Colitis
Research
Ways to Give
Get Involved
Psychological Risk Factors of Pain
Lifestyle and Social Risk Factors of Pain
The Impact of Pain
Pain Management
Coping with Pain
Talking to Health Care Providers
Accessing Pain Specialists
Pain in Older Adults
Pain in Children and Youth
Pain and IBD Research
Additional Resources

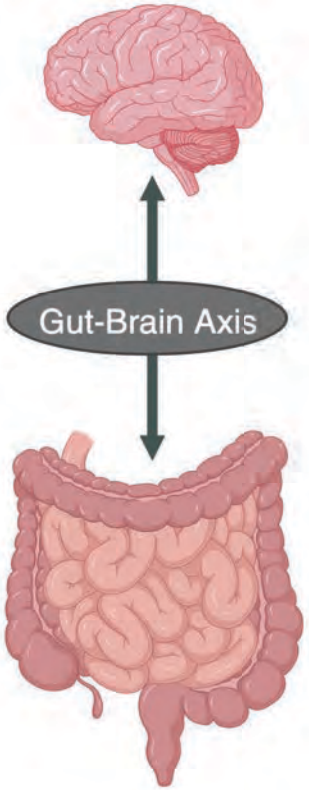
Objectives

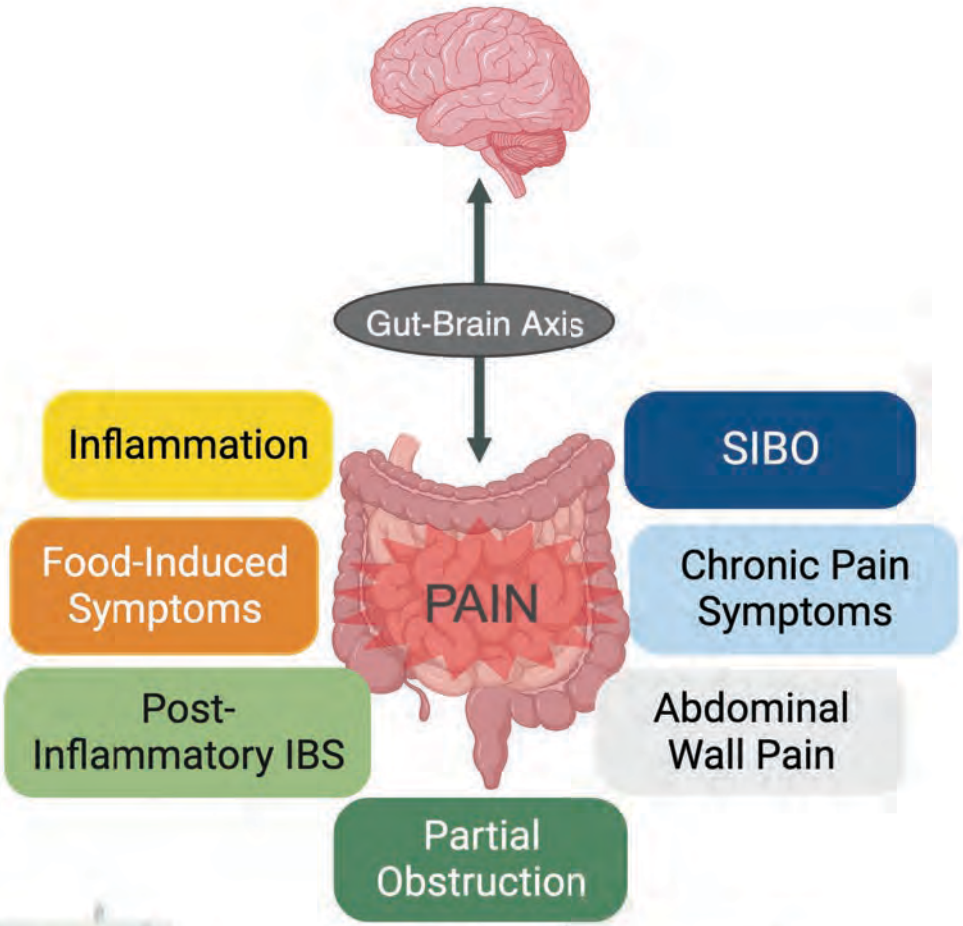
- Pathophysiological approach to treatment
- Therapeutic options
  - Opioids
  - NSAIDs
  - Cannabinoids
  - Nonpharmacologic approaches

