IRRITABLE BOWEL SYNDROME

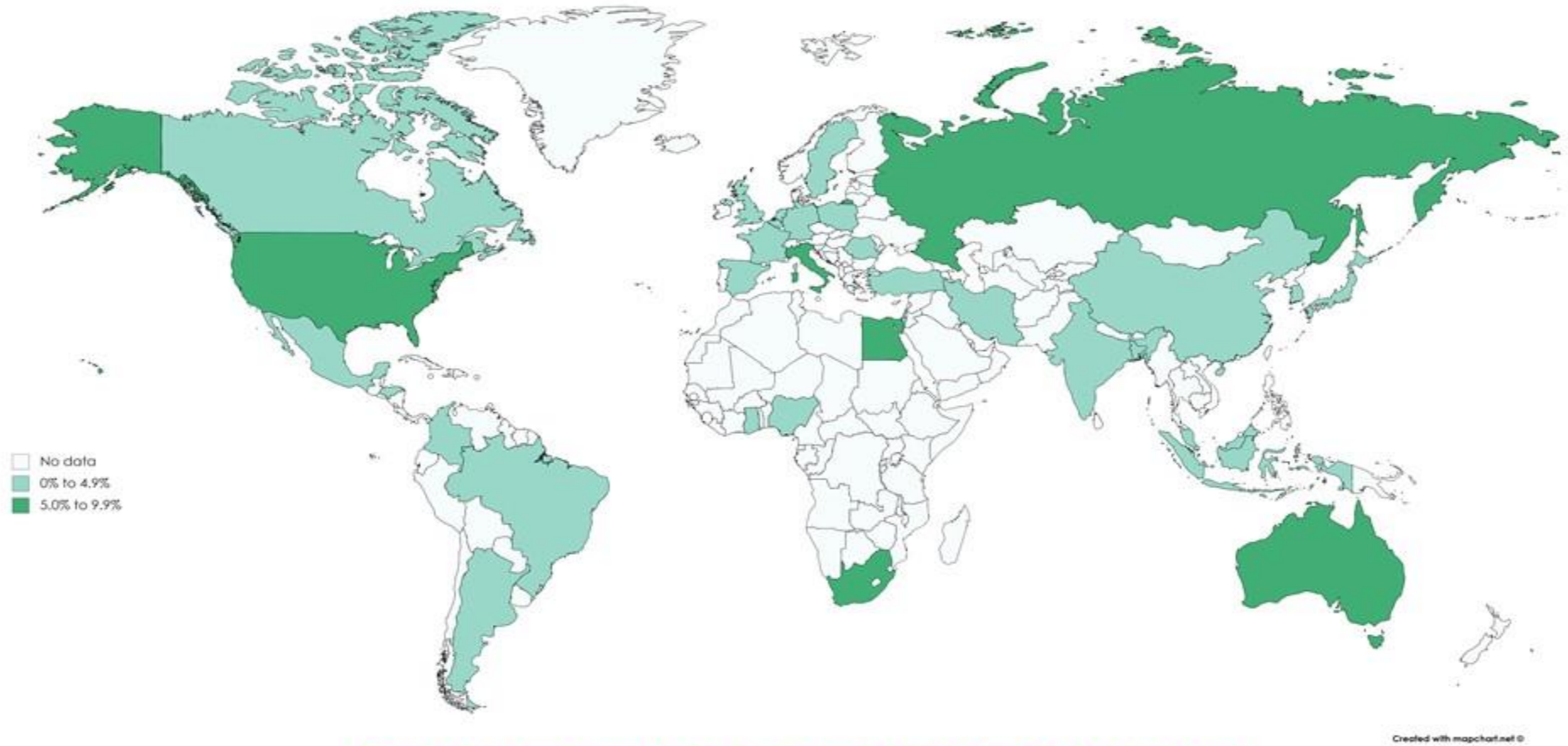
SIMON VEENSTRA

FACILITATOR: NONE RAMONATE

Introduction

- Chronic disorder of gut-brain interaction (formerly functional gastrointestinal disorder)
- Common: 5-10% of global population
- Up to 30% of visits to gastroenterologists
- Significant impact:
  - Patient QoL
  - Healthcare systems and cost
- Pathophysiology: relatively unknown although substantial advances

Worldwide Prevalence of IBS using Rome IV Criteria



Pooled prevalence in 6 studies = 3.8%; (95% CI 3.1%-4.5%)

Oka, Parr, Barberio *et al. Lancet Gastroenterol Hepatol* (in press)

Leeds Centre for Digestive Disease

UNIVERSITY OF LEEDS

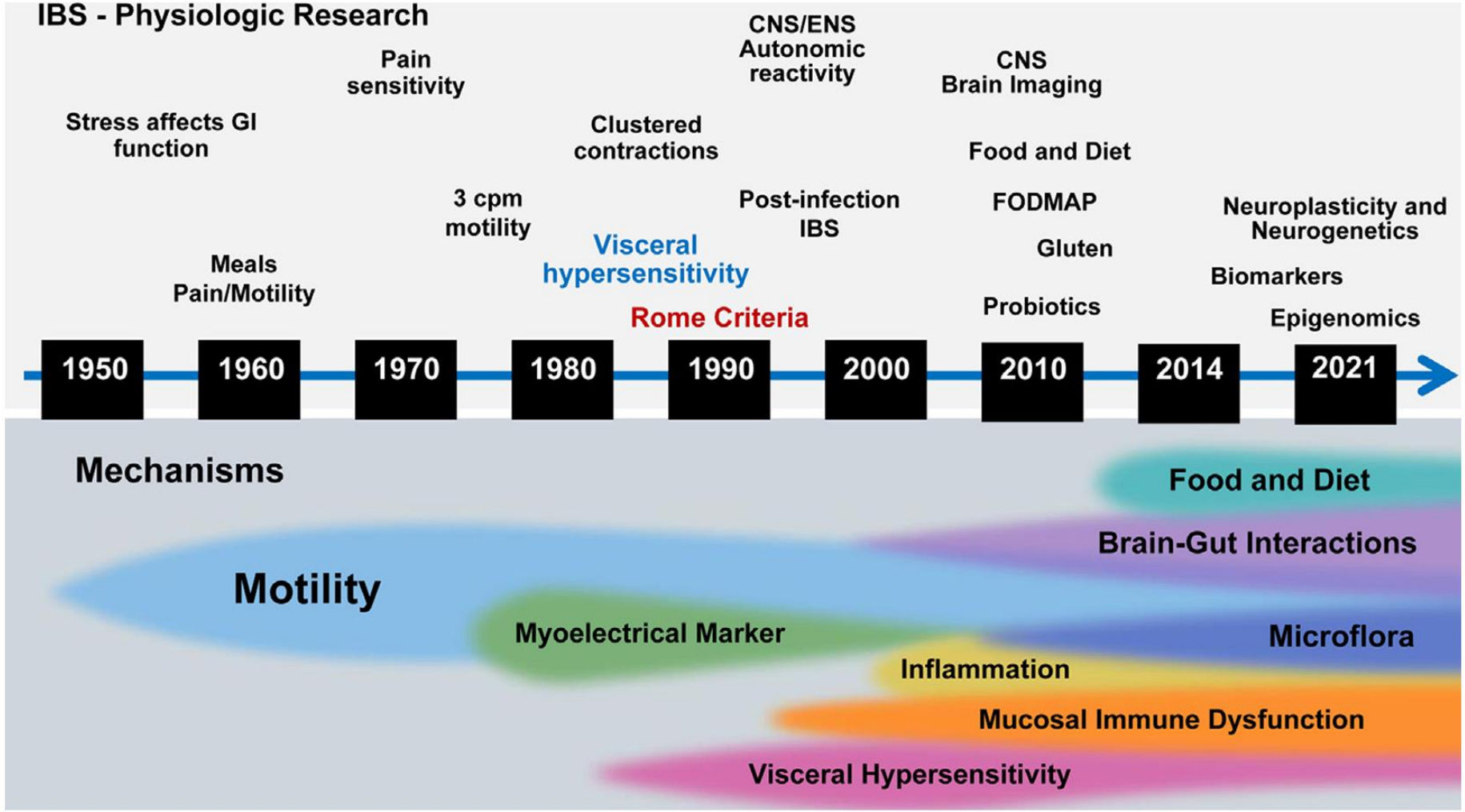
Rome IV Definition

Table 1. Rome IV diagnostic criteria for irritable bowel syndrome (4)

