Chronic Abdominal Pain Syndrome

CAPS vs IBS

Woman's health and Antenatal care Weekend

Gqeberha

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DISCLAIMER AND CONFLICT OF INTEREST DISCLOSURE

- View expressed in this presentation are my own
- Yes speaker's fees received for this presentation

Disclosure

[X] I have **NO** real, or perceived direct or indirect conflicts of interest that relate to the presentation

[ ] I have the following, real or perceived direct or indirect conflicts of interest that relate to this presentation

Affiliation	Nature of interest	Company Name

PRESENTATION OUTLINE

- INTRODUCTION
- CENTRALLY MEDIATED ABDOMINAL PAIN SYDROMES (CAPS)
- IRRITABLE BOWEL SYBNDROME (IBS)
- DISCUSSION

INTRODUCTION

- I can not take this pain anymore, you have to fix me
- I have been to different doctors no one seems to have a clue what is wrong
- You are my last resort
- I can not leave like this anymore
- This is not normal – I need answers

GENERAL APPROACH

1. Structural/Organic
   - Luminal (Peptic Ulcer disease, Crohns disease, SMAS etc)
   - Extraluminal (Chronic pancreatitis, Adhesions, Fatty liver disease, Bud-chiari syndrome etc)

2. Metabolic
   - Acute intermittent porphyria (Women, 30s, poor localization, normal Abd exam, GIT upset back and leg pains, loss of deep tendon reflexes, paranoid), Mesenteric adenitis, etc

3. Functional
   - **IBS**, Functional dyspepsia (FD), **CAPS**, Narcotic bowel syndrome (NBS) etc.

GENERAL CLINICAL APPROACH

1. History taking/physical examination
   - Listen, listen and listen – your focus should be on symptomatology and the story behind.
   - Thorough abdominal examination – you will thank me later

2. Labs
   - FBC, U+E, LFTs, Amylase, CMP, CRP, TSH + Stool (MCS, Fecal calprotectin)

3. Imaging
   - Abdominal x-ray (Erect and supine), Full abdominal USS, etc.

4. Endoscopy
   - Gastroscopy (Gastric and Duodenal biopsies) and Colonoscopy (Terminal ileum intubation)

FOCUS WILL BE ON CAPS AND IBS

- **CAPS**

  - Centrally mediated abdominal pain syndrome

  - Is characterized by continuous or frequently recurrent abdominal pain that is often severe and only rarely related to gut function.

  - Is associated with loss of function across several life domains, including work, intimacy, social/leisure, family life, and caregiving for self or others

  - Cannot be explained by a structural or metabolic factors

  - The predominance of pain is the central complaint (Colicky, prolonged, widespread)

CENTRALLY MEDIATED ABDOMINAL PAIN SYNDROME

- **Definition**

  - Chronic abdominal pain not explained by acute organic pathology with or without accompanying dyspepsia, bloating, nausea and vomiting among other symptoms, lasting for more than 3 months.

  - Pathophysiology is noted to be neurogenic, possibly stemming from visceral sympathetic nerves or abdominal wall afferent nerves.

EPIDEMIOLOGY (CAPS)

- Less common than other FGIDs, prevalence 0.5 – 2.1 %
- 2 x Women > men
- Peak age (35 – 44 years) and decreases with age (US survey)
- Multiple physician consults
- Have in common comorbidity with other pain syndromes, predisposing life events, and treatment responses

DIAGNOSTIC CRITERIA (CAPS)

- Continuous or nearly continuous abdominal pain
- No or only occasional relationship of pain with physiological events (eg, eating, defecation, or menses)
- Pain limits some aspect of daily functioning
- The pain is not feigned
- Pain is not explained by another structural or functional gastrointestinal disorder or other medical condition

DIAGNOSTIC CRITERIA (CAPS)

[a]Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

[b]CAPS is typically associated with psychiatric comorbidity, but there is no specific profile that can be used for diagnosis.