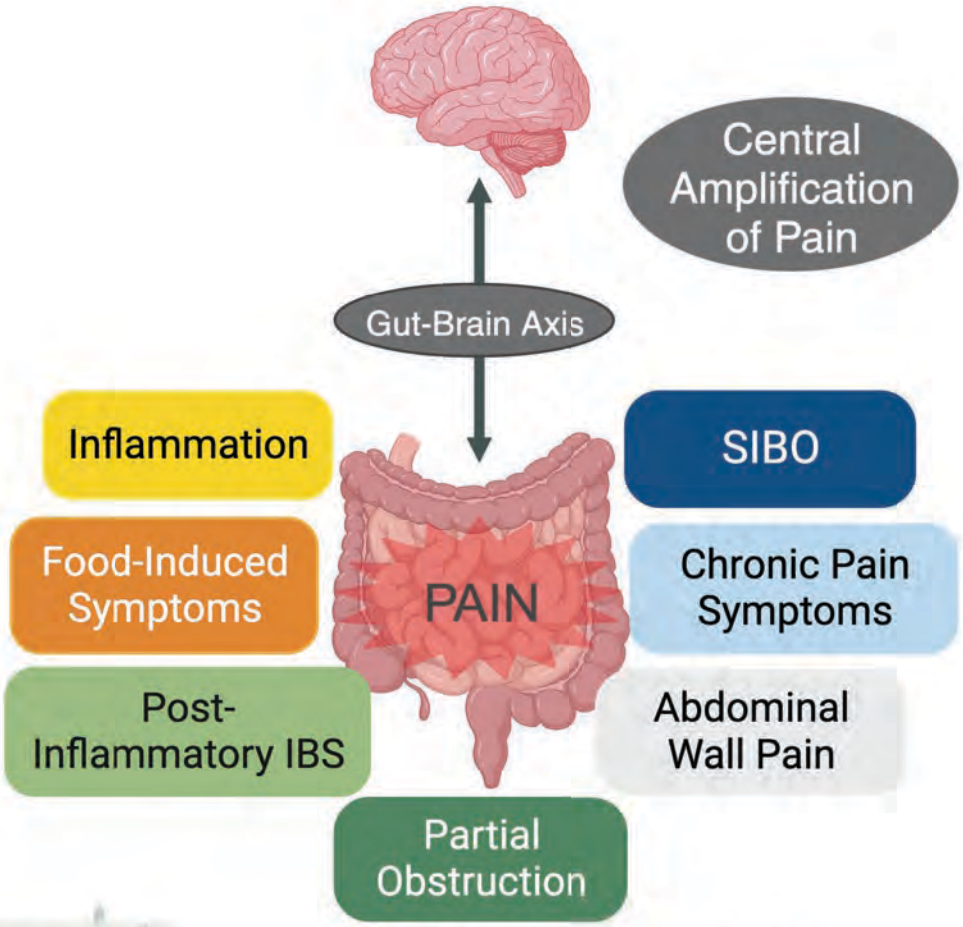
How do we treat abdominal pain?



“Send in the next three patients.”


Gut-Brain Axis


Gut-Brain Axis
Inflammation
SIBO
Food-Induced Symptoms
PAIN
Chronic Pain Symptoms
Post-Inflammatory IBS
Abdominal Wall Pain
Partial Obstruction


Central Amplification of Pain
Gut-Brain Axis
Inflammation
SIBO
Food-Induced Symptoms
PAIN
Chronic Pain Symptoms
Post-Inflammatory IBS
Abdominal Wall Pain
Partial Obstruction

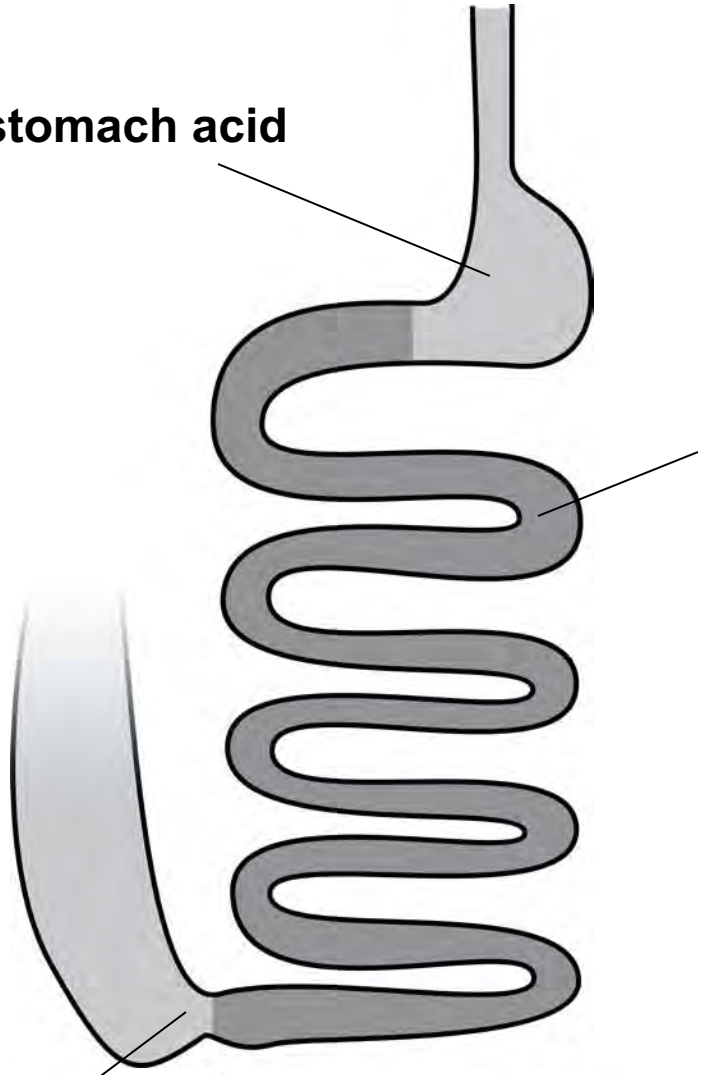
Inflammation

- Mechanistically intuitive
- Strong evidence for anti-TNF antibodies for analgesia lacking

  Swierczynski et al. Exp Rev Clin Pharm 2023
- Pain is multifactorial

SIBO in IBD - Major Predisposing Factors

Decreased stomach acid
PPIs



Stasis
Strictures,
Drugs,
Diverticula
Surgery

Loss of IC valve
Resection of the ileocecal valve
Gastrocolic or jejunocolic fistula

SIBO in IBD: Signs and Symptoms

Mechanism		**Signs and Symptoms**
Bile salt deconjugation	→	diarrhea, steatorrhea, ADE, wt loss
Bacteria compete for B12	→	megaloblastic anemia, neuropathy
Fermentation of CHO	→	bloating/**pain**, diarrhea
Loss brush border enzymes	→	diarrhea, bloating/**pain**, wt. loss
Protein malabsorption (bacteria, enterokinase, mucosal damage)	→	wt. loss, edema
Bacterial toxins	→	inflammatory cytokines, **pain**

