Neuromodulators in Disorders of Gut-Brain Interaction: A Practical Approach

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Objectives

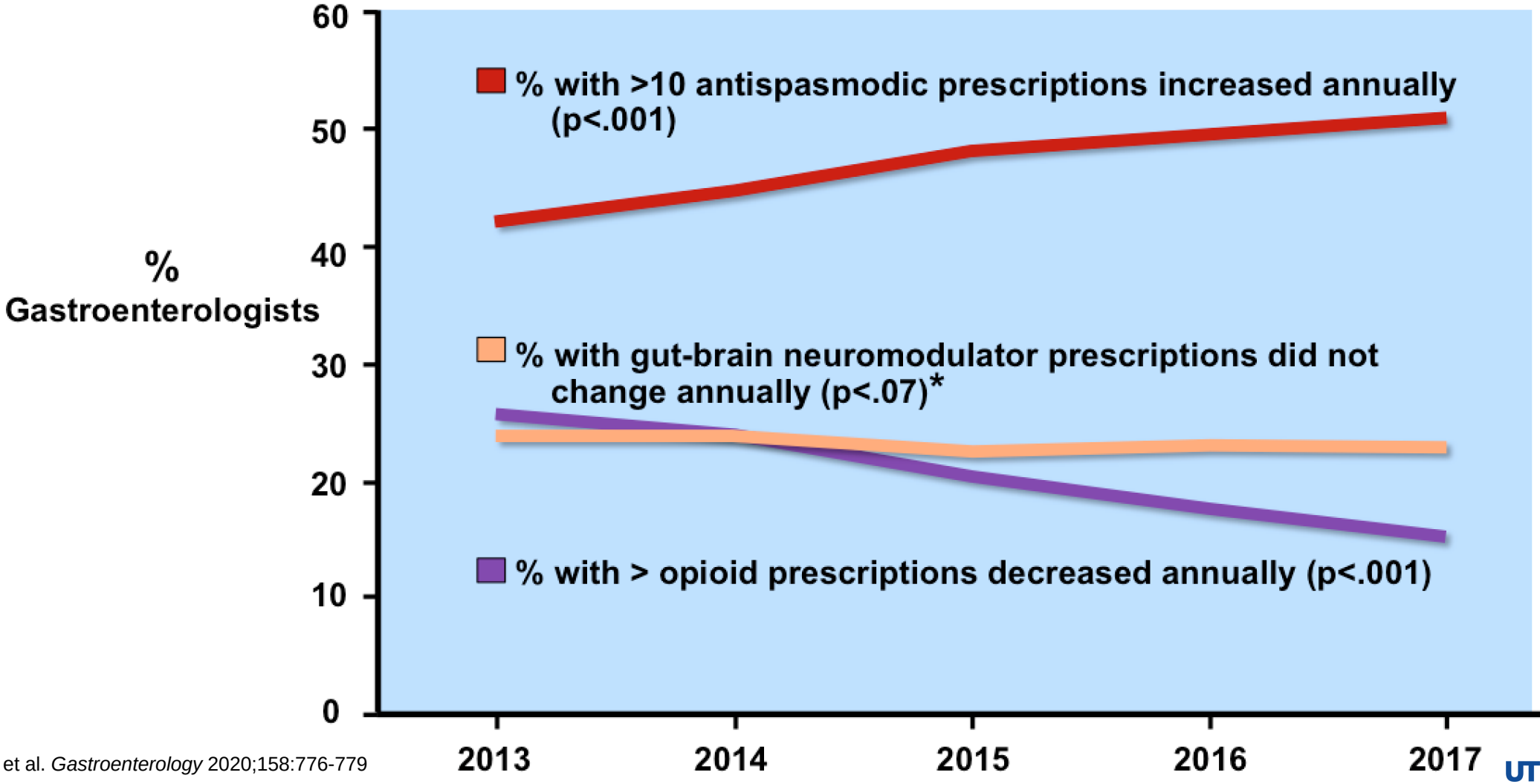
- Explain mechanism of action, side effect profiles, neuromodulators used to treat DGBIs
- Review efficacy of certain neuromodulators in treating symptoms of DGBI