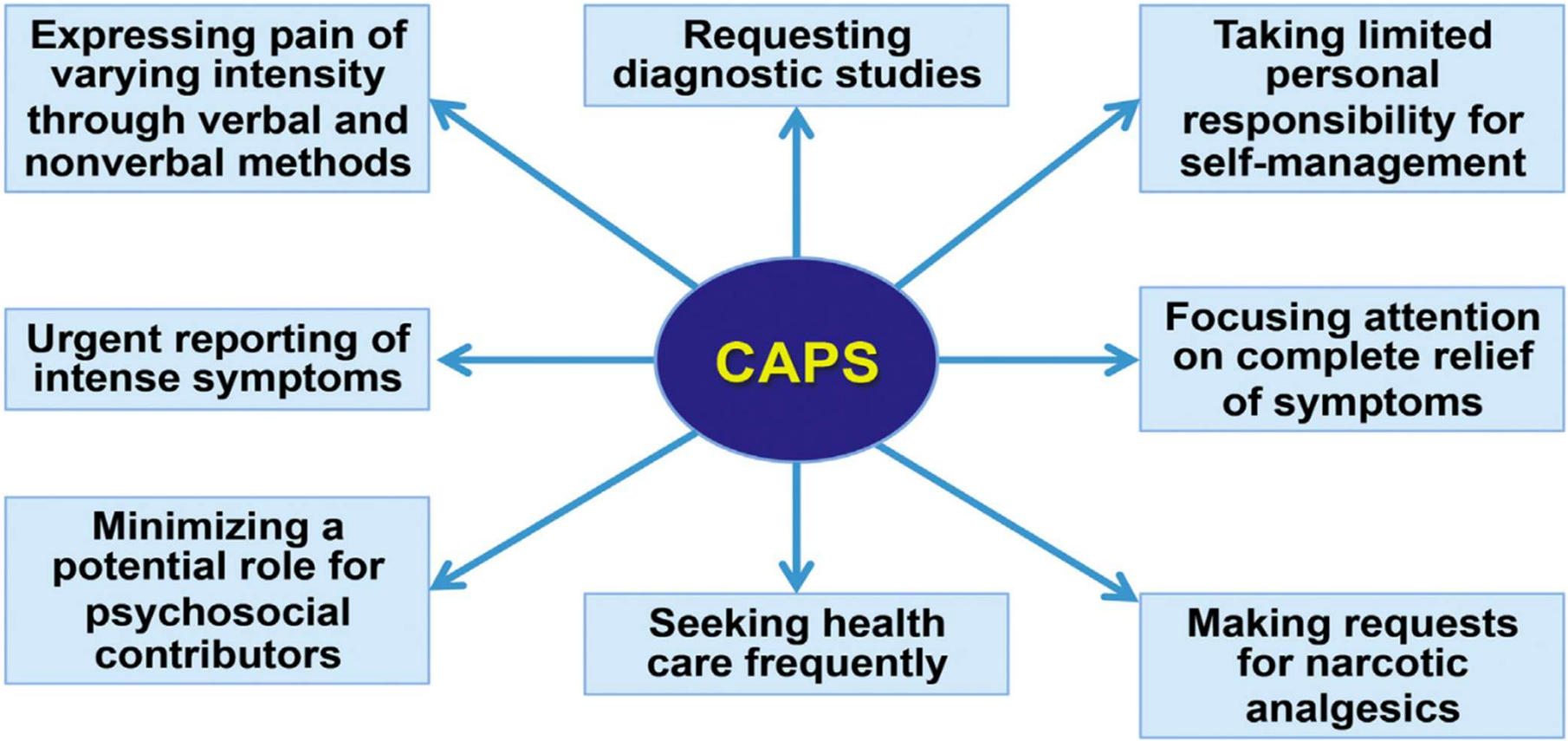
[c]Some degree of gastrointestinal dysfunction may be present.

[d]Daily function could include impairments in work, intimacy, social/leisure, family life, and caregiving for self or others.

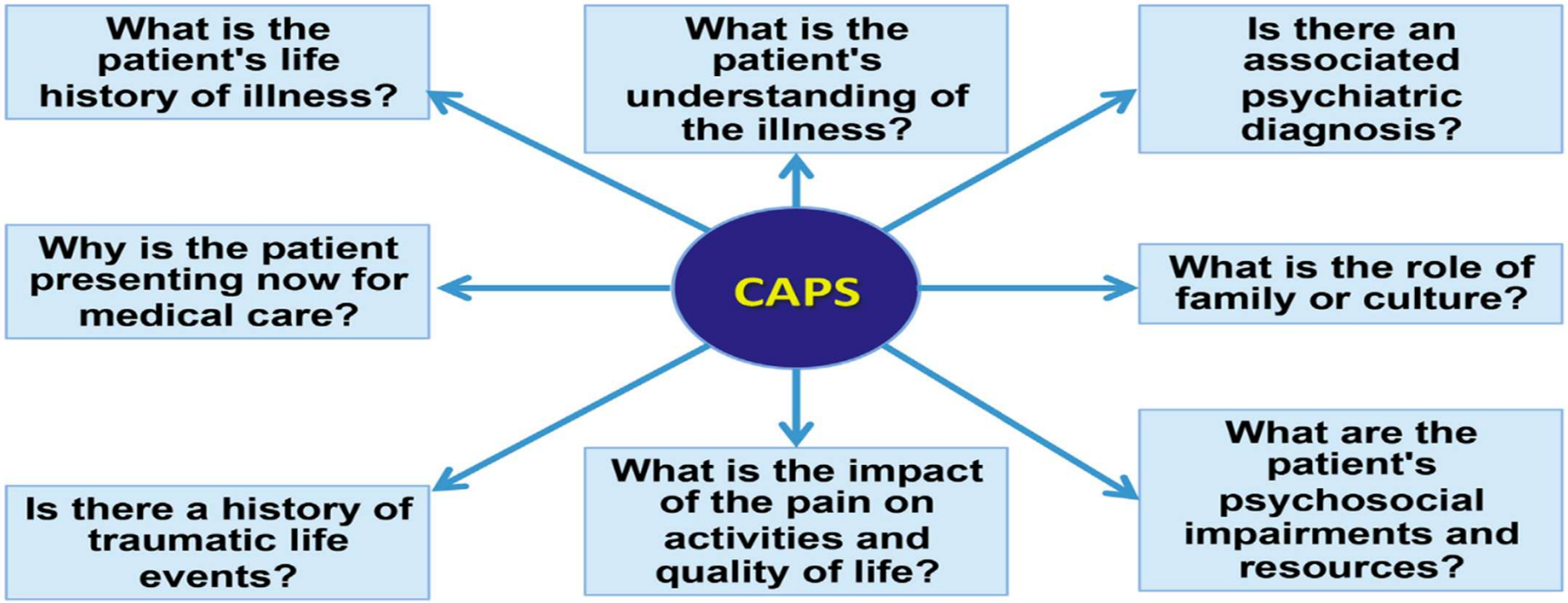
EVALUATION (CAPS)

- Should consist of a clinical and psychosocial assessment,
- Observation of symptom-reporting behaviours,
- A physical examination,
- Exclusion of alarm features,
- Conservative efforts to exclude other medical conditions in a cost-effective manner