SIBO in IBD patients

- Breath testing unreliable

  Vanner, S. Gut 2008

- Trial of therapy

- Caution in IBD-IBS patient without predisposing factors

IBD-IBS

Table 2. Prevalence of IBS in IBD according to disease activity and disease type

	Number of studies	Total number of subjects	Number meeting criteria for IBS	Pooled prevalence of IBS (%)	95% confidence interval	I^2	*P* value for I^2
All IBD patients	13	1703	583	39.0	30.0–48.0	92.6%	<0.001
IBD in remission	11	1197	363	35.0	25.0–46.0	63.5%	<0.001
Active IBD	3	299	115	44.0	24.0–64.0	NA[a]	NA[a]
All UC patients	10	772	251	36.0	25.0–47.0	89.9%	<0.001
UC in remission	9	596	163	31.0	21.0–43.0	88.2%	<0.001
Active UC	2	95	42	50.0	15.0–84.0	NA[a]	NA[a]
All CD patients	9	708	280	46.0	35.0–58.0	88.9%	<0.001
CD in remission	8	508	188	41.0	28.0–56.0	90.8%	<0.001
Active CD	2	135	52	48.0	20.0–77.0	NA[a]	NA[a]

Halpin and Ford. AJG 2012

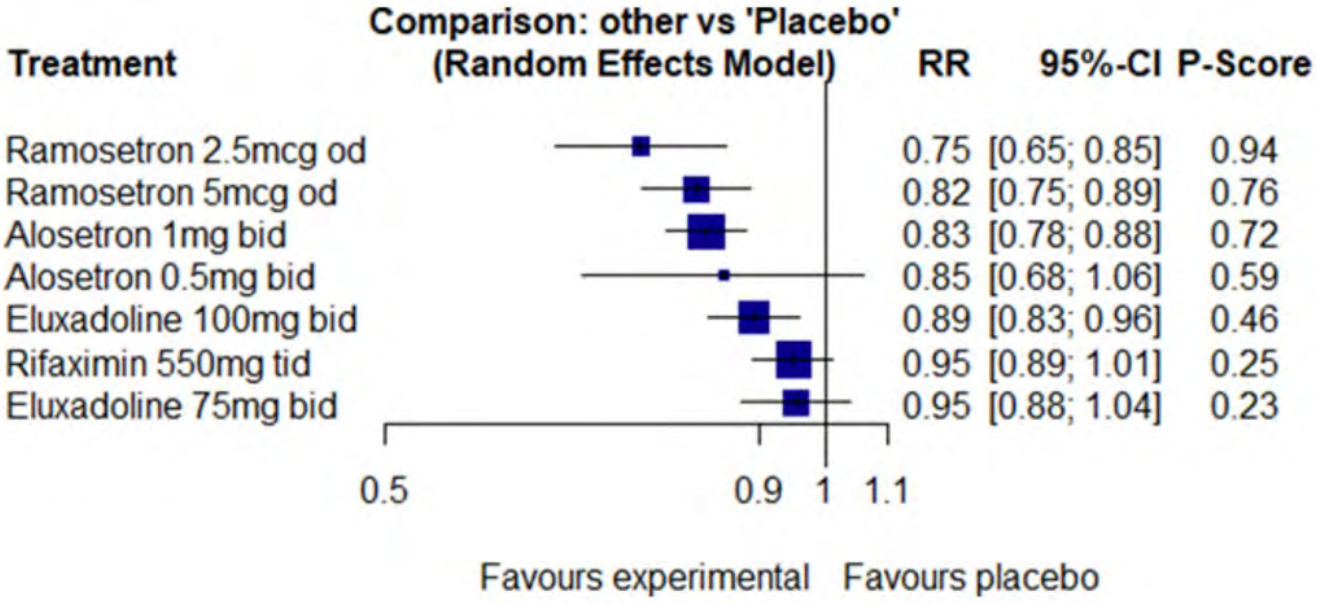
- even with most stringent criteria, ~25% met criteria for IBS. Crohn's > UC; more likely to have psychological co-morbidities

Fairbrass and Ford et al. Lancet GI Hepatol 2020

- IBS-type symptoms in 2/3 during > 6 years of follow-up; increased healthcare utilisation, and worse anxiety, depression, somatoform symptom and quality of life scores, but not adverse disease activity outcomes.

Fairbrass and Ford et al. APT 2022

Antibiotics in IBS are not effective to treat pain



Black CJ, *et al*. *Gut* 2020;**69**:74–82. doi:10.1136/gutjnl-2018-318160

Abdominal Wall Pain

Carnett's sign and Pinch test

- Local Heat
- TENs
- Trigger point injection - Combination of Bupivacaine +Triamcinolone

Pain Therapies

Non-pharmacology

- Life style
- Diet
- Psychological interventions

Pharmacology

- Acetaminophen
- Anti-depressants: TCAs, SSRIs, SNRIs
- Anti-convulsants: Gabapentin, Pregabalin
- IBS: anti-spasmotics, GC agonists, peripheral mixed opioid receptor agonists; foregut symptoms - mirtazapine, buspirone
- Probiotics?
- NSAIDs (arthritis)
- Cannabinoids
- Weak opioids: codeine, tramadol
- Strong opioids: oxycodone, morphine, fentanyl

Docherty et al. Managing Pain in IBD Gastro and Hepatol 2011

Opioid use in IBD

- Independent predictor of mortality; serious side effects
- Independent risk factor for serious infections
- Addiction risk
- Communication critical and pain specialists in complex cases

Kienzi et al. Clin Transl Gastro 2020
Docherty et al. Gastro Hepatol 2011
Swierczynski et al. Exp Rev Clin Pharm 2023
Drewes et al. Nature Reviews 2020

> Aliment Pharmacol Ther. 2019 Jan;49(1):74-83. doi: 10.1111/apt.15023. Epub 2018 Nov 14.