- No disclosures

Case: a 35 yo F with IBS, chronic interstitial cystitis, hypothyroidism presents with constipation and abdominal pain . She has tried laxatives and lubiprostone, linaclotide, and plecanatide with reasonable response in frequency of BMs but still c/o lower abdominal pain. Worsens with stress, travel, dietary triggers

Gastroenterologist Prescription Trends:

Opioid, Neuromodulator, & Antispasmodics



Chen FW, et al. *Gastroenterology* 2020;158:776-779

*gut brain neuromodulator includes antidepressants (TCA, SSRI, SNRI, mirtazapine) and gabapentin

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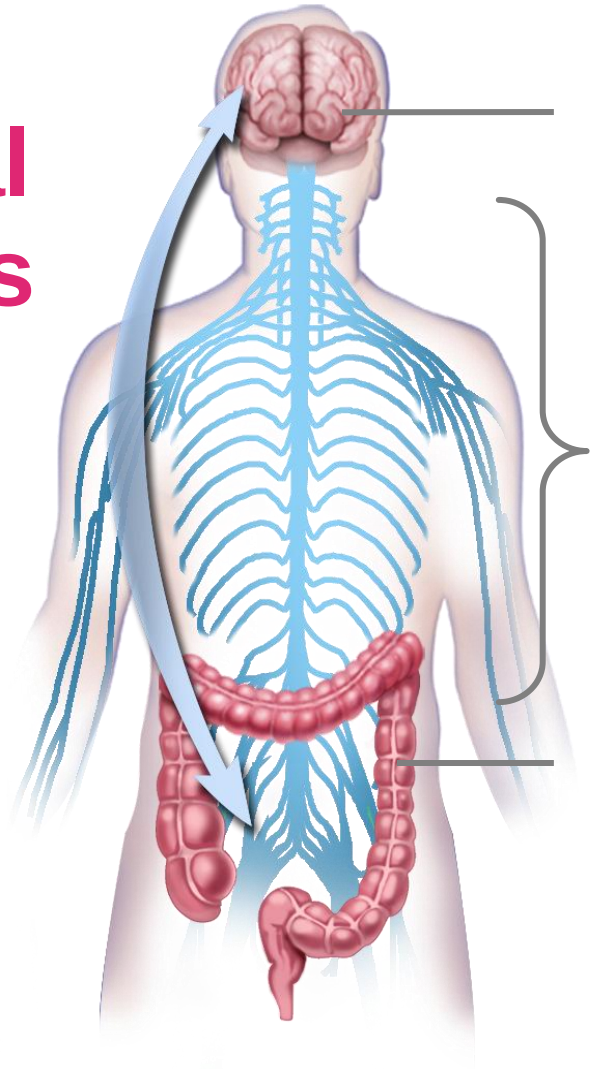
Current Practice among GIs

- Survey : Neuromodulators were described as extremely/very important in managing IBS by 55% of clinicians

- Why only used in 25% of IBS patients??
  - 59% concerned about addressing side effects
  - 33% not certain about neuromodulator selection
  - 28% do not feel comfortable prescribing

Nulsen B, et al. Aliment. Pharmacol. Ther. 2021;54(3):281-291

Effects of Central Neuromodulators in Gut-Brain Disorders with Pain



Antidepressant and Anti-anxiety effect

Visceral analgesia

Changes in motility

Drossman DA, et al. Gastroenterology 2018;154:1140-1171

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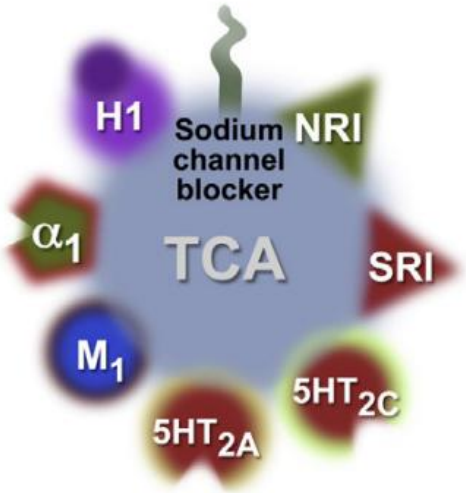
Classes of Neuromodulators

