2018 NCSCG 15TH ANNUAL POST-DDW SYMPOSIUM

Tips for Treating your Most Difficult Patients with Disorders of Gut-Brain Interaction

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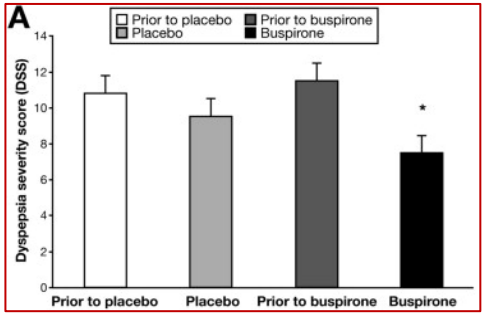
What patients are we talking about?

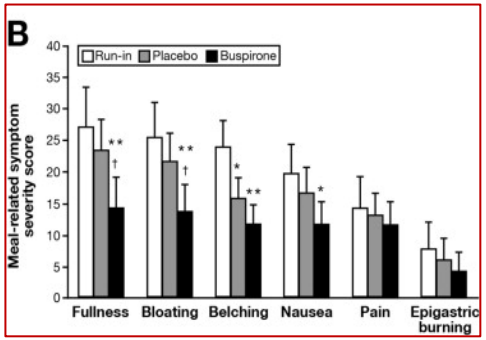
- Despite normal labs and endoscopy, continue to:
  - Lose weight
  - Visit the ER
  - Call frequently with persistent symptoms
  - Miss work or social activities due to symptoms

- Have failed or are too sick for:
  - Gluten Free/FODMAP/High Fiber and other standard diet recommendations
  - Weight loss and exercise
  - Antispasmodics like peppermint oil (IBGuard), hyoscyamine or dicyclomine
  - First-line medications like OTC laxatives, prescription laxatives, loperamide, rifaxamin, ondansetron, PPIs, etc

Buspirone and Functional Dyspepsia

- Impaired gastric accommodation and hypersensitivity to gastric distention →FD
- Buspirone (Buspar) is a 5-HT1 agonist → receptive smooth muscle relaxation in the fundus →improved accommodation
- RCT, double-blind, placebo controlled buspirone vs placebo, 17 patients 4 weeks 10mg tid crossover design, improved dyspepsia severity and meal-related symptom
- Side effects: sedation, headache
- Dose 10mg-60mg/day in 2-3 divided doses; start 5mg bid and aim for 15mg bid or 10mg tid

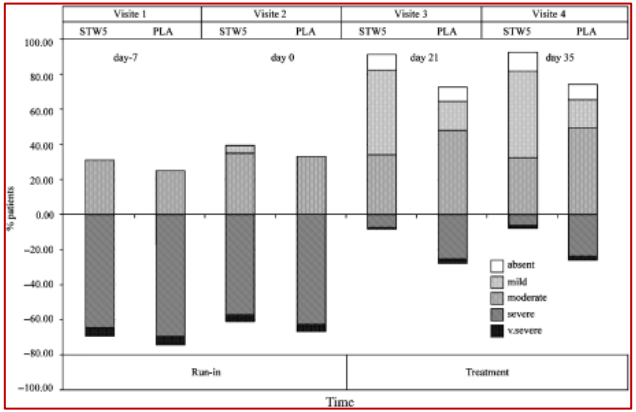


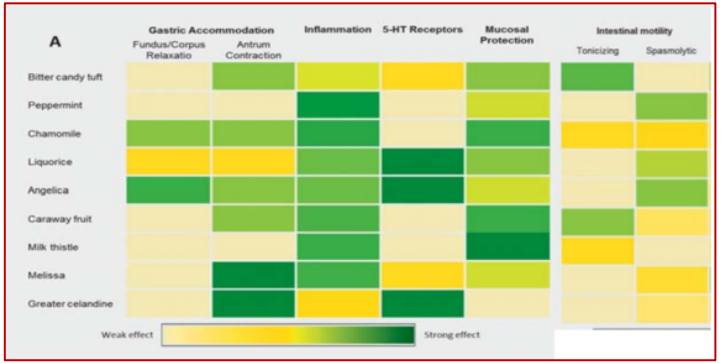


1. *Tack et al. CGH 2012;10:1239-1245*
2. Bisschops et al. NGM 2007;19:85-93.
3. Tack et al. Gastro 1998;115:1346-1352.
4. Van Oudenhove et al. APT 2008;28:1326-1333.