Recurrent abdominal pain on average at least 1 d/wk in the last 3 mo, associated with 2 or more of the following criteria
1. Related to defecation
2. Associated with a change in the frequency of stool
3. Associated with a change in the form (appearance) of stool
These criteria should be fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

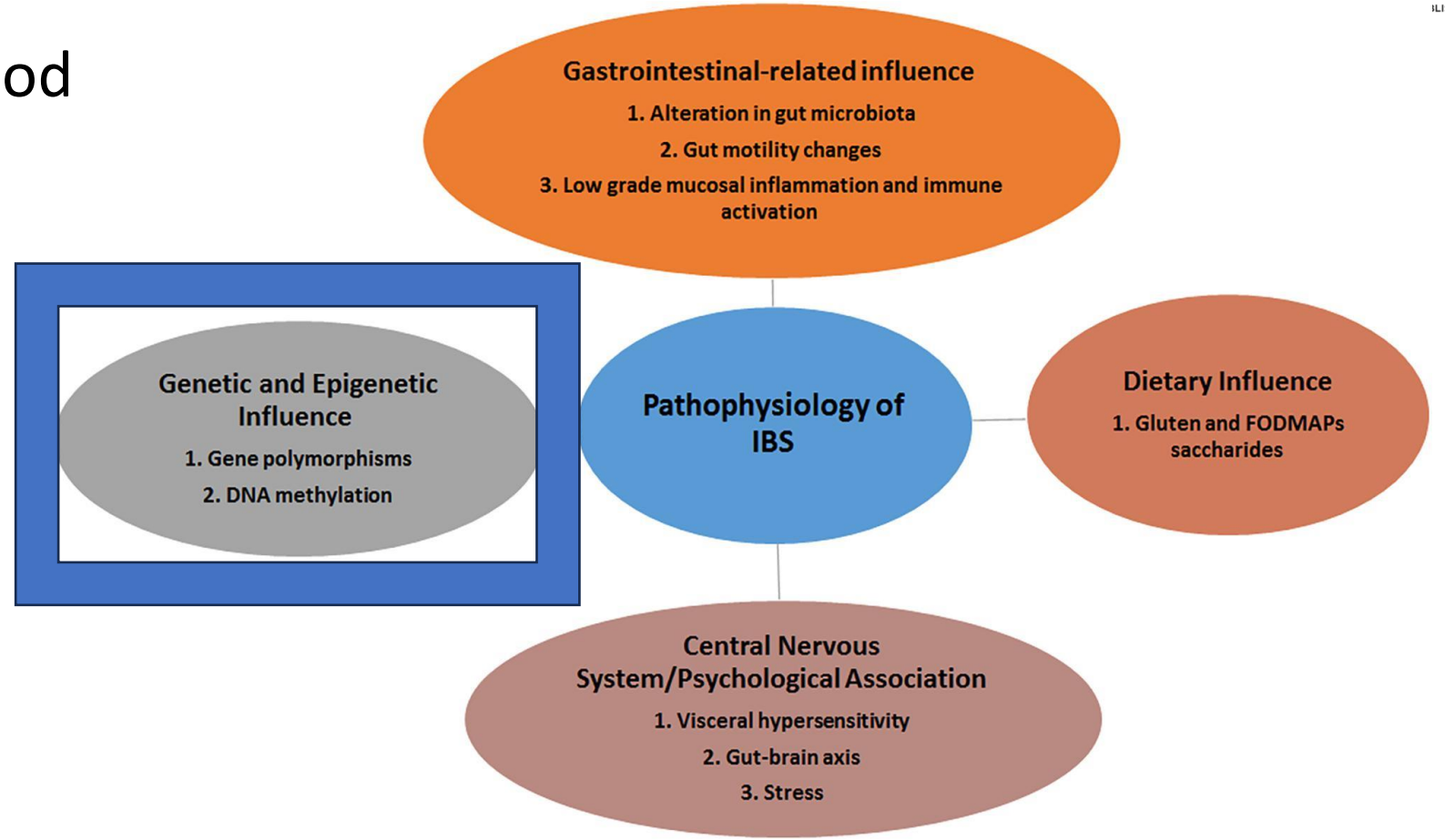
Adapted with permission from Bowel Disorders. *Gastroenterology* 2016;150: 1393–407.

Pathophysiology



Pathophysiology

- Poorly understood
- Multifactorial



Chong PP at al (2019) The Microbiome and Irritable Bowel Syndrome – A Review on the Pathophysiology, Current Research and Future Therapy. Front. Microbiol. 10:1136.