[Tricyclic] Antidepressants

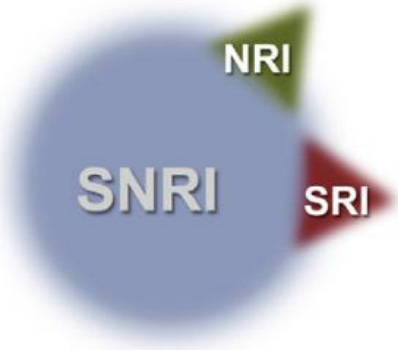


Amitriptyline
Desipramine
Nortriptyline
Imipramine

Selective serotonin reuptake inhibitors

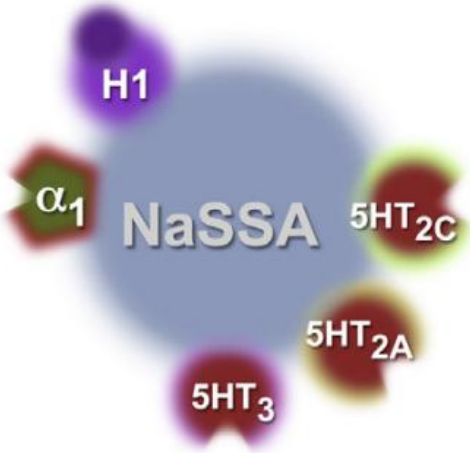
Fluoxetine
Paroxetine
Citalopram
Escitalopram
Sertraline

Serotonin noradrenalin reuptake inhibitors



Duloxetine
Venlafaxine
Desvenlafaxine
Milnacipran

Noradrenergic and specific serotonergic antidepressant



Mirtazapine
Trazodone
Mianserin

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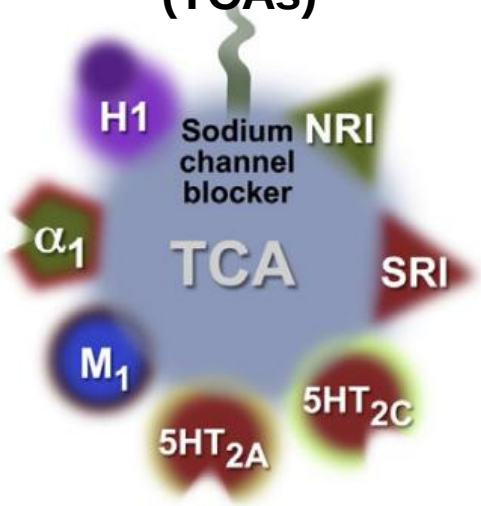
[Tricyclic] Antidepressants (TCAs)

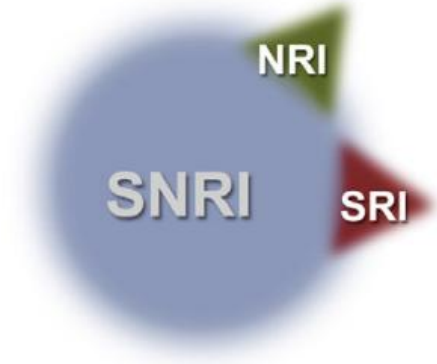


1st Line Treatment with Pain

Selective serotonin reuptake inhibitors (SSRI)