Incidence and predictors of new persistent opioid use following inflammatory bowel disease flares treated with oral corticosteroids

Mohamed Noureldin [1 2], Peter D R Higgins [1], Shail M Govani [3], Shirley Cohen-Mekelburg [1], Brooke C Kenney [4 5], Ryan W Stidham [1], Jennifer F Waljee [4 5], Akbar K Waljee [1 2]

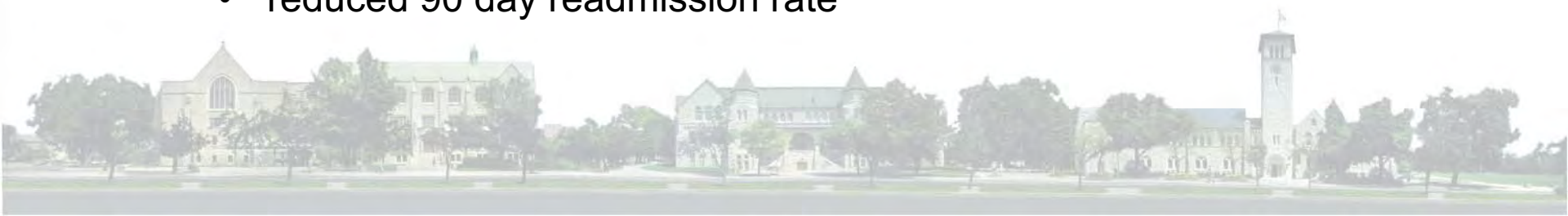
- 15119 IBD patients who received opioids around a flare
- 36% were opioid naïve and 35% developed persistent use
- Factors associated with persistent use: history depression, substance use Crohn's disease or indeterminate colitis, COPD

Targeted housestaff intervention reduces opioid use without worsening patient-reported pain scores and improves outcomes among patients with IBD: the "IBD pain ladder"

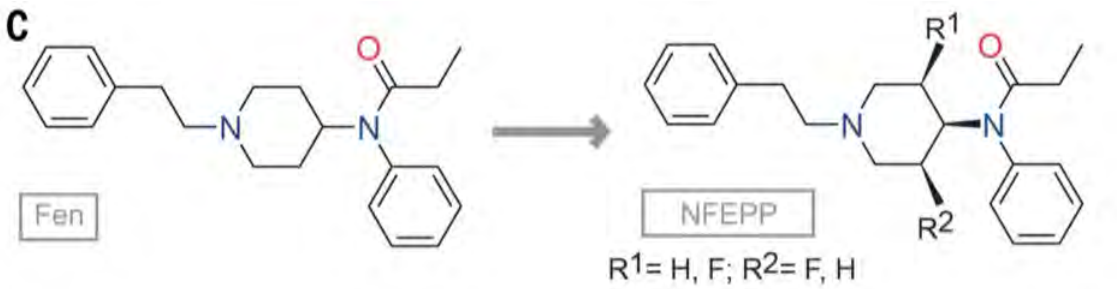
Pavlos Kaimakliotis ✉, Ajit Ramadugu, Jennifer Kang, Timothy McGorisk, Anne Polick, Effrosyni Votta-Velis & Itishree Trivedi

International Journal of Colorectal Disease **36**, 1193–1200 (2021) | Cite this article

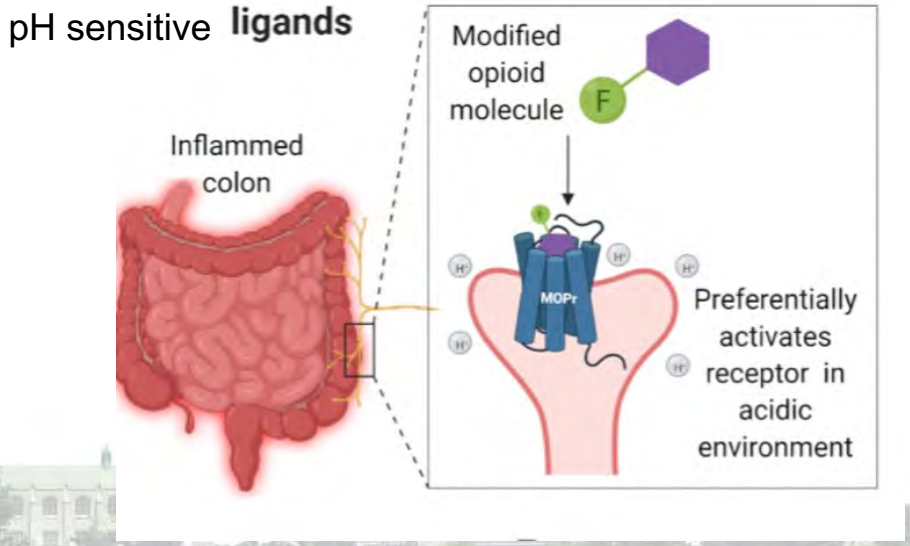
- 43.4 mg vs. 7.7 mg morphine equivalent
- no difference in patient reported pain scores
- reduction in pain prescriptions at discharge
- reduced length of stay
- reduced 90 day readmission rate