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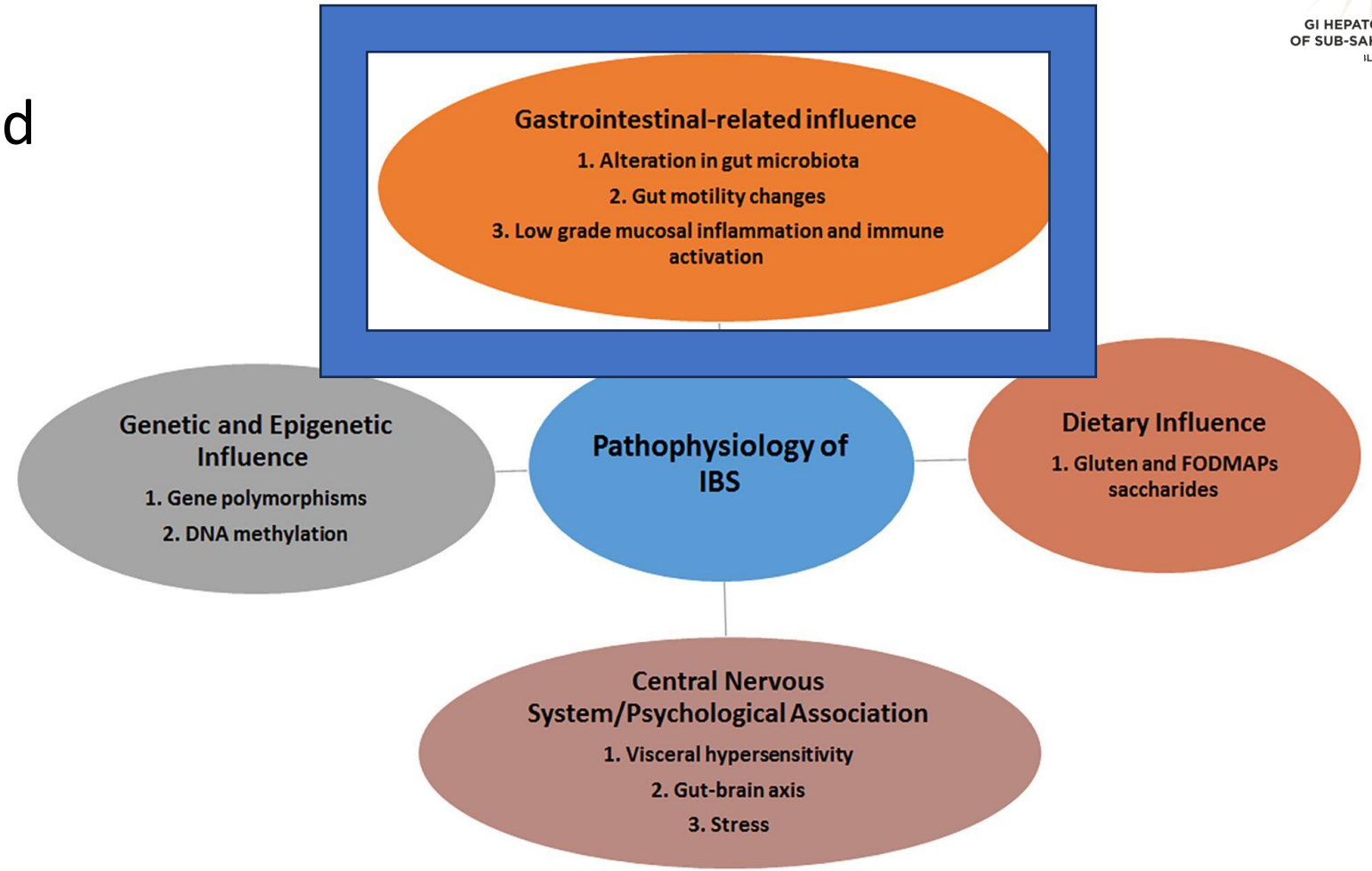

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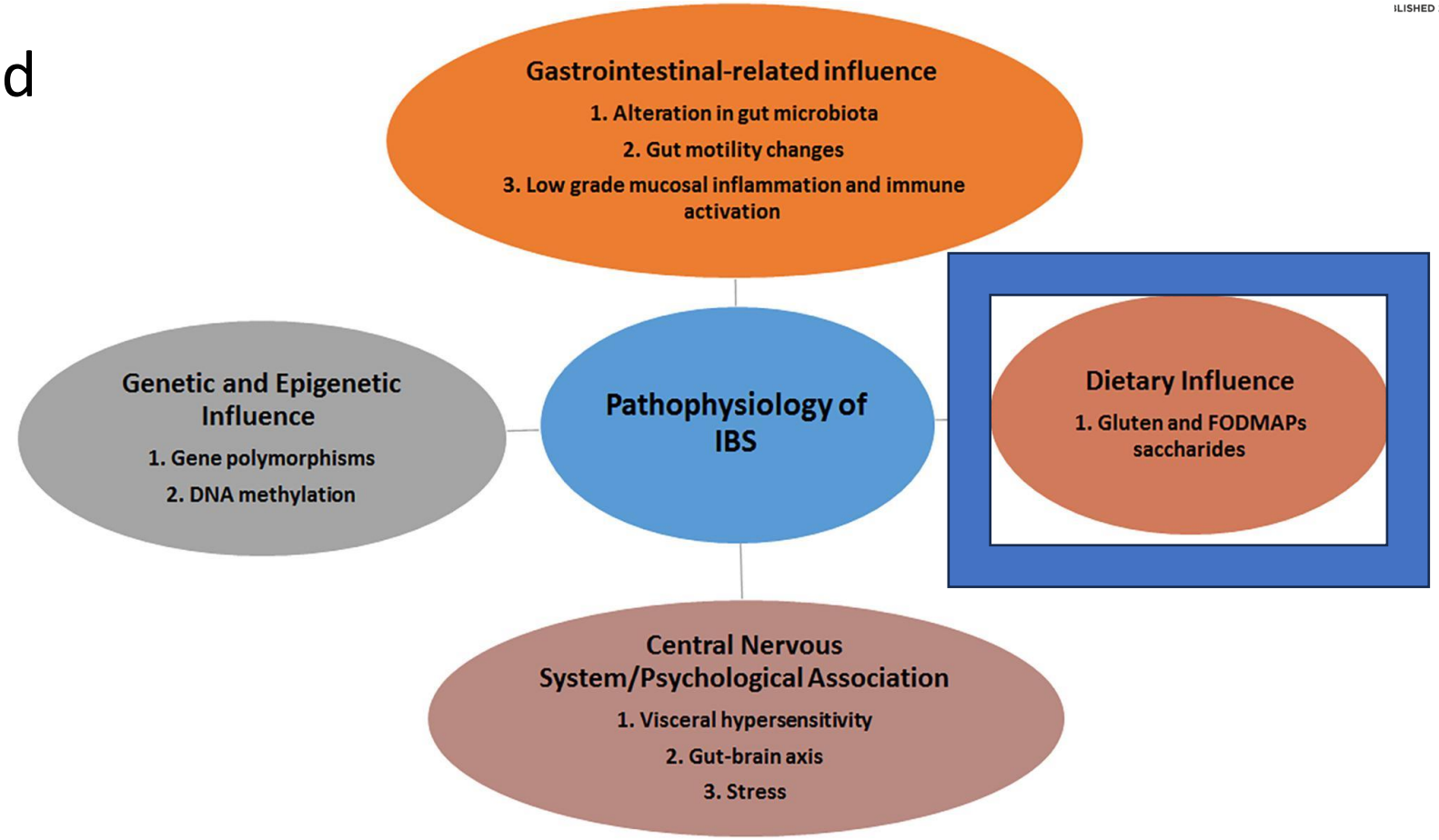