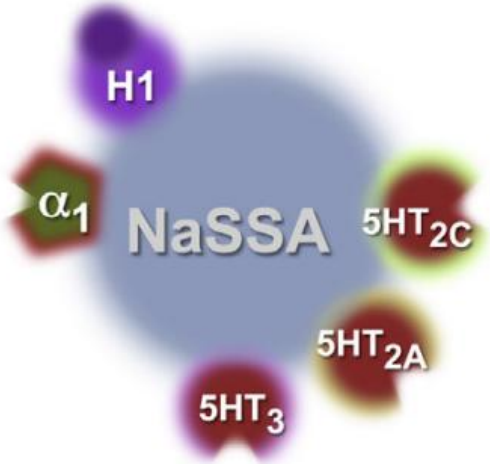
Prominent anxiety, depression and phobic features with DGBI; functional heartburn

Serotonin noradrenalin reuptake inhibitors (SNRI)



Predominantly treats Pain ; Second-line 2/2 side effects of TCAs

Noradrenergic and specific serotonergic antidepressant (Tetracyclic)



Treats Early Satiety, Nausea, Vomiting, Weight loss, Insomnia

Drossman DA, et al. Gastroenterology 2018;154:1140-1171

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Tricyclic Antidepressants

Improves pain and mood

Slows GI transit

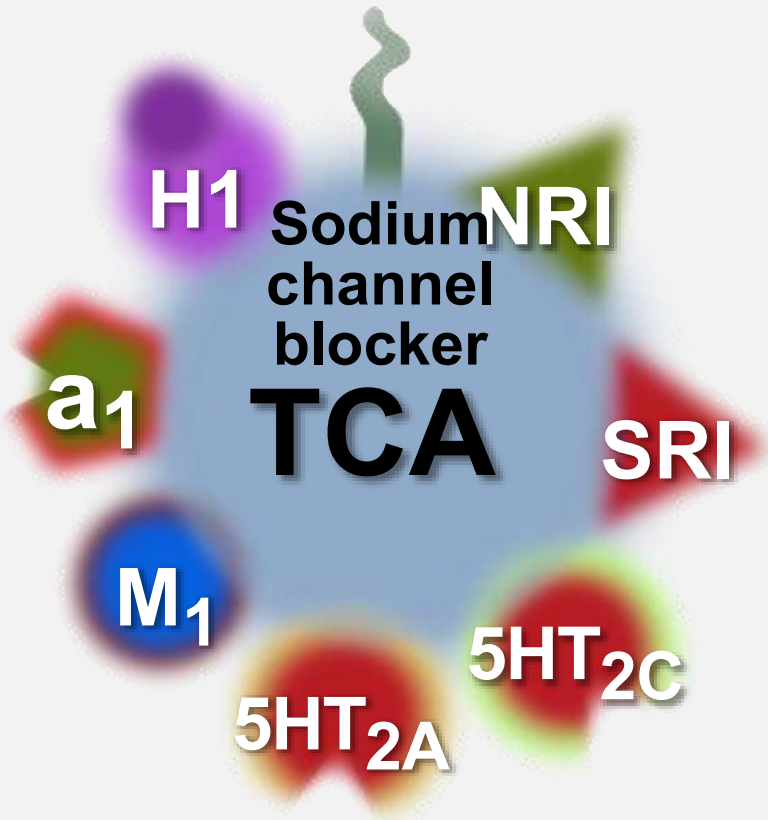
Modulate descending pain inhibitory pathways

Reduce response to noxious colon distension in rats

Tertiary amines more prone to side effects

Anticholinergic effects: Dry mouth, constipation, blurred vision, sexual dysfunction, arrhythmia

Antihistamine effects, Mast cell Degranulation: Drowsiness, dry eyes, weight gain



Secondary amines: Nortriptyline, Desipramine

Tertiary amines: Amitriptyline, Imipramine

Atlantis Phase 3 RCT Trial Amitriptyline in IBS:

Low Dose Amitriptyline 10mg-30mg Daily vs Placebo

Primary Endpoint at 6 months	Low-dose amitriptyline (n = 204)	Placebo (n = 197)	Effect*
Mean total IBS-SSS (SD)	170.4 (107.7)	200.1 (114.5)	-27.0 (-46.9, -7.1), p = 0.008
Change in IBS-SSS from baseline (SD)	-99.2 (112.9)	-68.9 (109.3)	--