Ligands targeted to acidic environments

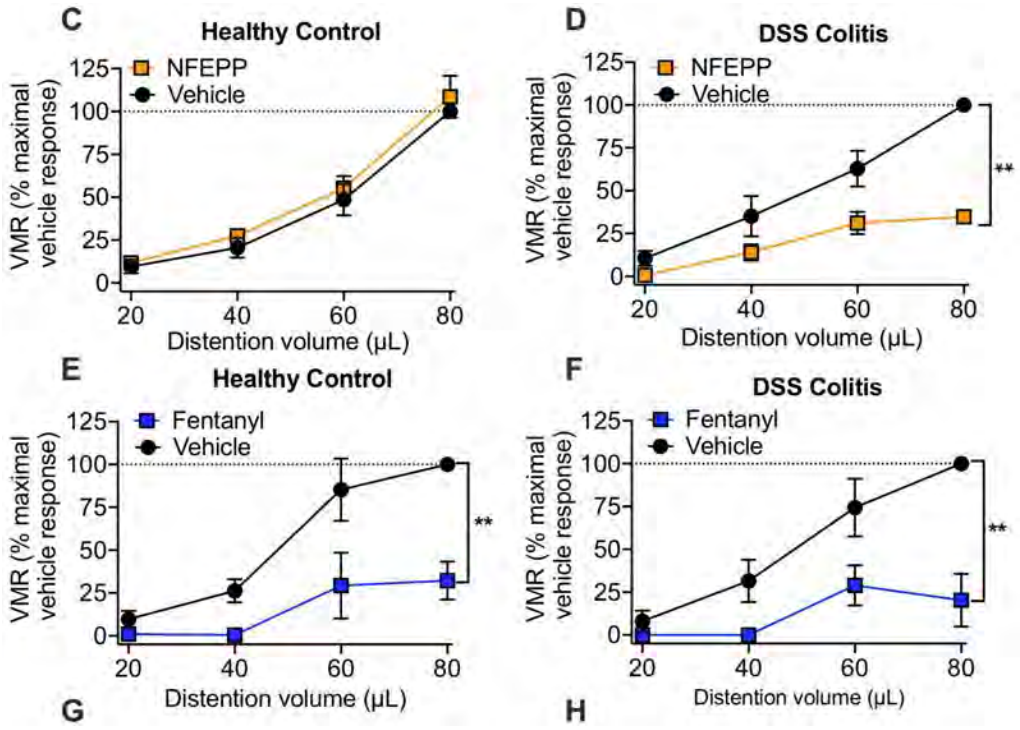


Spahn,V. et al. Science 355:2017



normal colon

colitis



Animal Models

- Arthritis
- Post-op pain
- Cancer pain

Supported by:

crohn's colitis canada

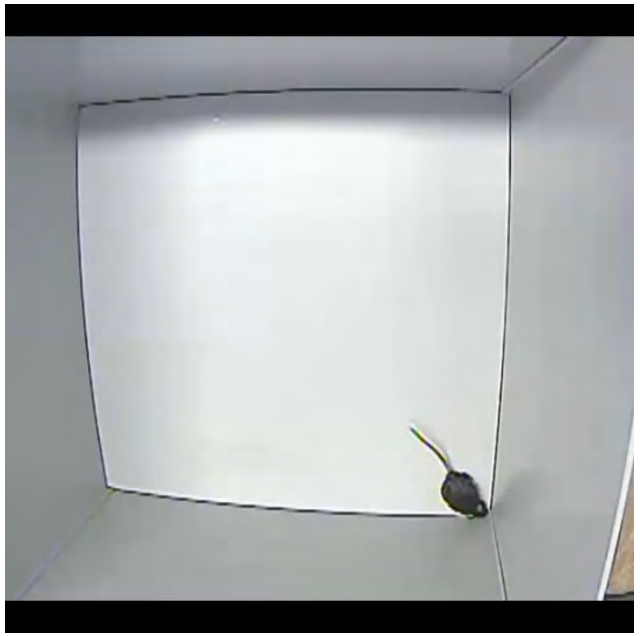
crohn colite canada

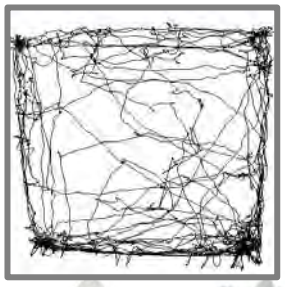
Jimenez-Vargas et al. GUT 2021

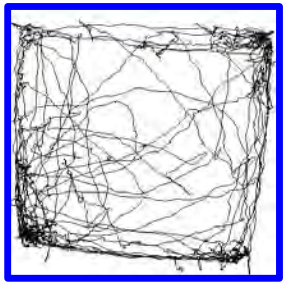
Vehicle

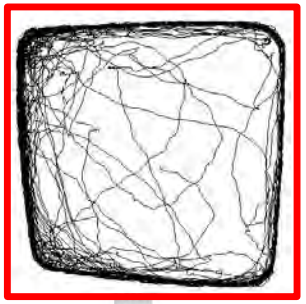
NFEPP

Fentanyl





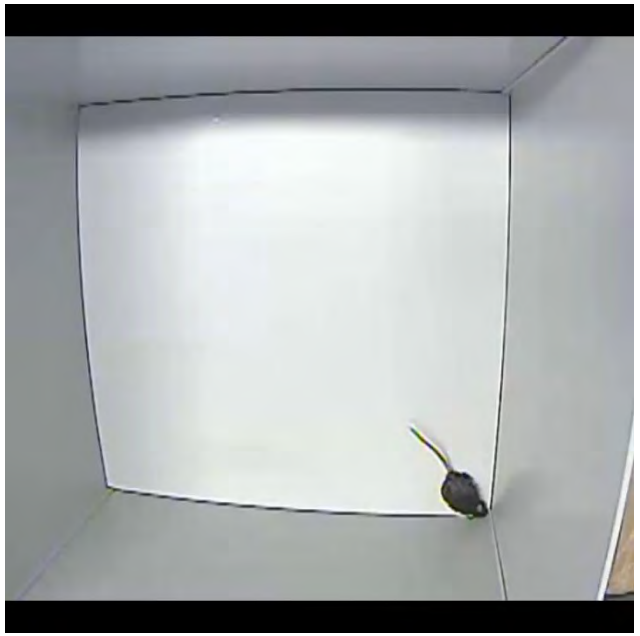


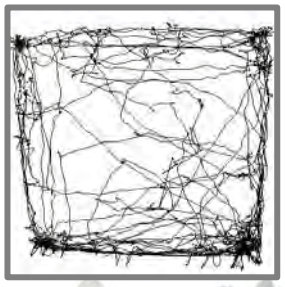


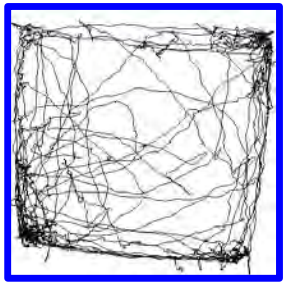
Vehicle

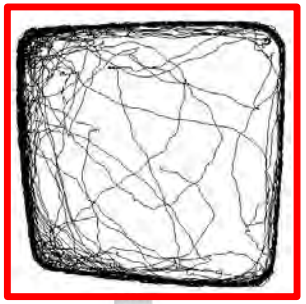
NFEPP

Fentanyl



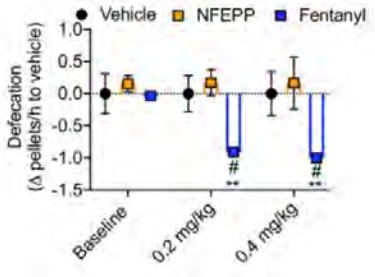




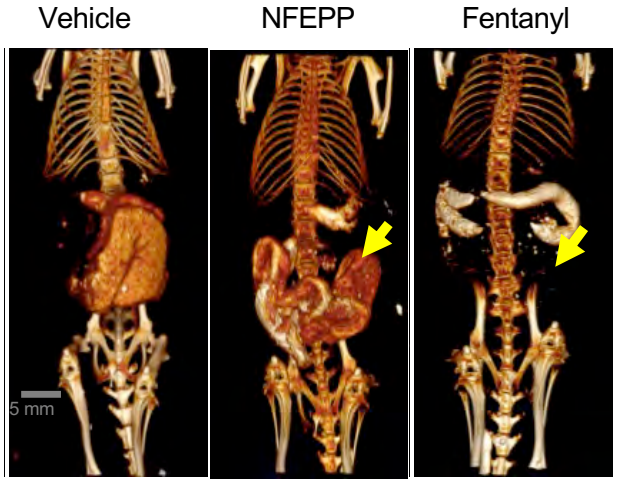


Safety Data: Serious Opioid Side Effects in GI tract and Lungs

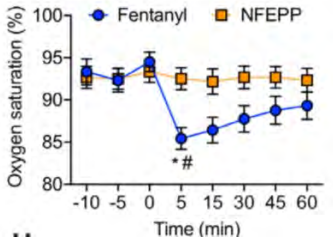
A



Oral gavaged contrast CT scans showing
Fentanyl but not NFEPP paralyzes GI motility



B



Degro et al Pain 2023
Jimenez-Vargas et al Gut 2022

NSAIDs and IBD

- Current recommendations are to avoid their use due to risk of IBD exacerbation
- Recent meta-analysis did not find consistent correlation; sensitivity analyses restricted to studies with low risk of bias - CD not UC

Moninuol,O. et al. APT 2018.

- COX-2 selective for arthritis, no difference in relapse compared to placebo

Sandborn et al. Clin Gastro Hepatol 2006

Cannabinoids and IBD

- Over 50% report using marijuana, ~ 25% using for symptom control and up to 10% using daily.
- Over 50% report using for pain control
- Decreased abdominal pain, stress, cramping, sleep issues, anxiety; 50% reduced analgesic use
- Anti-inflammatory benefits in clinical studies lacking

Scott. Crohn's Colitis 360, 2020
Hansen et al. Inf Bowel Dis, 2019
Hoffenberg et al. J Ped 2018
Benson et al. Crohn's Colitis 360, 2020

Patient reported side effects with chronic use

- Self reported memory impairment, fatigue, and drowsiness

  Benson et al. Crohn's colitis 360 2020

- 20% regularly craving marijuana, 13% neglecting home and school responsibilities

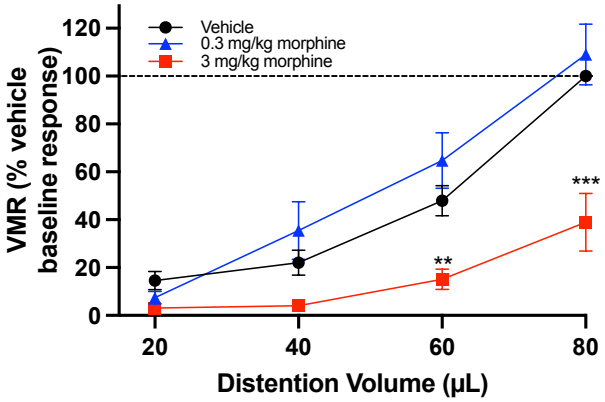
  Hoffenberg et al. J Peds 2018

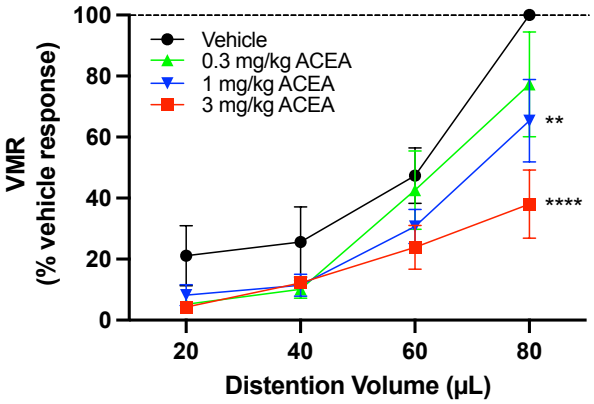
- Depression and impulsivity increased and increased substance abuse