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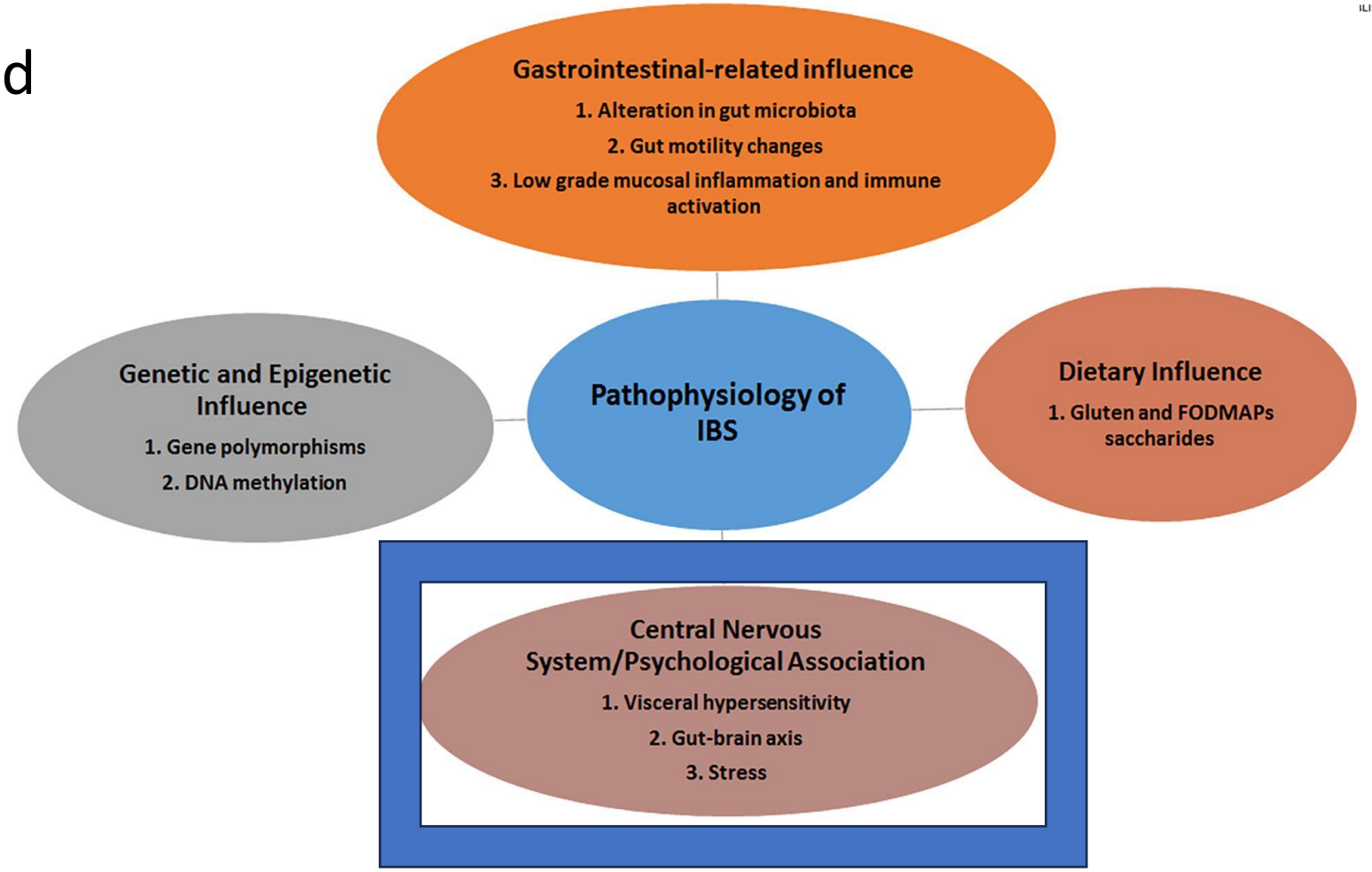

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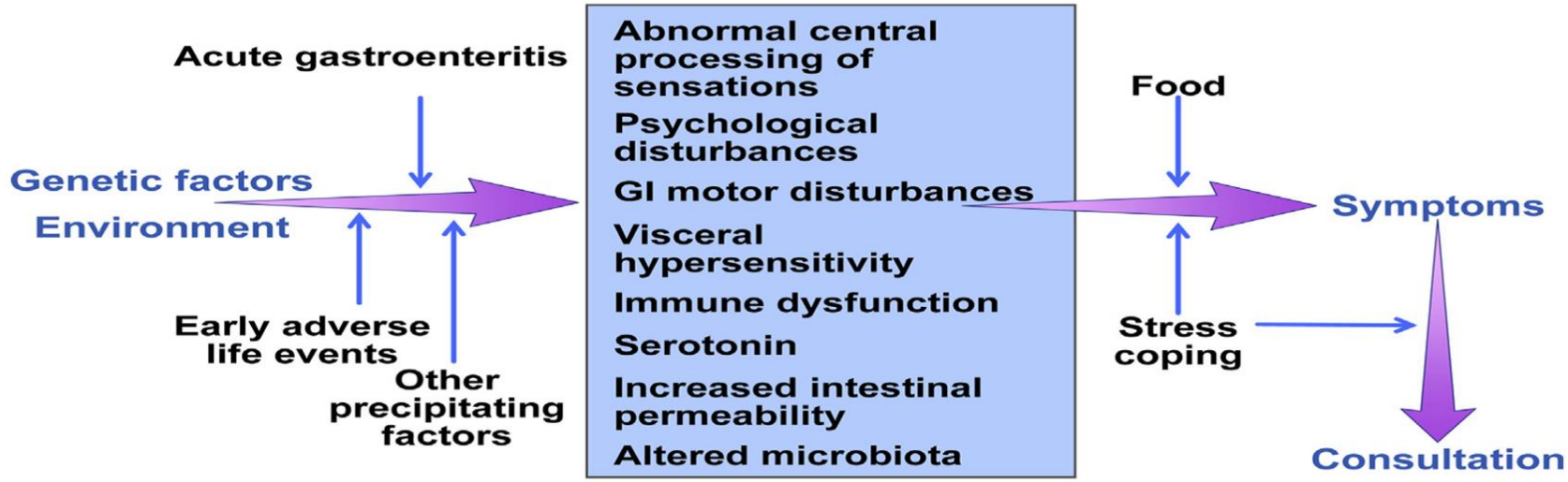


Fig. 2. Proposed pathophysiologic model of IBS. There are factors that increase risk of developing IBS, which include genetic factors and environmental factors such as early adverse life events, for example, abuse and infection. The alterations in brain–gut interactions result in multiple central and peripheral mediated pathophysiologic mechanisms (shown in the *blue box*). Once the symptoms of IBS occur, there can be triggers that increase symptom severity, such as food and stressors. The symptom burden and coping behaviors will influence health care seeking. (*Data from* Drossman DA, Chang L, Chey WD, et al. Rome IV Functional Gastrointestinal Disorders – Disorders of Gut-Brain Interaction. 4 ed. Raleigh, NC: Rome Foundation; 2016).