Ford AC, et al. Lancet. 2023;11;402(10414):1773-1785

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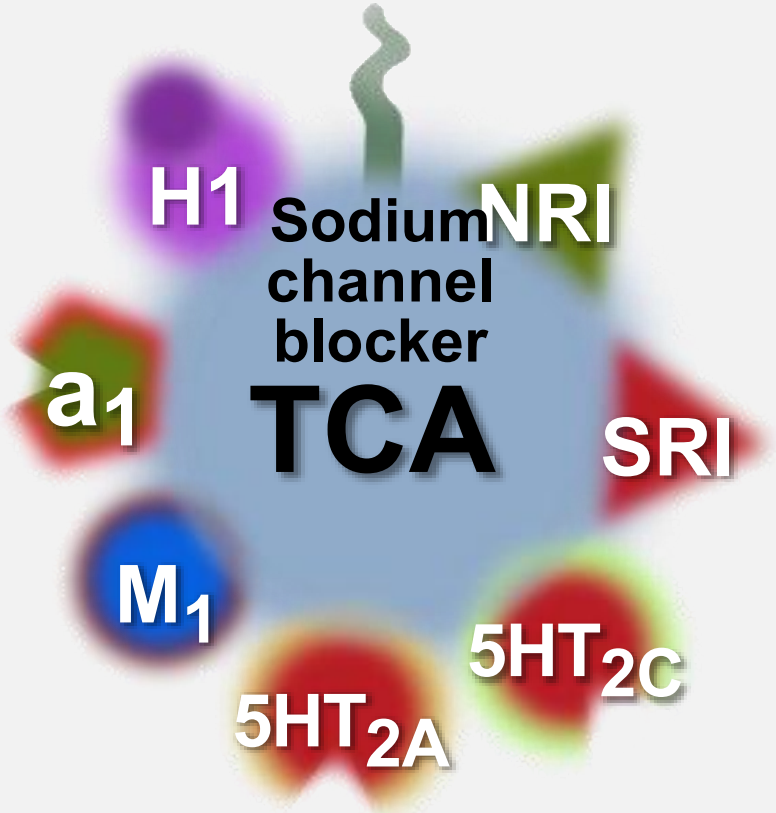
TCA's: Practical Points

- Low dose: Start at 10 or 25 mg qhs
- Increase to lowest most tolerated effective dose ideally 20-50 mg but can increase up to 75 mg
- Increase by 10 mg per week; maintain dose for ≥ 2 weeks if side effects occur
- Lower doses <75mg: no effect on mood
- Allow 6-8 weeks for significant reduction in pain
- Watch for QT prolongation in older patients esp with cardiac issues



IBS M or IBS C : Nortriptyline, Desipramine

IBS-D, Functional dyspepsia (EPS): Amitriptyline, Imipramine

ACG and AGA recommends the use of TCAs to treat global IBS symptoms

Recommendation
ACG: Strong
AGA: Conditional

Quality of Evidence
Moderate to Low

Lacy BE, et al. *Am J Gastroenterol.* 2021;116(1):17-44.
Lembo, A et al. *Gastroenterology.* 2022;163(1):137-151