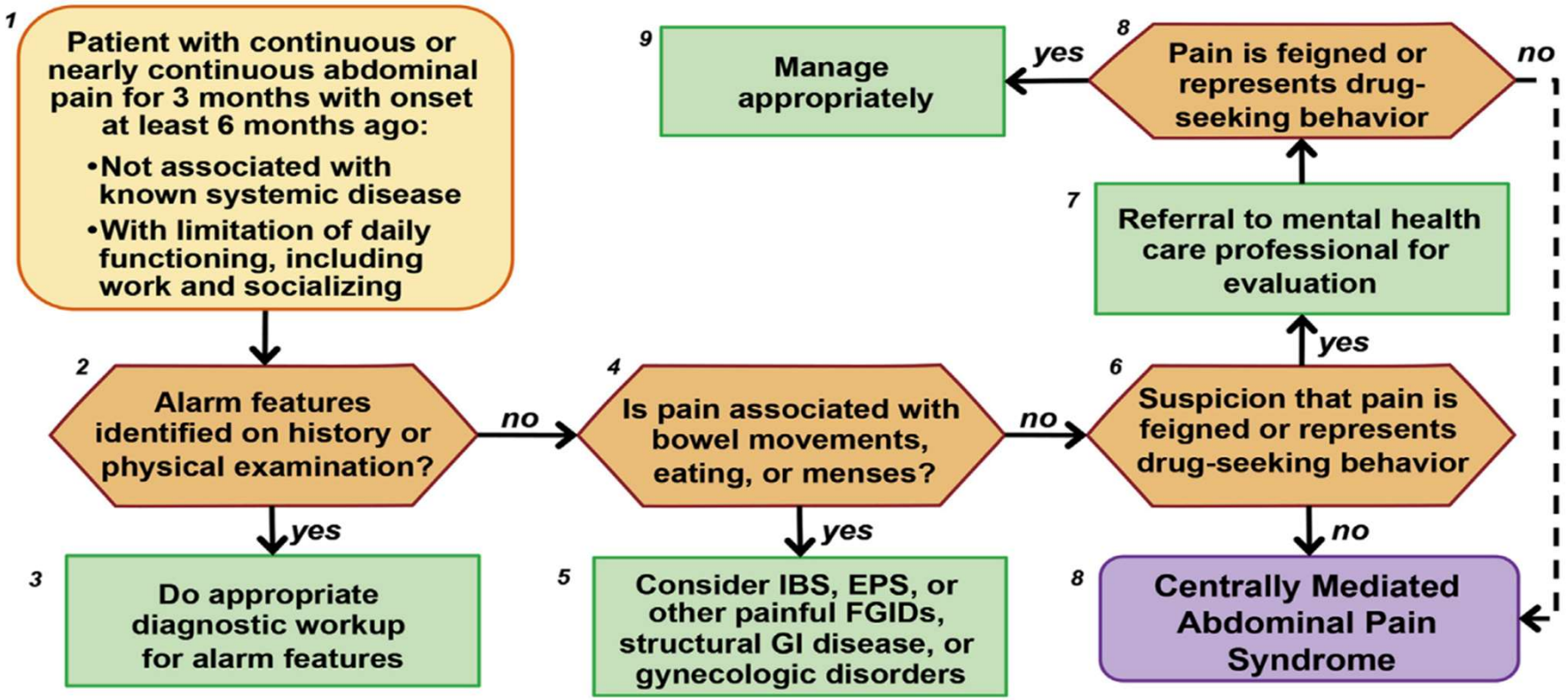
SYMPTOM RELATED BEHAVIOURS



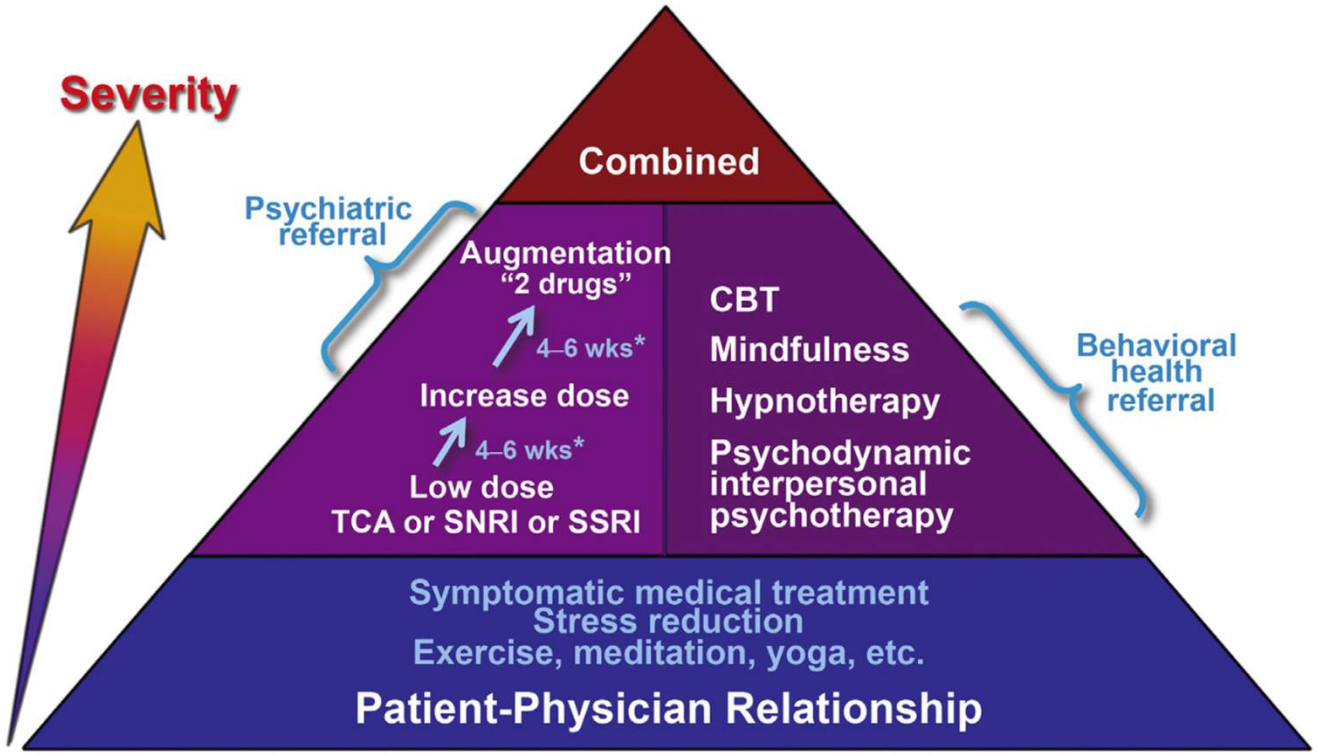
CLINICAL AND PSYCHOSOCIAL OVERVIEW



INVESTIGATION ALGORITHM FOR LONG STANDING ABDOMINAL PAIN



MANAGEMENT



*Monitor side effects

ANTIDEPRESSANT TREATMENT FOR CAPS

	Tricyclic antidepressants	Selective serotonin reuptake inhibitors	Serotonin-norepinephrine reuptake inhibitors
Treatment targets	Pain, depression	Pain, depression, panic, anxiety, obsessive compulsive disorder	Pain, depression
Adverse events	Sedation, hypo-tension, constipation, dry mouth/eyes, arrhythmias, weight gain, sex dysfunction	Insomnia, agitation, diarrhea, night sweats, headache, weight loss, sex dysfunction	Nausea, agitation, dizzi-ness, sleep disturbance, fatigue, liver dysfunction
Risk from overdose	Moderate	Low	Minimal
Dose adjustment	Yes	Not usual	Not usual

SUMMARY: CAPS

- CAPS can be diagnosed in time (Awareness)
- Compassion (Clinician – patient relationship is central)