Iberogast

- Combination of 9 herbal extracts
- Dose: 1mL (20 drops) three times a day (~$30/100mL bottle which is ~1 month supply)
- Has caraway and peppermint like FD-guard
- Meta-analysis of 3 double-blind placebo-controlled RCT
  - 273 patients with FD
  - Iberogast significantly better than placebo at improving “most bothersome symptom” (cramp, pain, nausea, regurgitation, vomiting, fullness, etc)
- Cluster analysis showing contribution of each extract to the overall effect of Iberogast on underlying pathomechanisms of FD





1. *Melzer et al. APT 2004:20:1279-87*
2. *Abdel-Aziz et al,. Planta Med 2017:83:1130-1140.*

Differential for Nausea and Vomiting

- If vomiting immediately after swallowing, may be more like obstruction/regurgitation suggesting esophageal dysmotility
  - Dx with esophagram, manometry +/-pH and treat accordingly

- If nausea is minimal and more like “effortless regurgitation” consider rumination
  - Dx with hx and manometry. Treat with diaphragmatic breathing.
- If symptom free periods, consider cyclic vomiting and/or cannabinoid hyperemesis syndrome
  - Dx based on history +/- rapid gastric emptying. Treat with tricyclics and marijuana cessation

Mirtazapine (Remeron)

- Tetracyclic antidepressant
- Similar 5HT-3 antagonism, longer half-life, and cheaper than ondansetron and granisetron.
- Helps with nausea, poor appetite, weight loss, insomnia; consider in functional dyspepsia and chronic nausea
- Start 15mg nightly, increase by 7.5-15mg every 1-3 wks, max 45mg

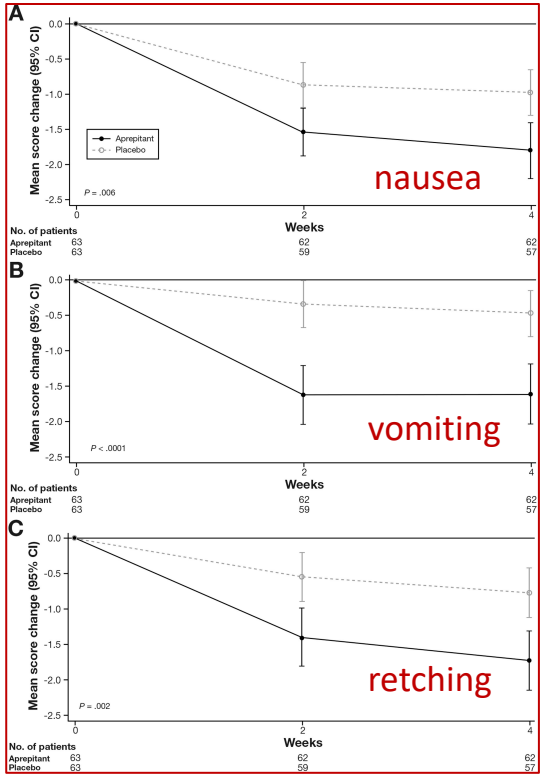
Table 1. Affinity/antagonism, pKa, average dose, average price

	H1	5-HT3	5-HT2A	T $^{1}/_{2}$ hours	Average dose (mg/day)	Average cost ($/day)
Mirtazapine	9–10	7–8	8	20–40	15–45	2–5
Olanzapine	6	6	5	20–50	5–15	8–24
Dolansetron	n.s.	10	n.s.	7–9	100 mg × 2	150
Granisetron	n.s.	10	n.s.	4–10	2 mg × 3	280
Ondansetron	n.s.	10	n.s.	3.5	8 mg × 2–3	141

1. Kast, RE, Eur J Cancer Care 2007
2. Kundu et al. WJG 2014;20:6671-6674
3. Yin et al. Neurogastro Motil 2010;22:1022-8
4. Gooden et al. J Med Case Rep 2013;6:38

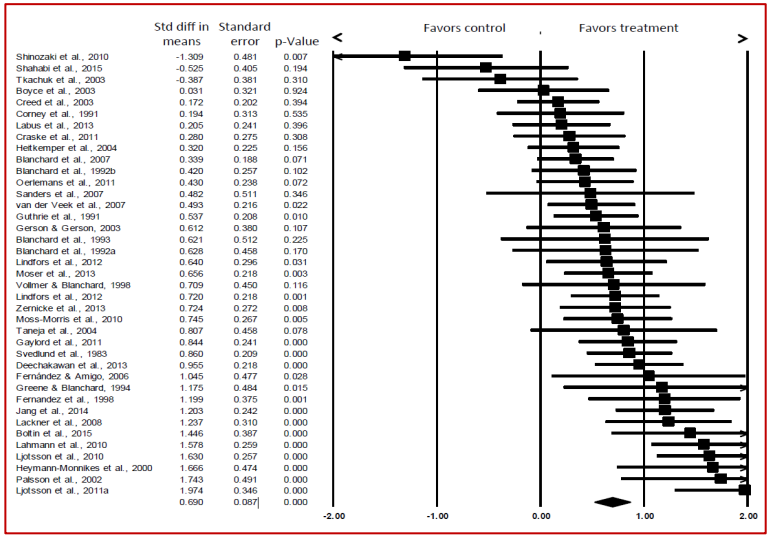
Aprepitant (Emend)