Gastroenterol Clin N Amer 50 (2021)505-522

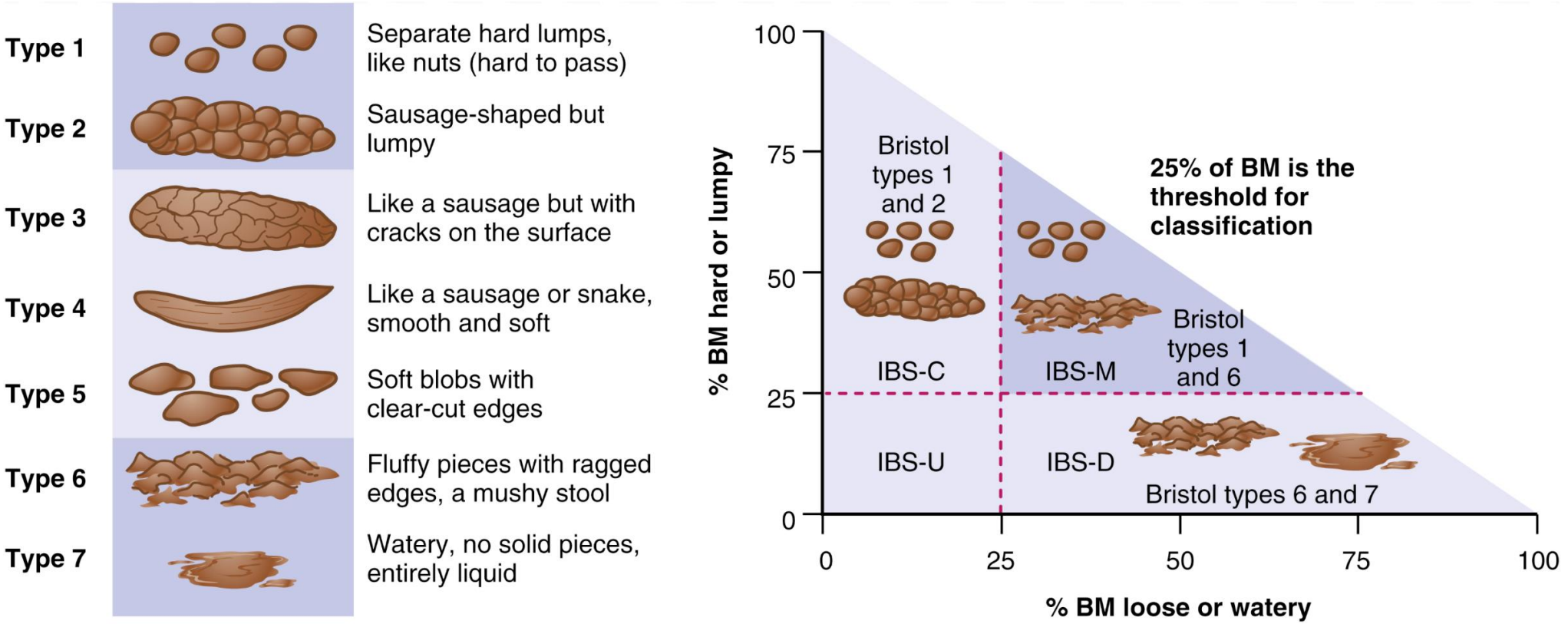
Risk Factors

- Post-infections
  - Strongest risk factor → 4-fold increase risk
  - GORD/dyspepsia, severe diarrhoeal illness, younger age, female, anxiety/depression or other stressful life event at time of illness
  - Type of pathogen: bacterial 13.8%, protozoal/parasitic 41.9%, viral 6.4%

Risk Factors

- Post-infections
- Higher socioeconomic status
- Previous antibiotic use
- Food intolerance
- Extra-intestinal somatic symptoms
- Perinatal factors
  - Young maternal age
  - Caesarian section
  - Low birthweight

Classification



The Bristol Stool Form Scale and classification of subtypes of IBS. *BM* , bowel movement; *C,* constipation; *D,* diarrhea; *M,* mixed; *U,* unsubtyped.

Diagnosis

- Move towards a POSITIVE diagnosis (∴ no longer diagnosis of exclusion)
  - Symptom based clinical diagnosis
  - Little utility for wide array of tests
  - Patient reassurance

- Abdominal pain is essential to the diagnosis
  - Chronic pain, usually recurrent and intermittent rather than continuous
  - Lower abdomen (SE Asian population might report upper abdominal pain)

Diagnosis

RULE OUT ALARM FEATURES

1. Blood in stool
2. Chronic diarrhoea
3. Unexplained weight loss
4. Unexplained recurrent vomiting
5. Progressive dysphagia
6. Fam hx of IBD, cancer or coeliac disease
7. Short duration of symptoms
8. Anaemia
9. New-onset symptoms in older age
10. Night time symptoms
11. Travel history (endemic location for parasitic disease)

1. Abdominal mass
2. Active arthritis
3. Dermatitis herpetiformis or pyoderma gangrenosum
4. Blood on DRE
5. Pallor
6. Signs of intestinal malabsorption
7. Signs of intestinal obstruction
8. Signs of thyroid dysfunction

Diagnosis

- Tests
  - RCT comparing positive diagnostic strategy vs standardised panel of Ix (serology, stool analysis, flexible sigmoidoscopy) [1]
    - →No cases of coeliac disease, IBD or CRC
    - →No difference in QoL, symptoms or patient satisfaction
    - →Increased costs in investigation arm
  - Meta-analysis: <1% chance of IBD in patients with symptoms suggestive of IBS with negative CRP and FCP [2]

1. Begtrup L.M.et al. Clin Gastroenterol Hepatol 2013; 11: pp. 956-962
2. Menees S.B et al. Am J Gastroenterol 2015; 110: pp. 444-454

Guidelines

- Coeliac serology in IBS-D
  - Important to exclude → long-term sequalae

- CRP and FCP (or lactoferrin) with alarm features or IBS-D
  - Pre-test probability of IBD in IBS is < 0.5-1.2%
  - Excellent at ruling out IBD

- No need for routine stool MC+S in all IBS patients
  - In appropriate clinical setting should be used i.e. risk factors for giardiasis

	AGA 2021	BSG 2021
	✓	✓
	✓	✓
	✓	✓

Guidelines

- No indication for routine colonoscopy in <45 years without alarm features
  - CRC screening independent of IBS symptoms in appropriate patients
  - Interestingly, in a large US study colon polyp rate lower in IBS compared with healthy controls (7.7% vs 26.1%), independent of age [1]

- Positive diagnostic strategy
  - Non-inferior to diagnosis of exclusion

- Accurate IBS subtyping important
  - Improves patient therapy
  - Current therapies usually target stool patterns
  - Continuous reassessment – up to half change subtype over 1 year

	AGA 2021	BSG 2021
	✓	✓
	✓	✓
	✓	✓

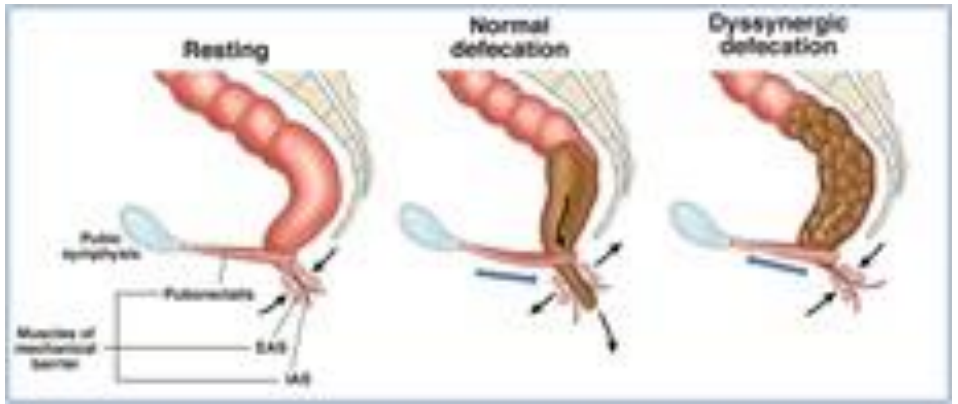
1. Chey WD et al. Am J Gastroenterol 2010;105:859–65