- Appropriate algorithmic approach minimize harm to the patient
- Early referral and proper management is key


Gqeberha!
(Port Elizabeth)

IRRITABLE BOWEL SYNDROME (IBS)

Interference with the normal function of the large intestine

Pain and feeling of abdominal distension

Abdominal discomfort, bloating and/or crampy abdominal pain

Altered stool frequency

Chronic-intermittent changes in defecation pattern, constipation and diarrhea, relief with defecation.

Spinelli. Clin Drug Invest 2007;27(1):15-33. Spiller. Brit Med Bull 2004;72:15-29.

IBS: A BRAIN GUT INTERACTION DISODER

Affects between 10-15% of the general population
Significant impact in quality of life and health economy

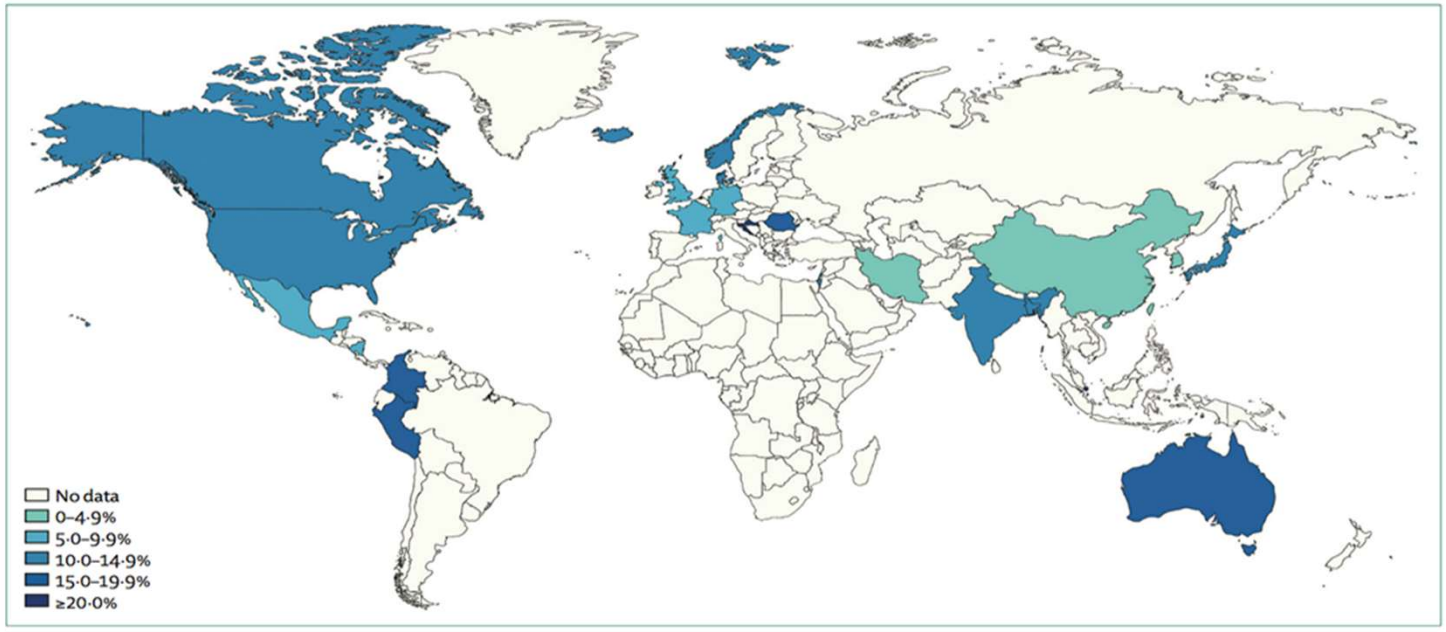


Figure 1: **Global prevalence of IBS according to the Rome III criteria**
Prevalence data taken from studies that used the Rome III criteria for IBS.[4,12,13] IBS=irritable bowel syndrome.