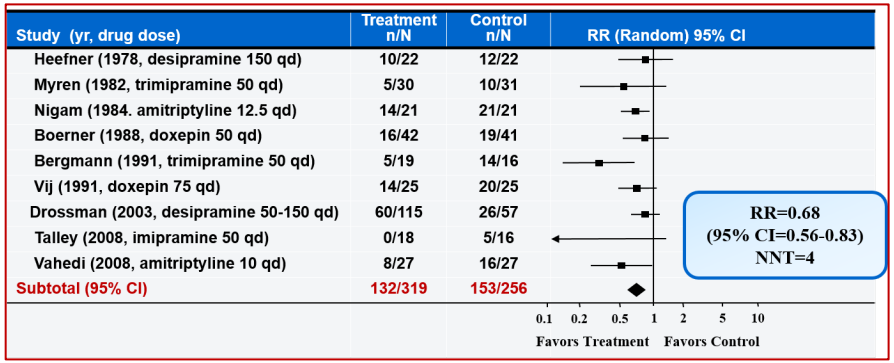
- NK1 receptor antagonist
- Approved for use with highly emetogenic chemotherapy
- APRON trial – RCT 125mg daily vs placebo in patients with gastroparesis and CUNV→ improved nausea, vomiting, retching based on symptom severity scales
- Price/coverage can be a barrier

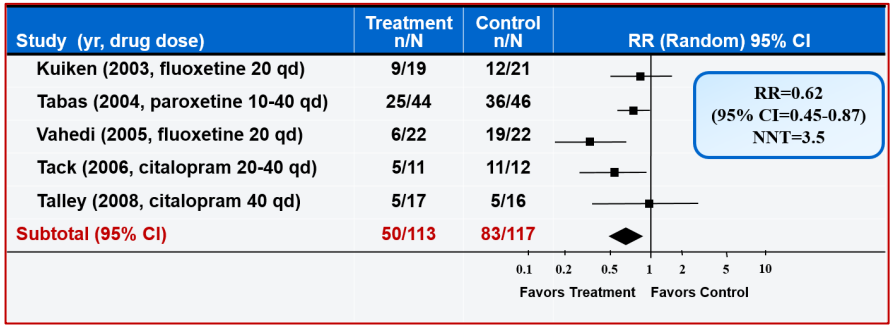


Parkman et al. Gastro 2017; 154(1): 65-76.

Psychological Therapies in IBS





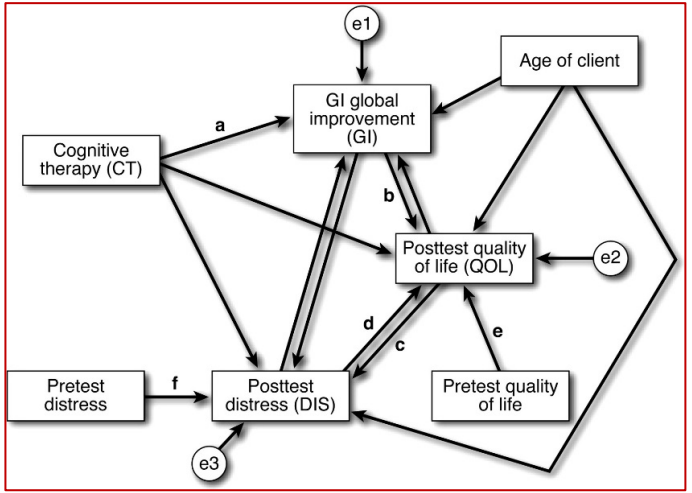


Laird et al. CGH 2016, doi: 10.1016/j.cgh.2015.11.020.
Ford AC et al. *Gut*. 2009;58:367-378.

How do CBT and neuromodulators work?

- CBT improves GI symptoms directly

- Review of 61 trials of antidepressants in neuropathic pain. “There appears to be no correlation between depression and pain relief.”