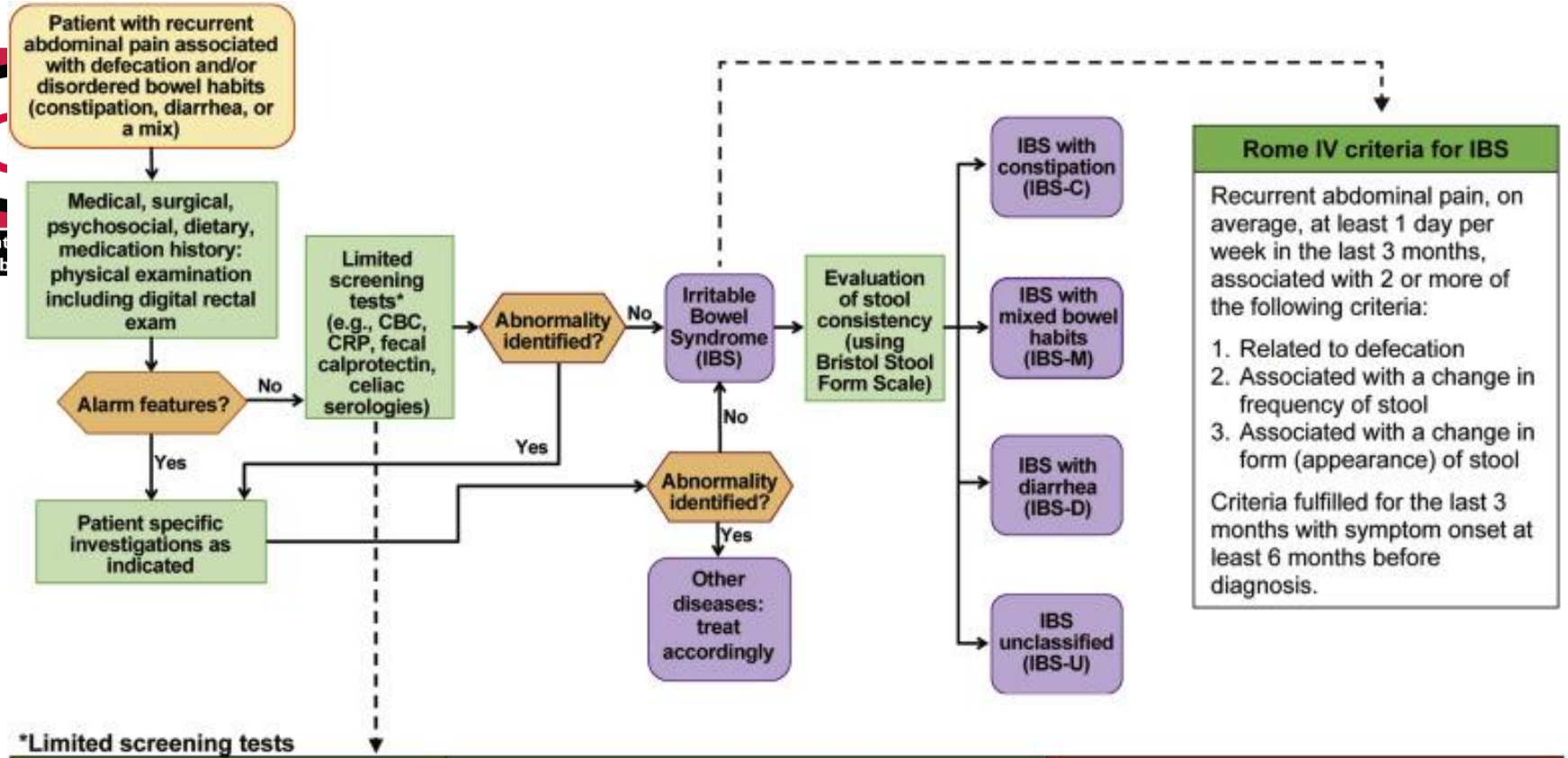
Guidelines

	AGA 2021	BSG 2021
	✓	✓
	✓	✓

- No routine testing of food allergies and food sensitivities
  - Up to 50% of IBS patients report adverse reactions to food > food intolerance or sensitivity
  - Testing likely to yield false positives (low specificity of tests available)

- Anorectal physiology testing in patients suggestive of pelvic floor disorder or refractory constipation
  - Can occur in all subtypes, prevalence estimated up to 40%
  - Diagnosis requires positive test in 2 of 3 tests (ARM, BET and/or impaired evacuation by imaging)





*Limited screening tests

Recommended	IBS population	Not recommended
Positive diagnostic strategy vs. diagnosis of exclusion	All IBS	Routine stool testing
Celiac serologies	IBS-D	Routine colonoscopy <45yrs
Fecal calprotectin/lactoferrin	IBS-D	Food allergy or insensitivities testing
C-reactive protein (CRP)	IBS-D	Lactulose or glucose hydrogen breath testing
Bile acid diarrhea testing	IBS-D where bile acid diarrhea is suspected	
Giardia stool antigen	IBS-D if Giardia is endemic	
Anorectal physiology testing	IBS with suspected pelvic floor dysfunction and/or refractory constipation	

Gastroenterology 2021;161:1092–1098

Management – General

- Doctor-patient relationship critical
  - Improved QoL
  - Reduction in symptoms
  - Reduction in health care visits
  - Improved treatment adherence

Management – General

- Doctor-patient relationship critical
  - Patients want increased empathy, support and information
  - Address concerns about serious illness
  - Understand life events and stressors
  - Important to communicate a positive diagnosis and management plan

Management – General

- Doctor-patient relationship critical
- Regular exercise

- Fibre and dietary therapies
  - Soluble fibre (insoluble fibre may exacerbate pain and bloating)
  - Advise to start low and build up 3-4g daily → 20-30g/day

Management – General

- Doctor-patient relationship critical
- Regular exercise

- Fibre and dietary therapies
  - Low FODMAP diet – 2nd line diet
  - FODMAPS increase colonic water and gas production → worsening of symptoms
  - Improve global symptoms
  - Elimination phase 2-6 weeks followed by gradual reintroduction
  - Long-term health risks as very restrictive diet
    - → micronutrient deficiencies
    - → changes in microbiome
  - Personalization phase – specific foods avoided after reintroduction
  - Should be performed by a GI dietician

Management – General

- Doctor-patient relationship critical
- Regular exercise

- Fibre and dietary therapies
  - Gluten free diet – has shown some benefit despite absence of coeliac disease
  - Benefit may be due to reduction in fructan (i.e. low FODMAP) rather than gluten
  - Overall no evidence to support a gluten free diet

Vasant DH, *et al*. *Gut* 2021;**70**:1214–1240

Management – General

- Doctor-patient relationship critical
- Regular exercise
- Fibre and dietary therapies (Low FODMAP diet)

- Probiotics
  - May be beneficial for global symptoms and pain (BSG)
  - AGA does not recommend currently but recognizes it is an important area of research
  - No evidence to support a specific strain or species Global symptoms: more days with control of urgency, firmer stools, fewer stools per day, fewer days with incomplete evacuation

Vasant DH, *et al*. *Gut* 2021;**70**:1214–1240

Management – General

- Doctor-patient relationship critical
- Regular exercise
- Fibre and dietary therapies (Low FODMAP diet)
- Probiotics

- Antispasmodics not recommended
  - Limited data to support there use
  - Side effects are common (particularly in elderly)

Vasant DH, *et al*. *Gut* 2021;**70**:1214–1240

Management – General

- Doctor-patient relationship critical
- Regular exercise
- Fibre and dietary therapies
- Probiotics
- Low FODMAP diet
- Antispasmodics not recommended

- `Peppermint oil
  - Recommended to provide relief of global IBS symptoms
  - Recent meta analysis: NNT to prevent 1 patient from having persistent symptoms was 3 for overall symptoms and 4 for abdominal pain
  - AEs similar to placebo (heartburn – enteric coated preparations may be beneficial)

Vasant DH, *et al*. *Gut* 2021;**70**:1214–1240

Guidelines - Drugs

- PEG not recommended alone
  - Does not improve overall symptoms or pain in IBS-C
  - Excellent for chronic constipation (NNT=3)

Guidelines - Drugs

- PEG not recommended alone

- Chloride channel activators are recommended (secretagogue)
  - Lubiprostone (PG1 analog) with high affinity for type 2 Cl channels → increased intestinal secretion and peristalsis
  - Highly effective for relieving global and individual symptoms
  - Good safety profile (AEs: N&V, diarrhoea → low discontinuation rate)