SSRIs

Paroxetine, Fluoxetine, Sertraline, Citalopram, Escitalopram

Improves mood

Prokinetic effects

May have benefit in functional esophageal disorders ie functional heartburn

Usual doses are effective

Can use to augment TCA

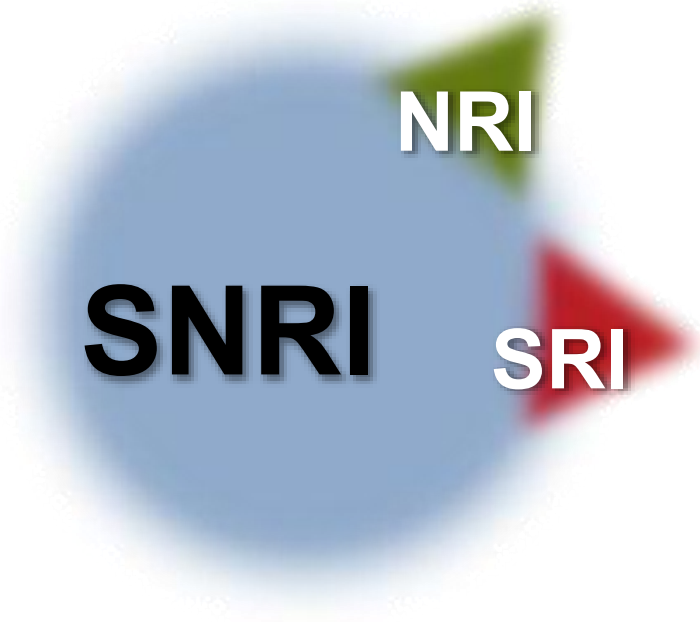
Low overall quality of evidence in IBS

No relief of symptoms in IBS or FD

Serotonin syndrome: fever, tremors, confusion, tachycardia, muscle stiffness, seizures

SNRIs

Duloxetine, venlafaxine, desvenlafaxine, milnacipran



Improves pain and mood

Slows GI motility mildly

Used as second line for pain

Fewer side effects than TCAs

Start duloxetine at 30mg daily for 1-2 weeks then increase to 30mg twice daily

Duloxetine 60mg -120mg effective dose

Tetracyclic Antidepressants

Mirtazapine, Trazodone, Mianserin

Treatment of early satiety, nausea, vomiting

Improves pain and mood

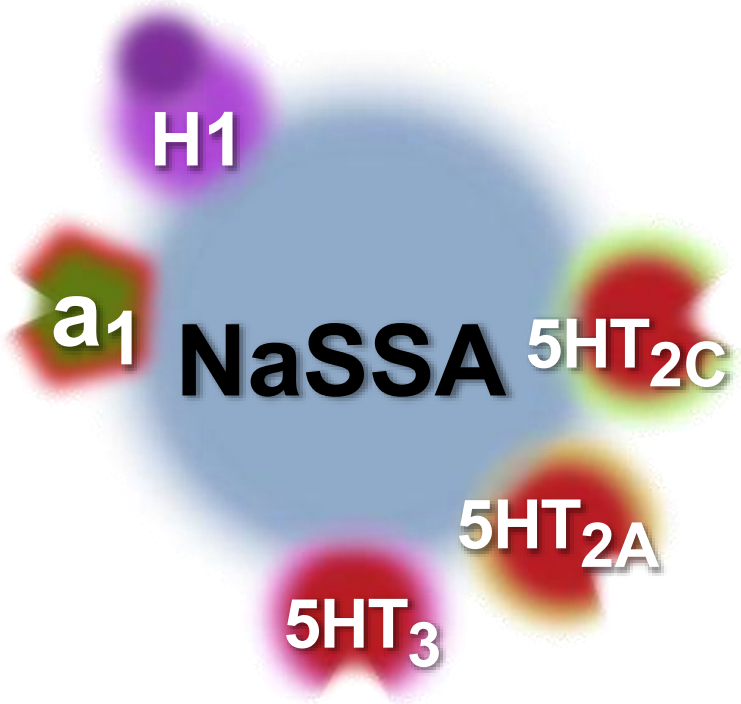
Mildly slows GI transit by noradrenergic and α-adrenergic effects

Can be used in FD or PDS, IBS-D, and cyclic vomiting syndrome

Mirtazapine 7.5mg for one week, then to 30mg at bedtime daily trial for 4-8 weeks for FD

Antihistamine effects cause drowsiness, weight gain (dose-dependent), fatigue

5-HT_3 antagonist effects reduce nausea



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Additional Neuromodulators to Consider