1. Lackner *et al, Gastro 2007;133:433-444*
2. Tabas et al. Gastro 204;99:914-920.
3. Tack et al. Gut 2006;55:1095-103.
4. Saarto et al. Cochrane Datab Syst Rev 2007;17:CD005454.

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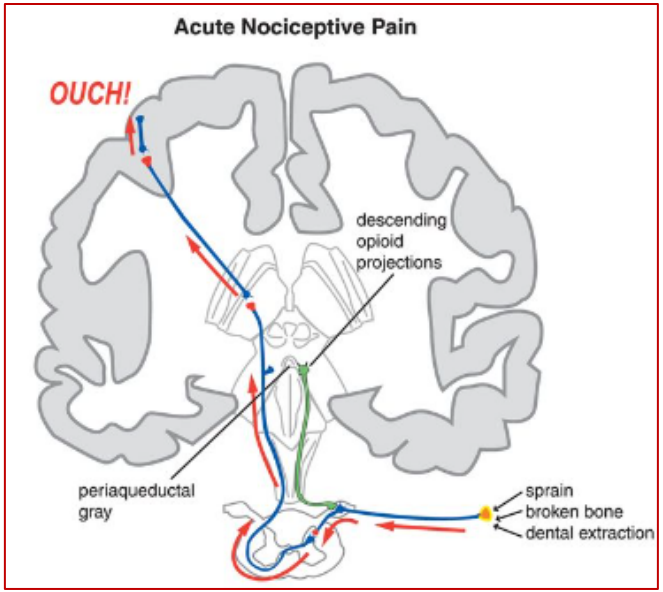
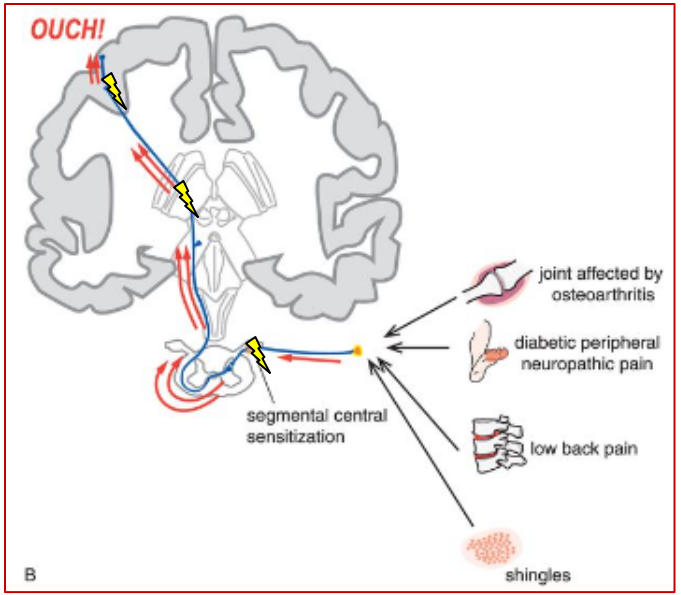
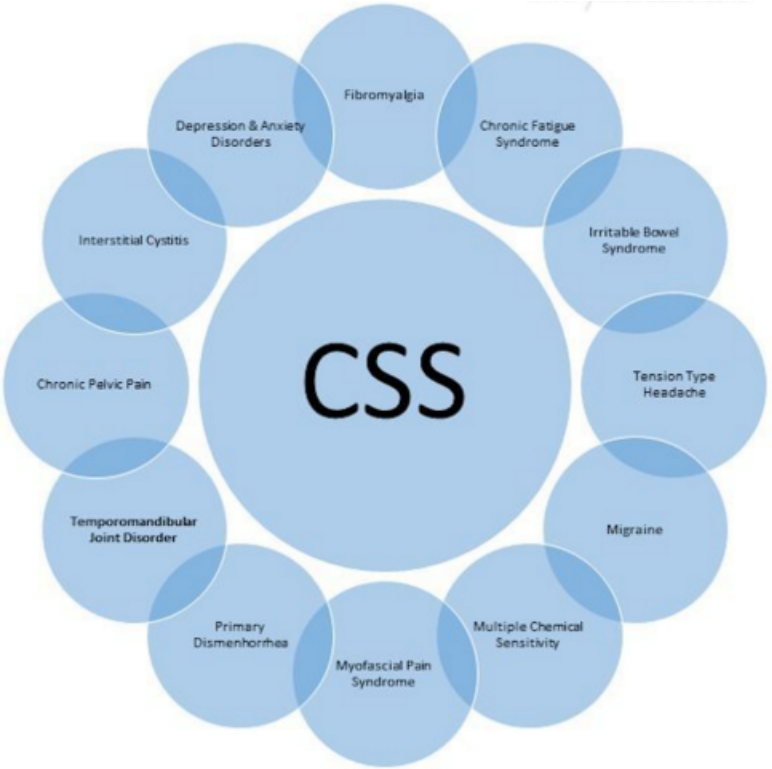