Guidelines - Drugs

- PEG not recommended alone
- Chloride channel activators are recommended (secretagogue)

- Guanylate cyclase activators are recommended (secretagogue)
  - Linaclotide and plecanatide: both effective in relieving overall and individual symptoms of IBS-C
  - Activate GC-C receptors → increase fluid secretion and peristalsis
  - Diarrhoea most significant AE, discontinuation rates low

Guidelines - Drugs

- PEG not recommended alone
- Chloride channel activators are recommended (secretagogue)
- Guanylate cyclase activators are recommended (secretagogue)

- 5-HT_4 agonist tegaserod is recommended for IBS-C in women <65 years and with ≤ 1 CVS risk factor
  - No response to other therapies
  - Stimulates peristaltic reflex and hastens GI transit
  - Reduces visceral hypersensitivity
  - Small but increased risk of CVS adverse events

Guidelines - Drugs

- PEG not recommended alone
- Chloride channel activators are recommended (secretagogue)
- Guanylate cyclase activators are recommended (secretagogue)
- 5-HT_4. agonist tegaserod is recommended for IBS-C in women <65 years and with ≤ 1 CVS risk factor

- Bile acid sequestrants not recommended to treat global IBS-D symptoms
  - Can be used in a subset of patients at risk of BAM

Guidelines - Drugs

- PEG not recommended alone
- Chloride channel activators are recommended (secretagogue)
- Guanylate cyclase activators are recommended (secretagogue)
- 5-HT_4 agonist tegaserod is recommended for IBS-C in women <65 years and with ≤ 1 CVS risk factor
- Bile acid sequestrants not recommended to treat global IBS-D symptoms

- Rifaximin to treat global IBS-D symptoms
  - Rifaximin is a non-absorbed antibiotic
  - Treats the dysbiosis hypothesis
  - Very safe NNH 8971 (TCA: NNH 18)
  - Two thirds likely to relapse but retreatment effective with little resistance

Guidelines - Drugs

- Aloseteron recommended to relieve IBS-D in women with severe symptoms & failed conventional therapy
  - 5-HT3 antagonist thereby slows intestinal transit
  - Originally withdrawn from the market in 2000 → ischemic colitis, complicated constipation and death
  - Re-introduced on a risk evaluation and management strategy limiting it women with severe symptoms
  - Ondansetron (TRITON trial 2023)[1] did not meet primary endpoints
    - Pooled meta-analysis suggests improvement in urgency and stool consistency
    - BSG guidelines say it's a reasonable alternative

1. *Aliment Pharmacol Ther.* 2023;57:1258–1271.

Guidelines - Drugs

- Aloseteron recommended to relived IBD-D in women with severe symptoms & failed conventional therapy

- Mixed opioid agonists/antagonists recommended to treat global IBS-D
  - Eluxadoline
    - Small risk of pancreatitis & sphincter of Oddi dysfunction
  - Loperamide not recommended as first line therapy because does not improve global IBS symptoms

Guidelines - Drugs

- Aloseteron recommended to relived IBD-D in women with severe symptoms & failed conventional therapy
- Mixed opioid agonists/antagonists recommended to treat global IBS-D

- TCAs should be used to treat global symptoms of IBS
  - Improve pain (due to anticholinergic effects and central effect on norepinephrine and dopaminergic receptors)
  - At higher doses slow GI transit therefore improve diarrhoea

Guidelines - Drugs

- Aloseteron recommended to relived IBD-D in women with severe symptoms & failed conventional therapy
- Mixed opioid agonists/antagonists recommended to treat global IBS-D
- TCAs should be used to treat global symptoms of IBS

- Na-H exchange inhibitor (Tenapanor)
  - Improves bloating, abdominal pain, constipation
  - Safe, most common side effect is diarrhoea

Guidelines - Other

- Gut directed psychotherapies for global IBS symptoms
  - Adjunctive to medical therapy particularly for IBS-U/IBS-M
  - Skills based techniques: relaxation training, cognitive reframing, techniques that alter pain perception
  - RCT: hypnotherapy vs low FODMAPs suggested equivalence [1]

1. Peters SL et al. Aliment Pharmacol Ther 2016;44:447–59.

Guidelines - Other

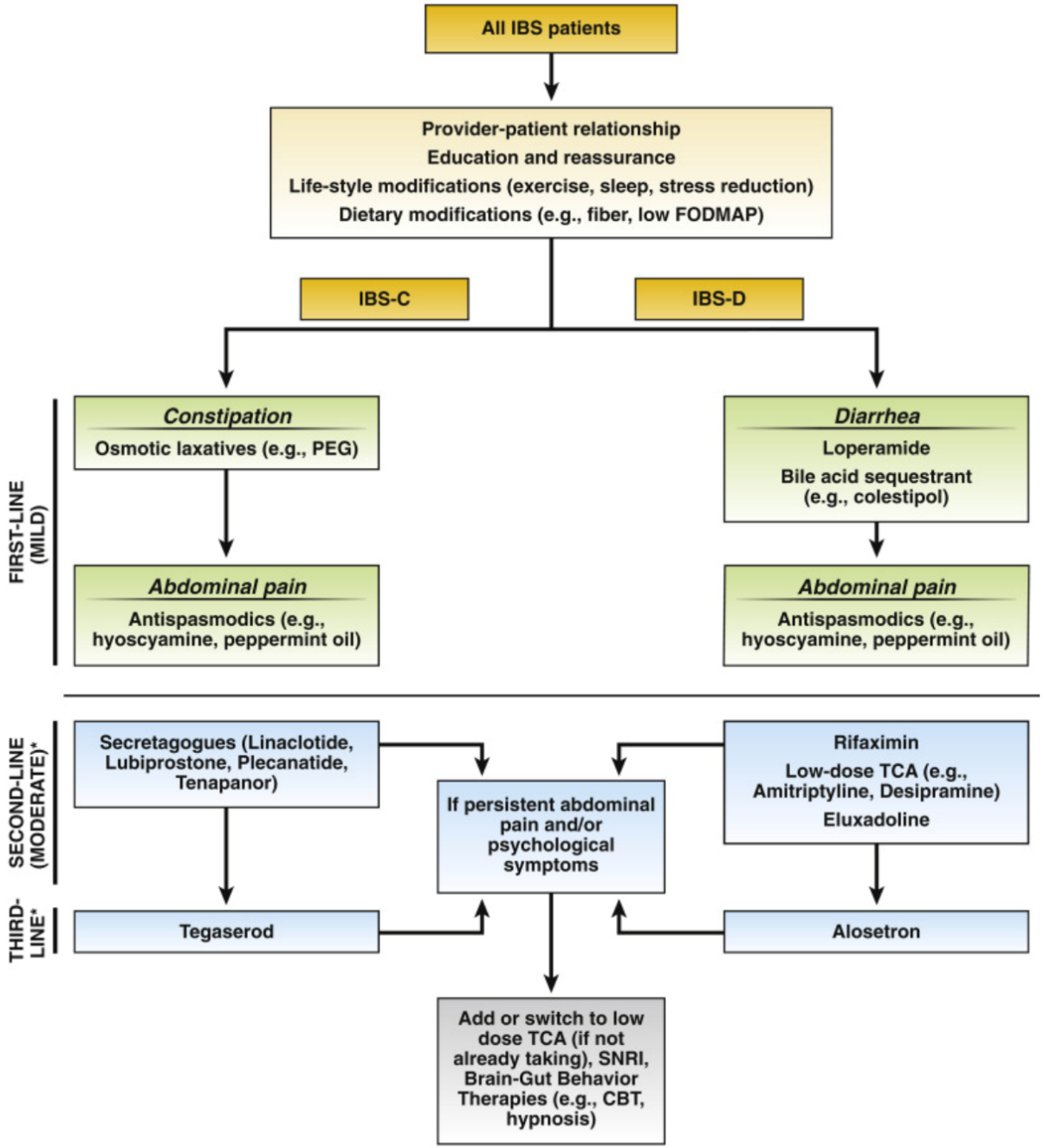
- Gut directed psychotherapies for global IBS symptoms