+ **Delta Ligands (Pregabalin, Gabapentin)**

  Used in IBS with significant pain. functional dyspepsia, and gastroparesis

  Use in fibromyalgia, chronic pain

  Pregabalin 150mg-600mg/day

+ **Atypical Antipsycotics (Olanzapine, Quetiapine, Sulpiride)**

  Dopamine-2 Receptor, 5-HT3 antagonist activity

  Used in functional dyspepsia and gastroparesis

  Nausea, vomiting and pain, disturbed sleep

  Olanzapine 2.5mg daily to 5mg/10mg over 2 weeks

+ **Azapirones (Buspirone and Tandospirone)**

  Non-benzo anxiolytics

  Increases contractility in esophagus, improved gastric accommodation

  Early satiety, nausea and fullness

  Used in Functional dyspepsia and gastroparesis

  7.5-10mg TID with meals

Drossman DA, et al. Gastroenterology 2018;154:1140-1171

Effects of NM on GI Symptoms, Motility, and Psychological Symptoms

	↓ Abd Pain	↑ GI Transit Rate	↓ GI Transit Rate	↓ Anxiety	↓ Nausea	↓ Depression
Tricyclics	+	-	+*	+/-	-	+
SSRIs	-	+**	-	+	-	+
SNRIs	+	-	+/-	+	-	+
Tetracyclics	+/-	-	+/-	+/-	+***	+
Atypical Antipsychotics	+****	-	-	+/-	+*****	+/-

Exceptions:
*Desipramine, Nortriptyline
**Paroxetine
***Particularly Mirtazapine
****Effective when used to augment an antidepressant
*****Particularly Olanzapine>Quetiapine

Hanna-Jairala I, Drossman DA. Am J Gastroenterol. 2024;119(7):1272-1284

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Gut-brain modulators for Disorders of Gut Brain Interaction

SSRIs
(paroxetine, fluoxetine, sertraline, citalopram, escitalopram)

When anxiety, depression, and phobic features are prominent with FGIDs

TCAs
(amitriptyline, nortriptyline, imipramine, desipramine)

First-line treatment when pain is dominant in FGIDs

Tetracyclic antidepressant
(mirtazapine, mianserin, trazodone)

Treatment of early satiety nausea/vomiting, weight loss and disturbed sleep

SNRIs
(duloxetine,venlafaxine, desvenlafaxine, milnacipran)

Treatment when pain is dominant in FGIDs or when side effects from TCAs preclude treatment

Insufficient effect or dosage restricted by side effects

Augmentation

Azapirones (buspirone, tandospirone)
Dyspeptic features, anxiety prominent

Delta ligands (gabapentin, pregabalin)
Abdominal wall pain, comorbid fibromyalgia

SSRI
When anxiety and phobic features dominant

Atypical antipsychotics
Pain with disturbed sleep (quetiapine) anxiety, nausea (olanzapine, sulpiride) additional somatic symptoms ("side effects")

Bupropion
Fatigue and sleepiness prominent

Psychological Treatment
CBT when maladaptive cognitions and catastrophizing present