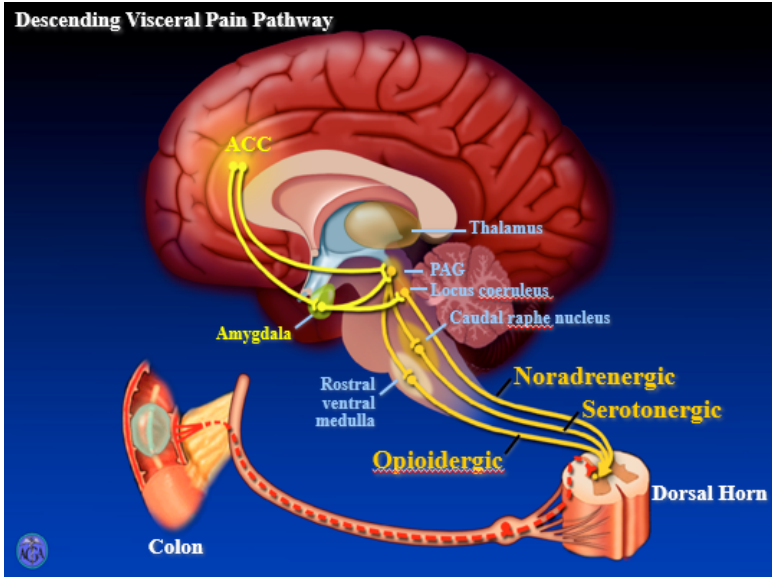
Stahl, S. M. (2013). Stahl's essential psychopharmacology: Neuroscientific basis and practical applications. Cambridge: Cambridge University Press.

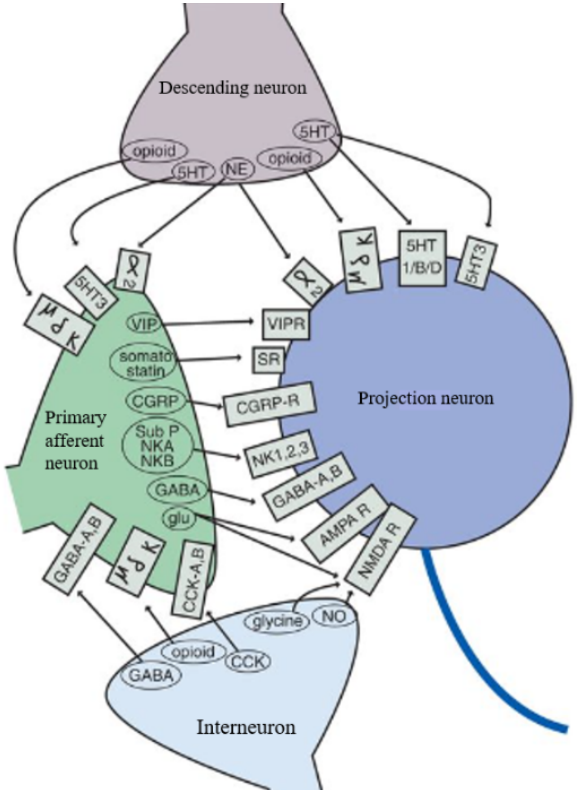
Central Sensitization Syndromes



Woolf. Pain 2011;152:2-15.