IRRITABLE BOWEL SYNDROME DEFINITION

Diagnostic criteria for IBS: ROME IV

Recurrent **abdominal pain**, on average, at least 1 day per week in the last 3 months associated with 2 or more of the following:

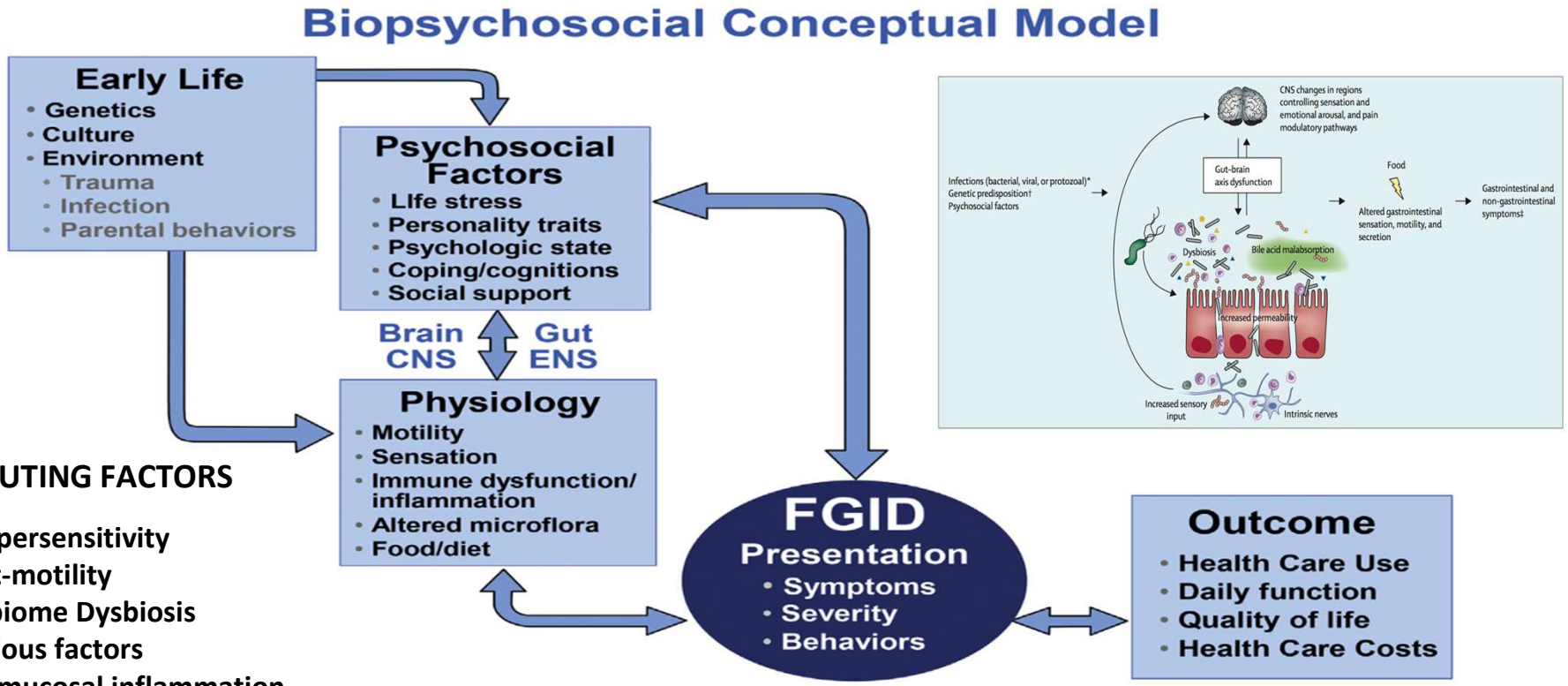
1. Related to defecation
2. Associated with change in frequency of stool
3. Associated with a change in form (appearance) of stool

***Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnostic**

Clinical diagnosis rather than exclusion

Lacy et al. Gastroenterology 2016;150:1393-1407.