- Against the use of FMT for global IBS
  - Limited evidence and low quality

Management – Drugs

- Therapies usually directed towards predominant system
  - IBS-D
  - IBS-C
  - Abdominal pain

Clinical Decision Support Tool: IBS Treatment



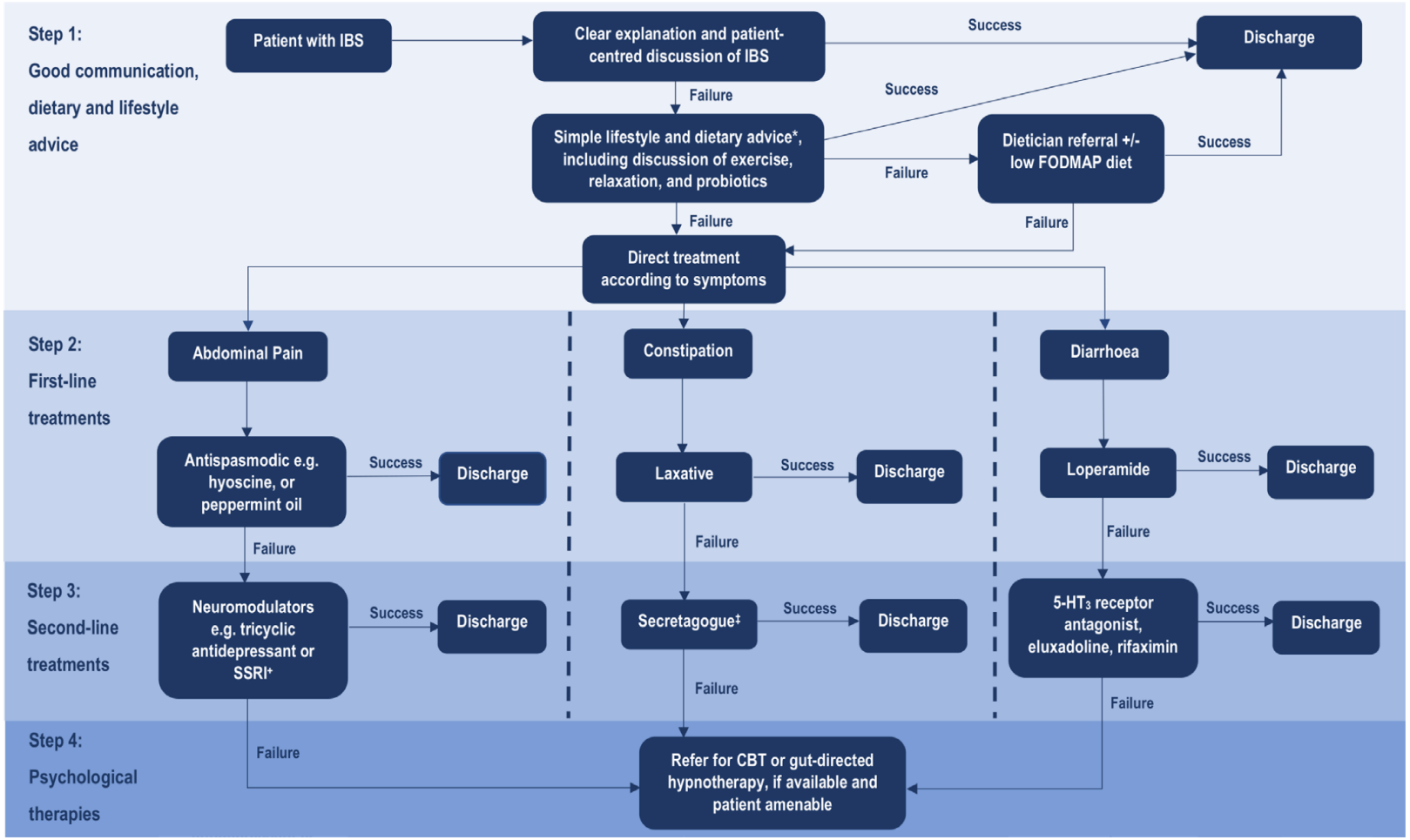


Figure 1 Suggested algorithm for the management of irritable bowel syndrome. CBT,cognitive behavioural therapy; FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides and polyols; IBS, irritable bowel syndrome; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; 5-HT_3, 5-hydroxytryptamine-$_3$. *As per NICE IBS dietary advice sheet, plus consider ispaghula husk. +Tricyclic antidepressants should be first choice, starting at a dose of 10mg at night, and titrating slowly (e.g. by 10mg per week) according to response and tolerability. Continue for at least 6 months if patient reports symptomatic response. ‡Review efficacy after 3 months of treatment, and discontinue if no response.

Black CJ, Ford AC. *Frontline Gastroenterology* 2021;**12**:303–315

Central modulators

Table 7. Activity of central neuromodulators on abdominal pain, intestinal motility, anxiety, and depression

	Reduce abdominal pain	Increase intestinal transit rate	Reduce intestinal transit rate	Reduce anxiety	Reduce nausea	Reduce depression
Tricyclics	+	–	+[a]	+/–	–	+
SSRI	–	+[b]	–	+	–	+
SNRI	+	–	+/–	+	–	+
Tetracyclics	+/–	–	+/–	+/–	+[c]	+
Atypical antipsychotics	+[d]	–	–	+/–	+[e]	+/–

AAP, atypical antipsychotic agent; SNRI, serotonin and noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.
[a]Exceptions: desipramine and nortriptyline.
[b]Exception: paroxetine.
[c]Particularly mirtazapine.
[d]Effective when used to augment an antidepressant.
[e]Particularly olanzapine >quetiapine.

Activity of central neuromodulators on abdominal pain, intestinal motility, anxiety, and depression

Hanna-Jairala et al.. The American Journal of Gastroenterology 119(7):p 1272-1284, July 2024.

Summary

- Common & significant impact on QoL
- Provider-Patient relationship
- Positive diagnosis
- Rule out alarm features (good history and exam)
- Subclassification to guide therapy
- Empower and educate
- MDT

References

1. Lacy, Brian E *et al.* ACG Clinical Guideline: Management of Irritable Bowel Syndrome. The American Journal of Gastroenterology 116(1):p 17-44, January 2021.
2. Vasant DH, Paine PA, Black CJ, *et al*. *Gut* 2021;**70**:1214–1240.
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4. Hanna-Jairala, Ignacio *et al.* Central Neuromodulators in Irritable Bowel Syndrome: Why, How, and When. The American Journal of Gastroenterology 119(7):p 1272-1284, July 2024.
5. Alexander C. Ford, Nicholas J. Talley. Sleisenger and Fordtran's Gastrointestinal and Liver Disease, 122, 2008-2020.e6
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