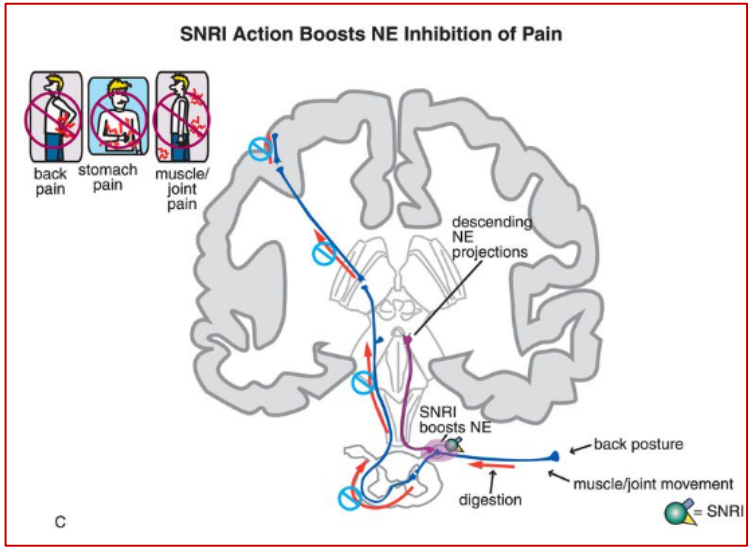
Pain and central sensitization

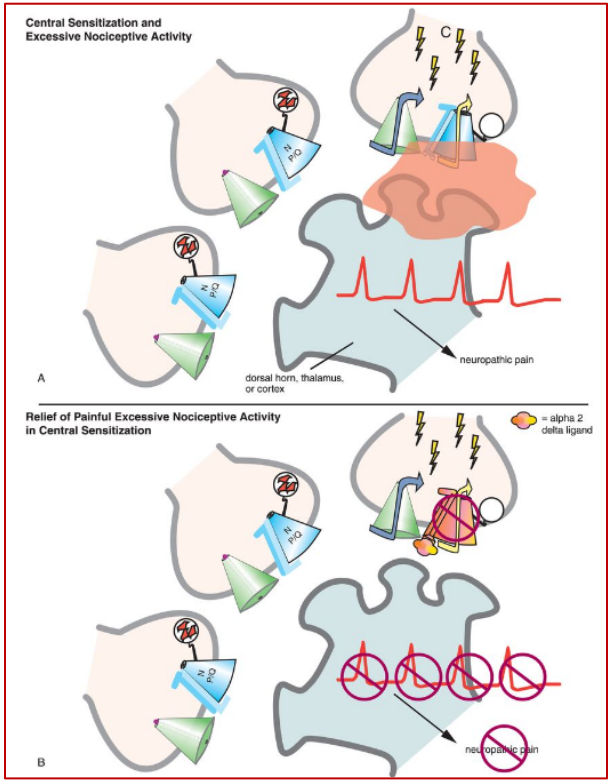




1. *Stahl, S. M. (2013). Stahl's essential psychopharmacology: Neuroscientific basis and practical applications. Cambridge: Cambridge University Press.*
2. Van Oudenhove et al. Gastro 2018;154(4):1140-1171

So how do exactly do they work ?





Stahl, S. M. (2013). Stahl's essential psychopharmacology: Neuroscientific basis and practical applications. Cambridge: Cambridge University Press.