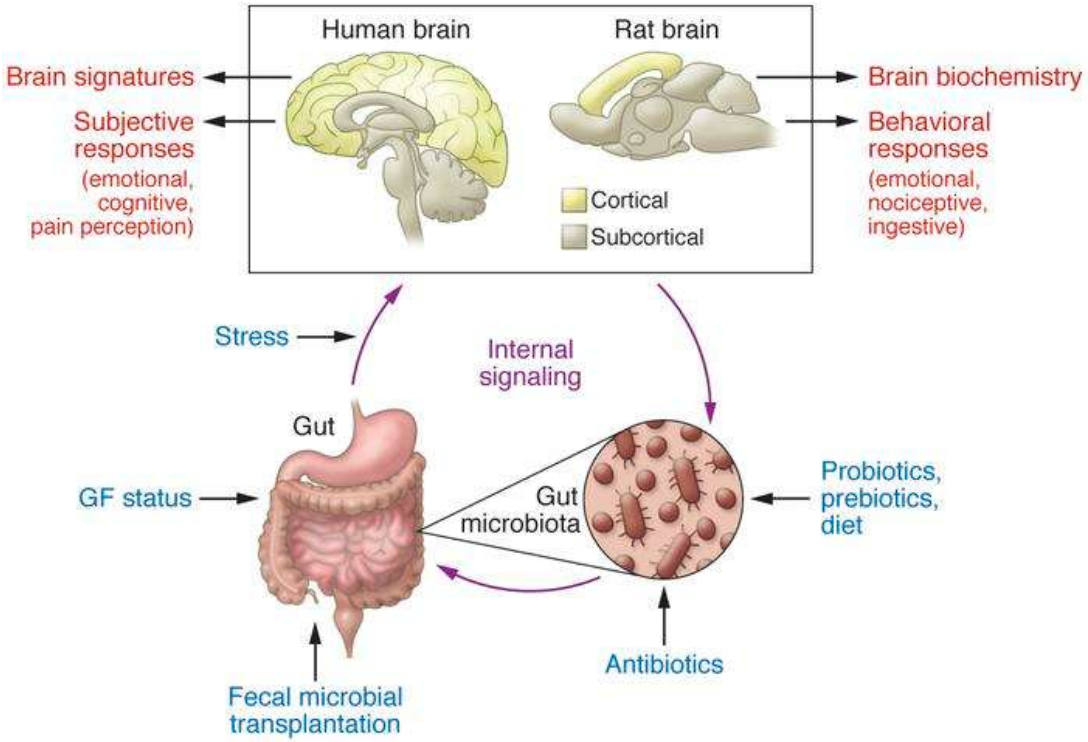
PATHOPHYSIOLOGY – CONCEPT MODEL



KEY CONTRIBUTING FACTORS

- **Visceral hypersensitivity**
- **Altered gut-motility**
- **Gut-microbiome Dysbiosis**
- **Post Infectious factors**
- **Low grade mucosal inflammation**
- **Genetic predisposition and epigenetic factors**
- **Psychosocial factors**

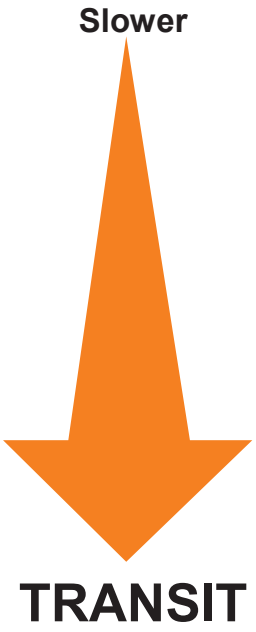
GUT/BRAIN AXIS AND THE MICROBIOTA



J Clin Invest DOI: 10.1172/JCI76304

BRISTOL STOOL CHART

Type 1		Separate hard lumps, like nuts (hard to pass)
Type 2		Sausage-shaped but lumpy
Type 3		Like a sausage but with cracks on the surface
Type 4		Like a sausage or snake, smooth and soft
Type 5		Soft blobs with clear-cut edges
Type 6		Fluffy pieces with ragged edges, a mushy stool
Type 7		Watery, no solid pieces, entirely liquid



IBS SUBTYPES

IBS-M: More than one-fourth (25%) of bowel movements with Bristol stool form types 1 or 2 and more than one-fourth (25%) of bowel movements with Bristol stool form types 6 or 7

IBS-U: Patients who meet diagnostic criteria for IBS but whose bowel habits cannot be accurately categorized into 1 of the 3 groups above should be categorized as having IBS unclassified

IBS-C: More than one-fourth (25%) of bowel movements with Bristol stool form types 1 or 2 and less than one-fourth (25%) of bowel movements with Bristol stool form types 6 or 7

IBS-D: More than one-fourth (25%) of bowel movements with Bristol stool form types 6 or 7 and less than one-fourth (25%) of bowel movements with Bristol stool form types 1 or 2

OVERVIEW OF THE EXTRAINTESTINAL COMORBIDITIES OF THE IBS

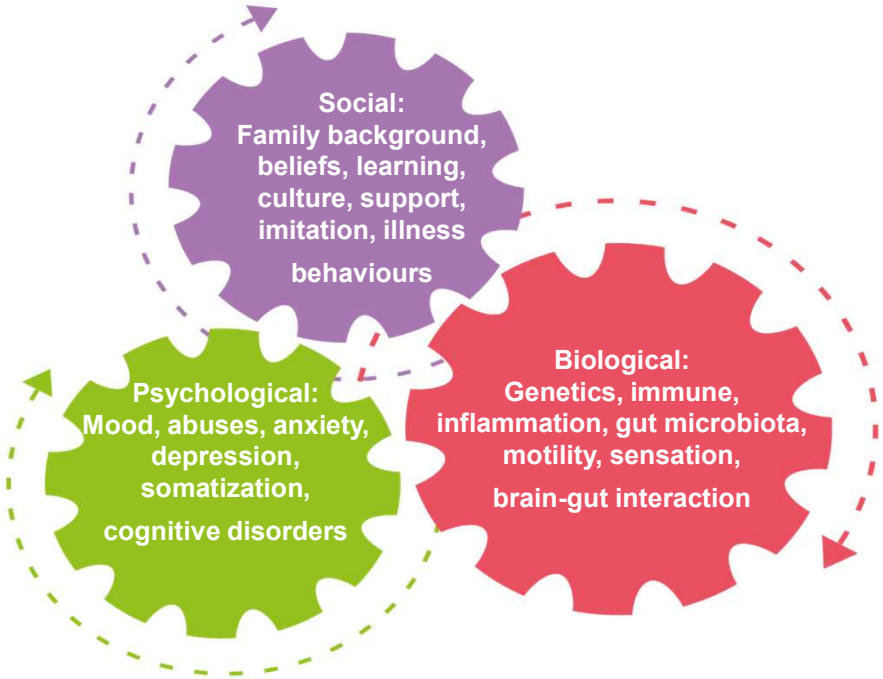
Pain Syndromes	Urogenital Syndromes	Bronchopulmonal Syndromes	Cardiac Syndromes	Other Syndromes
<u>Cerebral</u> - Headache - Migraine <u>Muscoloskeletal</u> - Fibromyalgia - Temporo-mandibular joint disorder - Back pain <u>Urogenital</u> - Chronic pelvic pain	- Dysuria - Detrusor dysfunction - Interstitial cystitis - Urinary stones - Disturbed sexual function - Premenstrual syndrome - Dysmenorrhea	- Asthma - Bronchial hyperreactivity	- Palpitations	- Sleep difficulties - Chronic fatigue syndrome