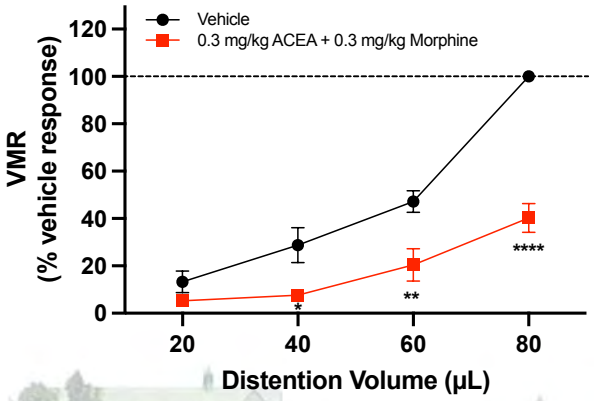
  Hansen et al. Inf Bowel Dis 2019

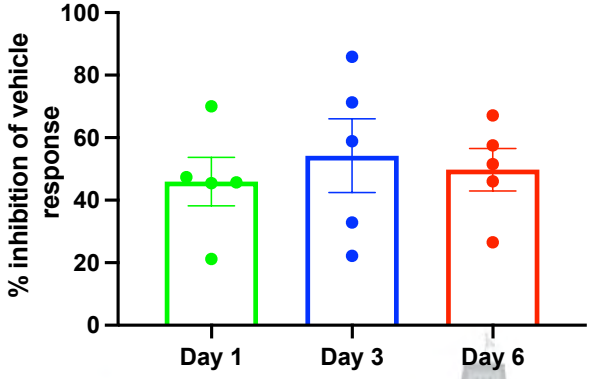
Combination Drugs targeting GPCRs

Subthreshold CB1 agonist + morphine



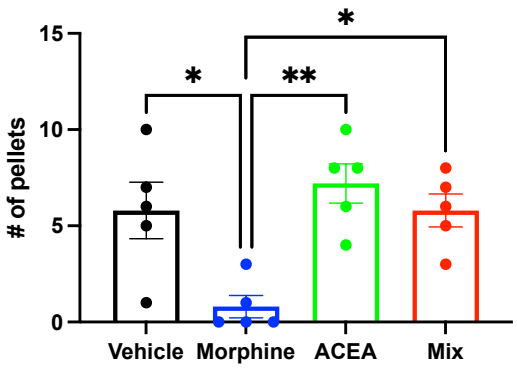


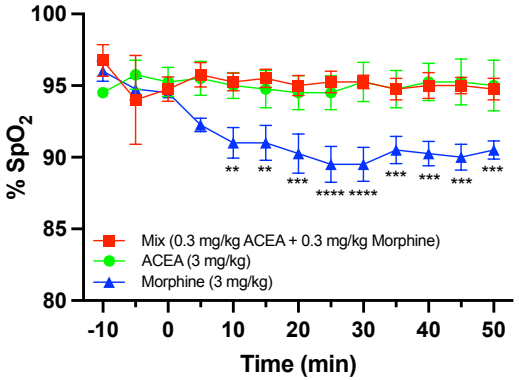


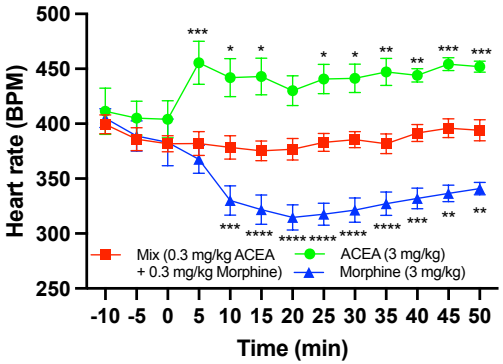


Tsang et al. J. Neurosci 2021

Subthreshold combination lacks Morphine side effects







Tsang et al. J. Neurosci 2021

Behaviour and non-pharmacological pain therapies

- Diet
- Sleep
- Psychological interventions

Low FODMAP diet in quiescent IBD

- A number of studies showing improved symptoms including pain
- Theoretical concern regarding negative impact on microbiota/metabolites
- No evidence in clinical and preclinical models that exacerbates inflammation

Tuck et al. NGM 2019

Sleep Quality Drives Next Day Pain and Fatigue in Adults With Inflammatory Bowel Disease: A Short Report

Livia Guadagnoli,[a] Jamie Horrigan,[b] Marta Walentynowicz,[c] Jessica K. Salwen-Deremer[d]

J Crohn's Colitis 2023

Table 1. General estimating equation models demonstrating sleep as predictor of abdominal pain, fatigue, and physical activity