Talking to patients about neuromodulators

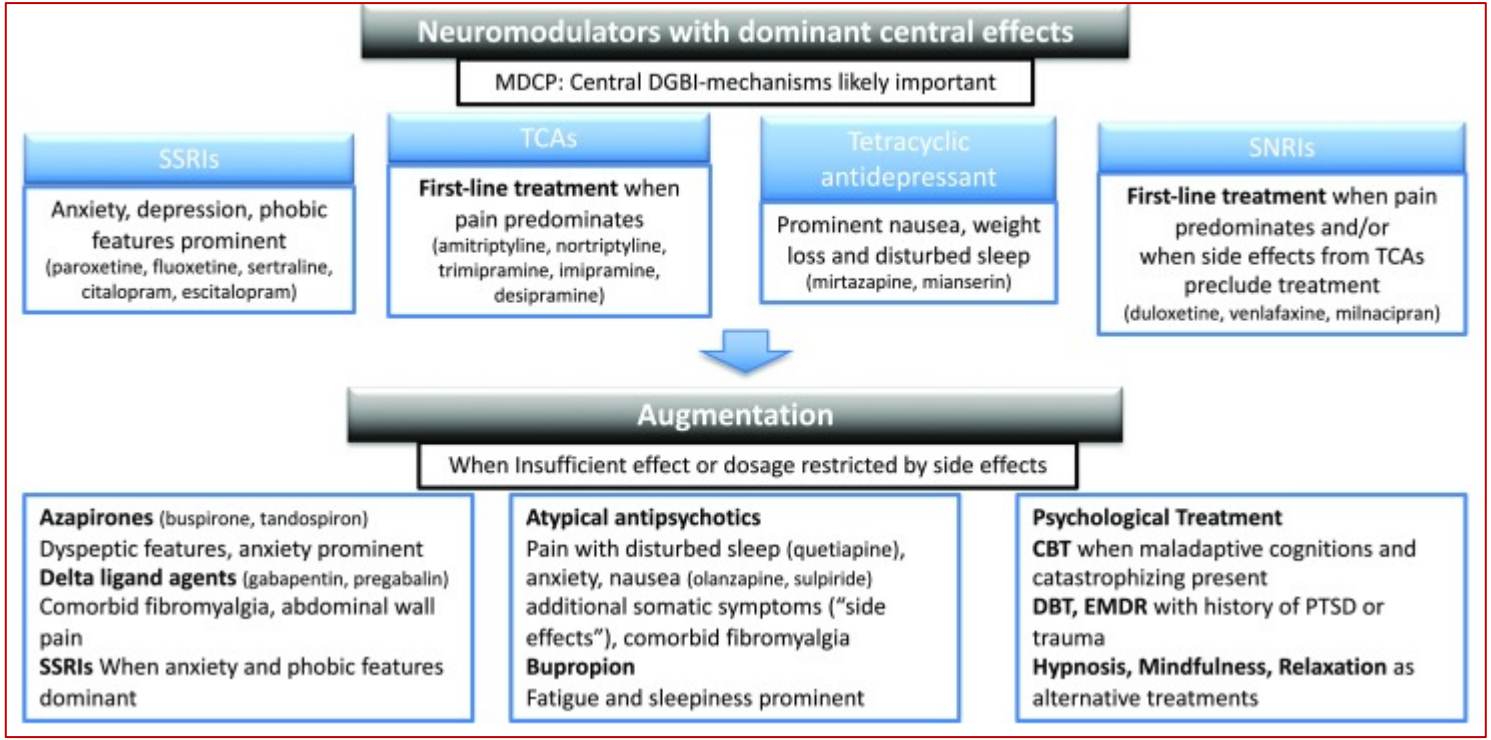
- Sometimes pain is not an indicator of a problem, it IS the problem. “Check engine” light example.
- I’m not trying to manage your mental health - the gut and the brain talk to each other with the same messengers that are involved in other processes like migraines, seizures, pain, depression and anxiety. “Antidepressants” are really neuromodulators that are used for many different conditions, just like aspirin can be used to prevent heart attacks and to treat a headache. In your case we’re using neuromodulators to fix a miscommunication between your gut and your brain not to treat your mental health.
- We may not be able to get you completely pain-free or eating a totally unrestricted diet but we can make things better than they are now. That said, its important to think about whether your symptoms are more bothersome than the potential side effects of these medications.

Neuromodulators

- Nortriptyline (Pamelor) - TCA
  - Helps with IBS-D, CVS, chronic abdominal pain
  - Less likely to cause Ach side effect, drowsiness, hypotension, weight gain compared to other TCA
  - Side effects: drowsiness, dry mouth, constipation, rarely QT prolongation/arrythymia
  - start 10-25mg nightly and increase by 10-25 every 1-3 weeks, up to 150mg; no data to support doses less than 25mg!
  - Can dose by blood level, target 50-150 ng/mL, check at ~50-75mg if not responding
  - check baseline/periodic EKG
- Duloxetine (Cymbalta) – SNRI
  - Helps with chronic abdominal pain; avoid if significant nausea
  - Side effects: nausea, insomnia, sexual dysfunction
  - Better balance of serotonin and norepinephrine effects than venlafaxine
  - Start 20-30mg, increase to 60mg prn. No good data that 90mg or 120mg better than 60mg for pain.
- Escitalopram (Lexapro) or Sertraline (Zoloft) – SSRI
  - Helps with IBS-C, comorbid anxiety. Not helpful for pain.
  - Side effects: agitation/insomnia, diarrhea, sexual dysfunction (all a little less with escitalopram, pro/con)
  - escitalopram 10-20 mg, Sertraline 50-150mg
- Pregabalin (Lyrica) – Anticonvulsant, Alpha2Delta ligand
  - Helps with abdominal wall pain, comorbid fibromyalgia, comorbid anxiety
  - Can combine with TCA/SNRI
  - More potent and better tolerated than gabapentin
  - Side effects: sedation, can improve over time
  - Start 75-300mg in 2 divided doses (ex. 75qd->75 bid->75/150, 150/150), increase every 1-3 weeks. At higher doses, tolerability may improve by splitting into 3 doses or giving higher dose at night
- Olanzepine (Zyprexa) – Atypical antipsychotic
  - Helps with nausea and poor appetite/weight loss
  - Augmentation of TCA or SNRI in treating pain
  - Helps with insomnia, anxiety
  - Side effects: sedation, weight gain
  - Dose range 2.5mg-10mg qhs
- Quetiapine (Seroquel) – Atypical antipsychotic
  - Augmentation of TCA or SNRI in treating pain
  - Helps with insomnia, anxiety
  - Side effects: sedation, dizziness, weight gain
  - Dose range 25mg-150mg qhs (dose for schizophrenia/mania 400-800mg)