IBS Differential diagnosis

Carcinoid tumor	Hyperthyroidism
Celiac disease	Hypothyroidism
Colorectal cancer	Inflammatory bowel disease (e.g., Crohn disease, ulcerative colitis)
Diverticular disease	Ischemic colitis
Drug use (opiate analgesics, calcium channel blockers, antidepressant	Lactose intolerance
Gastrointestinal infection (e.g., Giardia, Amoeba, human immunodeficiency virus, bacterial overgrowth)	

Wilkins et a. Am Fam Physician 2012;86(5):419-26.

IBS IS A BIOPSYCHOSOCIAL DISEASE



ORGANIC CAUSALITY – RED FLAGS

ALARM FEATURES

Age >50 years

Short history of symptoms

Documented weight loss

Nocturnal symptoms

Male sex

Family history of colon cancer

Anemia

Rectal bleeding

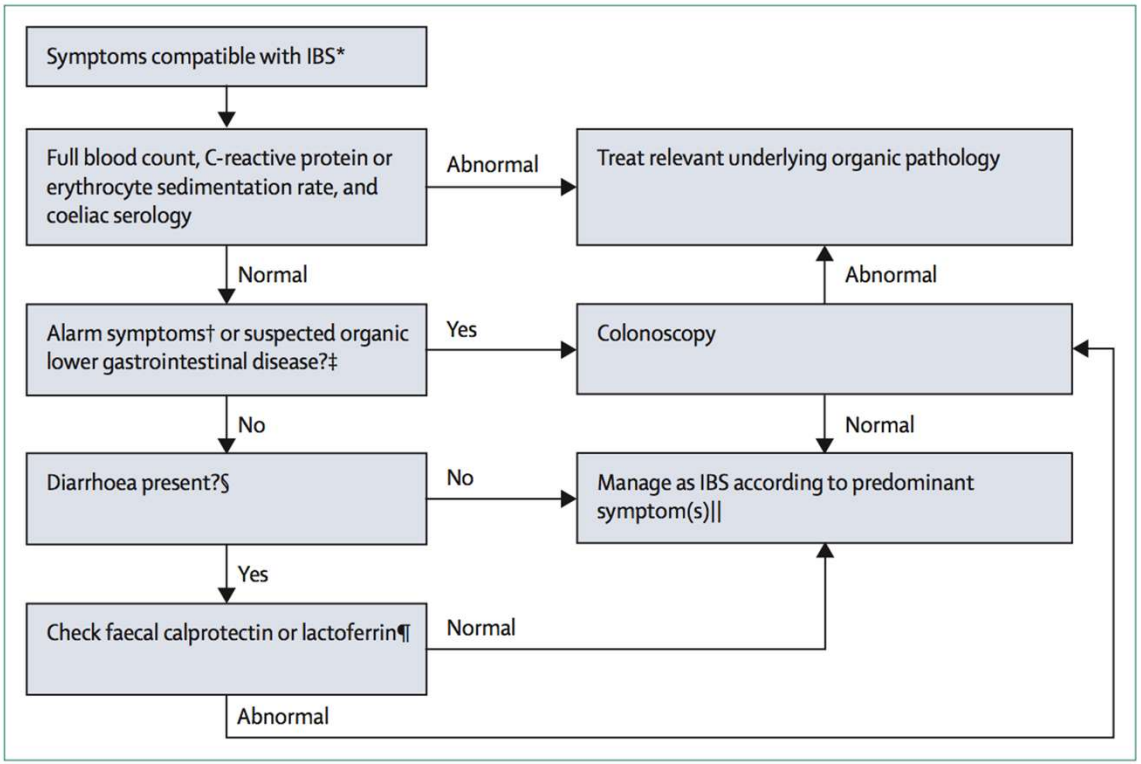
Recent antibiotic use

Spiller et al. Gut 2007;56:1770-1798.