DBT, EMDR with history of PTSD or trauma

Hypnosis, Mindfulness, Relaxation as alternative treatments

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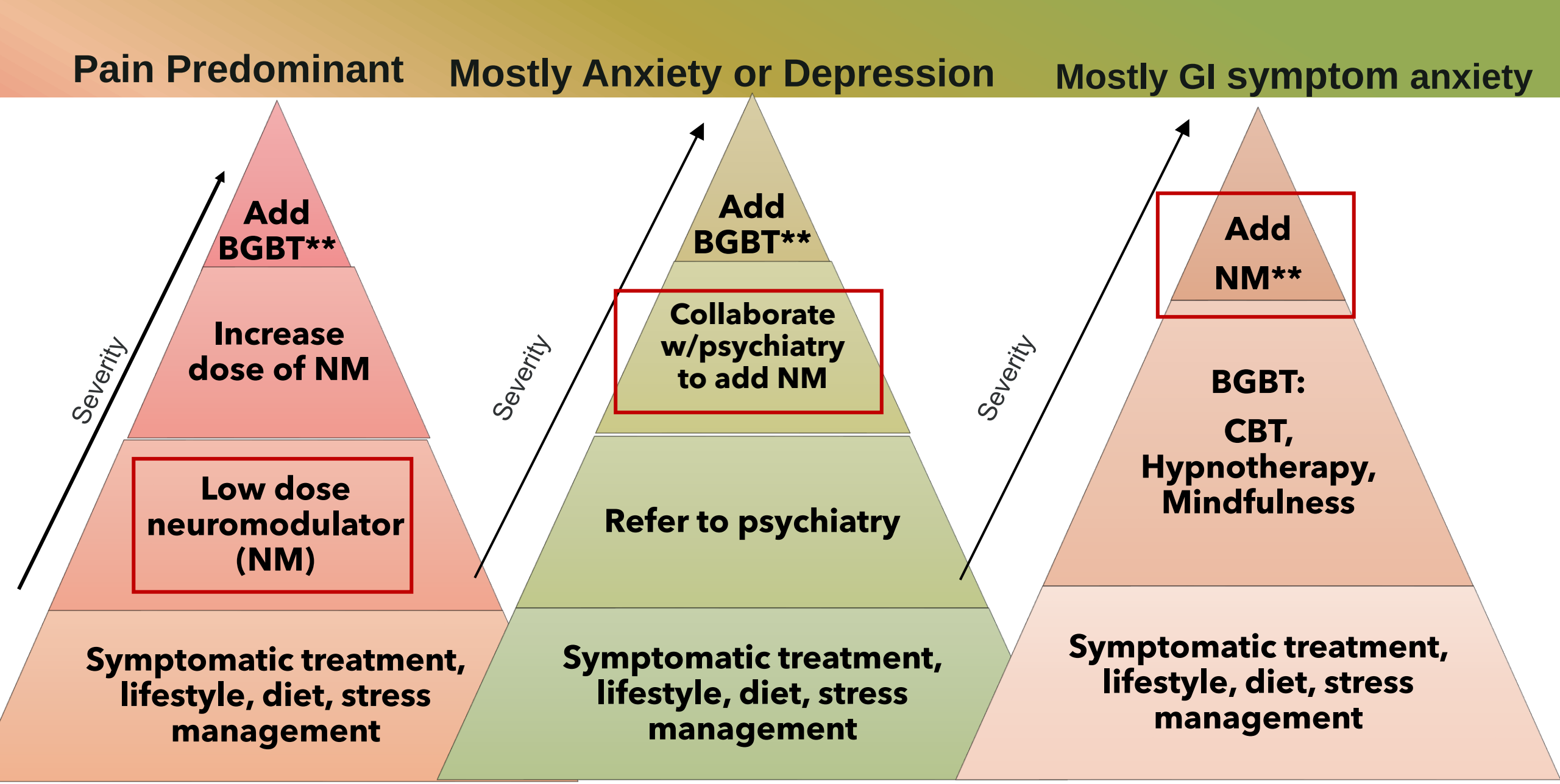
Drossman DA, et al. Gastroenterology 2018;154:1140-1171



Integrating NMs with Behavioral Therapy

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Keefer L, et al. Gastroenterology 2022;162:300-315

Take Home Points

- TCAs are 1st line for abdominal pain/DGBI: amitriptyline vs desipramine and ramp up dose to lowest effective dose (CVS 75mg)
- Side effects of TCAs: dry mouth, sedating, constipation, weight gain
- SNRIs for pain and second line: can start low but need 60mg Duloxetine
- SSRIs for mood disorders and functional heartburn
- Mirtazapine for upper DGBIs and IBS-D; for nausea, early satiety, weight loss (up to 15-45mg qhs)
- Consider pregabalin for IBS with other pain disorders (225mg bid)
- Augment neuromodulators with other neuromodulator classes (low dose TCA with SSRI) or brain-gut behavioral therapy
- Give medications time to work ~6 weeks
- Be mindful and educate about side effects and use them to the patient's advantage

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