Stahl, S. (2020). Prescriber's Guide: Stahl's Essential Psychopharmacology (7th ed.). Cambridge: Cambridge University Press

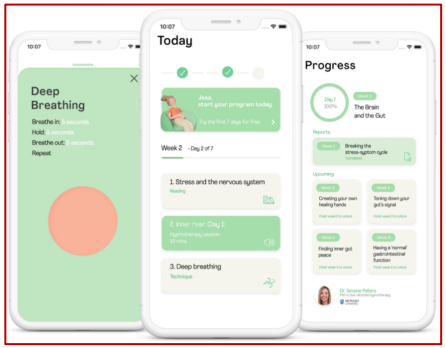
Augmentation

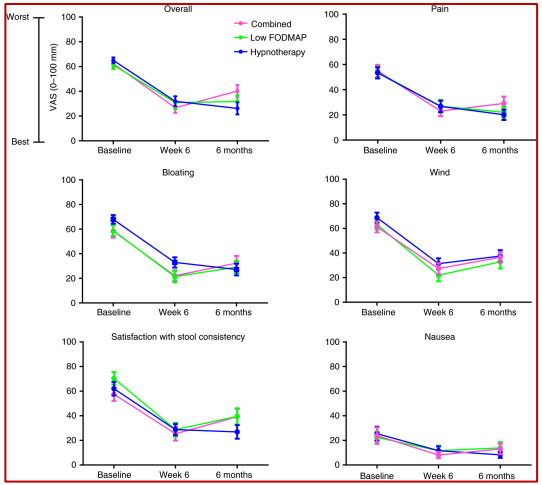


Drossman etal. Curr Gastro Rep 2018;20:58
Oudenhove et al. Gastro 2018;154:1140-1171

Nerva

- App based gut-directed hypnotherapy
- 6 week program, 15min/day hypnotherapy + optional educational reading, breathing exercises, visualizations
- 7d free trial then $69.99; maintenance plan with flareup mode after completion of initial 6 week treatment
- Can get free access as health practitioner
- RCT hypnotherapy vs low FODMAP vs both, 74 participants, all groups improved, no difference between groups





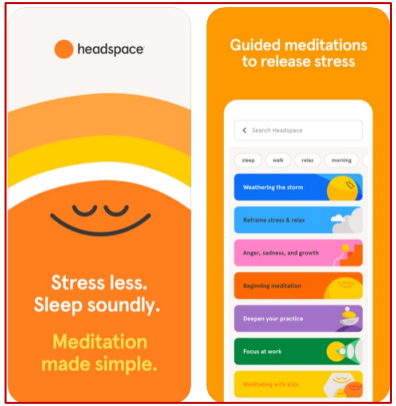
Gibson et al. APT 2016;44 (5): 447-459.
www.mindsethealth.com/nerva

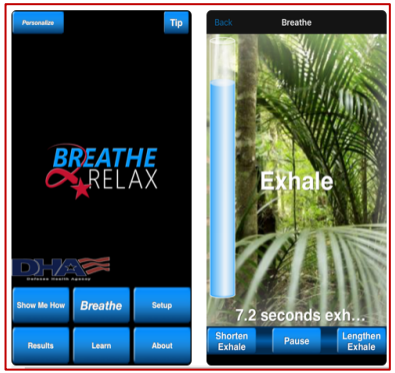
Headspace, Diaphragmatic breathing

- Headspace
  - Meditation and mindfulness app
  - Hundreds of meditations on everything from pain to insomnia to coping to sadness to anxiety etc.

- Breathe2Relax
  - Instructions and practice exercises for diaphragmatic breathing
  - Ability to tailor inhale/exhale ratios
  - Videos and literature on breathing and stress

- BellyBio Interactive Breathing
  - Smartphone placed on lower abdomen so that tilts back and forth with abdominal breathing
  - Music provides biofeedback – only plays if tilt consistent with deep abdominal breathing





Take Home Messages

- Educating patients about the gut-brain interaction helps!
- Setting expectations is important
- Try to incorporate neuromodulators and complimentary therapies into your practice – pick 2, start using them, and you'll be amazed how quickly you see results
- When it comes to neuromodulators, start low, go slow BUT keep going and keep adding
- Theres an app for everything!