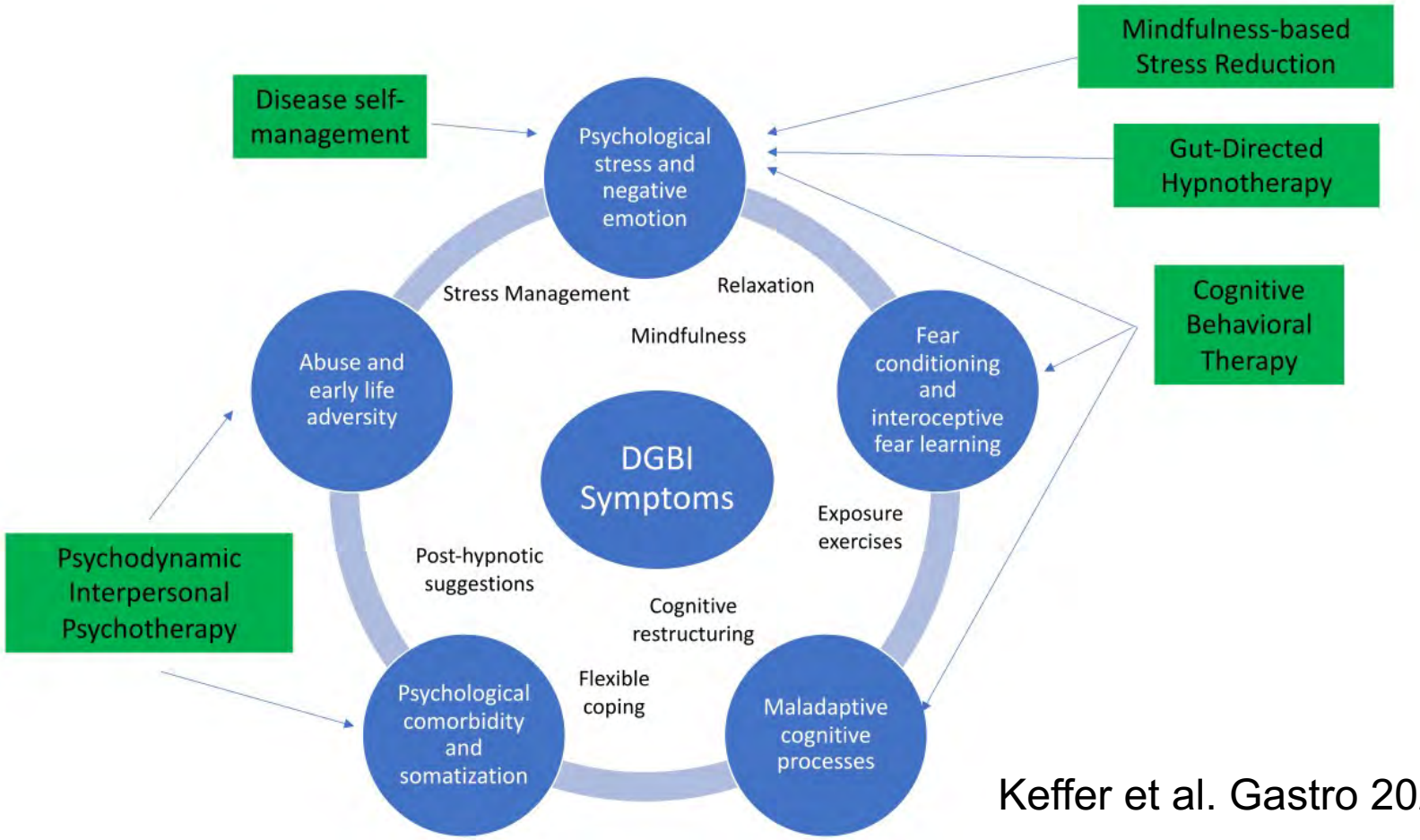
	Abdominal pain				Fatigue				Physical Activity			
	β	SE	Raw *p*-value	Adjusted *p*-value[a]	β	SE	Raw *p*-value	Adjusted *p*-value[a]	β	SE	Raw p-value	Adjusted p-value[†]
Sleep quality	-0.10	0.03	<0.001***	<0.01**	-0.37	0.09	<0.0001***	<0.0001***	80.40	87.10	0.36	.72
WASO	0.002	0.005	0.30	0.60	0.004	0.003	0.21	0.24	-15.95	4.38	<.001***	<.001***
Awakenings	-0.01	0.04	0.84	0.84	0.15	0.10	0.12	0.24	-234.0	264.0	0.37	.72

Poor subjective sleep quality predicts symptoms in Irritable Bowel Syndrome using the Experience Sampling Method

Topan, Rabia MBChB, BSc, MRCP[1]; Vork, Lisa MD PhD[2]; Fitzke BSocSci, Heather MSc PhD[3]; Pandya, Shraya BSc[1]; Keszthelyi, Daniel MD PhD[2,a]; Cornelis, Jan[6]; Ellis, Jason PhD[7]; Van Oudenhove, Lukas MD PhD[4,5,8]; Van Den Houte, Maaike PhD[4,5,*]; Aziz, Qasim PhD, FRCP[1,*]

- poor subjective sleep quality predicted next day abdominal pain ($0.036 < p < 0.040$)

Psychological Interventions in IBD



Keffer et al. Gastro 2022

Psychological Interventions

- Relatively few studies in IBD
- Extrapolation from other disorders including IBS suggest efficacy
- Need patient engagement and accessibility to therapists

Norton, C. et al. Systematic review: interventions for abdominal pain Management in inflammatory bowel disease. APT 2017
Riggott,C. Efficacy of psychological therapies in people with IBD: a Systematic review and meta-analysis. Lancet Gastro Hepatol 2023

Summary

- Pathophysiological based approached – personalized approach
- Avoid conventional opioids whenever possible
- Need for more basic and clinical studies in IBD pain