SIMPLE DIAGNOSTIC ALGORITHM

REMEMBER

Porphyria
Mic Colitis
Bila Salt Diarrhea
Thyroid Disease
Celiac Disease

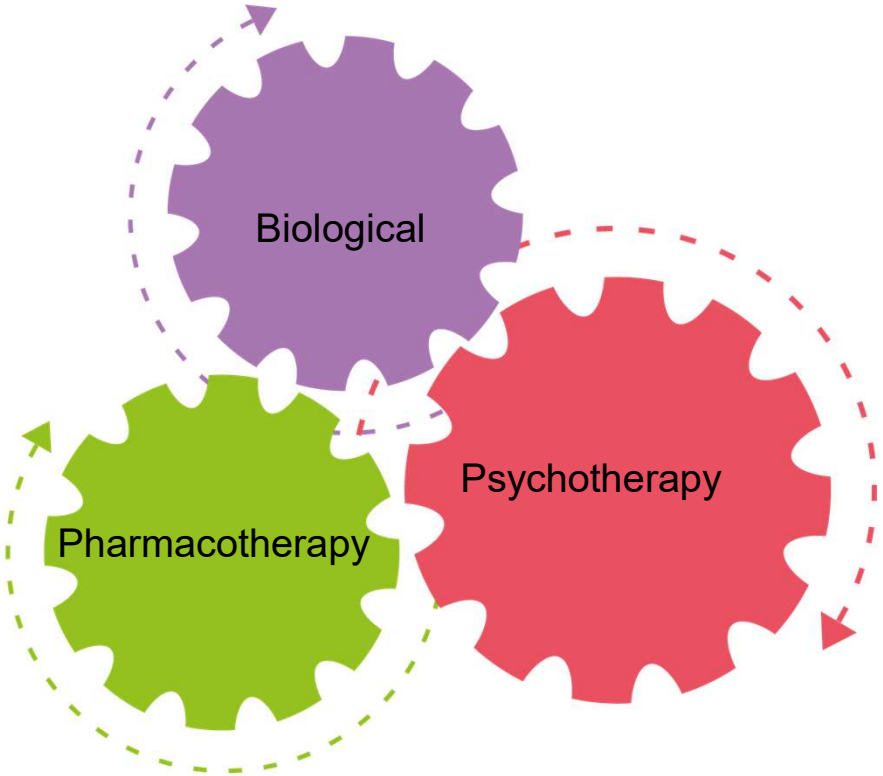


No universal biomarker, prevent exhaustive investigations, make a positive diagnosis

NATURAL HISTORY: IBS

- Typical disease course is of fluctuating symptoms
- Causes morbidity but not mortality
- Affects quality of life to the same degree as organic disorders i.e. Crohns disease
  - Work production, social integration, psychological state

TREATMENT APPROACH: THREE



MANAGEMENT KEY PRINCIPLES: IBS

- No medical therapy has been proven to alter the natural history of IBS
- Empathic approach – positive diagnosis, suitable explanation
- Treatment is directed towards the common symptoms
  - Realistic goals as most therapies improve symptoms in only 25 – 30% of cases
- Involve the multidisciplinary team
  - Including the patient

DIET, LIFESTYLE AND PROBIOTICS

- Eat small meals, avoid known triggers, reduce alcohol and caffeine, gluten free?
- FODMAP restriction
  - Isolate specific FODMAPS via a dietician led exclusion / reintroduction program
- Exercise instructed by a therapist improved symptoms significantly
- Non fermentable fiber supplementation
  - Ispagulla husk was more efficacious than bran (RR of remaining symptomatic 0.83)

OVERVIEW OF CURRENT TREATMENTS: IBS

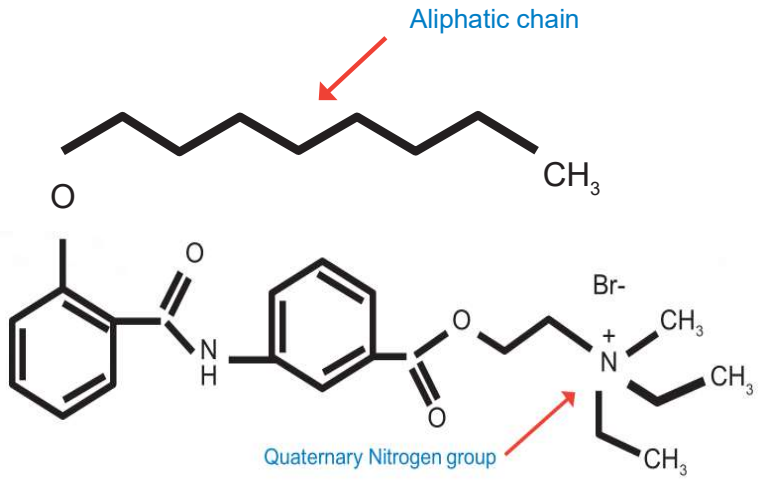
Category	Functions	Examples
Antispasmodics	**Antagonists of muscarinic receptors and calcium channels of smooth muscle**	Cimetropium bromide, dicyclomine, hyoscine, butylbromidemebeverine, **Otilonium Bromide**, peppermint oil, pinaverium bromide, trimebutine maleate
Antidiarrheals	Antagonist of μ-opioid receptors	Loperamide
Laxatives	Osmotic, stimulant	Bisacodyl, lactulose, magnesium citrate, magnesium sulfate, polyethylene glycol
Bulking agents	Water binding to increase stool bulk	Methylcellulose, psyllium, wheat bran

FIRST LINE MEDICAL THERAPIES

- Laxatives
  - Osmotic laxatives, PEG
  - Little evidence for stimulant laxatives
- Antidiarrheal
  - Loperamide as required
- Antispasmodics
  - Hyoscine (buscopan), Mabeverine
  - Peppermint oils
  - **Otilonium Bromide(Spamomen)**

OTILONIUM BROMIDE(SPAMOMEN)

Quaternary ammonium derivatives (QADs) are widely used in gastroenterology for the treatment of irritable bowel syndrome (IBS) and motility disorders associated with pain, thanks to their spasmolytic activity.



Chemical name: diethyl methyl{2-[4-(2-octyloxybenzamido)benzoylox]-ethyl}ammonium bromide
Molecular formula: $C_{29}H_{43}BrN_{2O4}$
Molecular weight: 563.6

Therapeutic indications

Irritable colon syndrome and spastic-painful manifestations of the distal enteric tract

Evangelista. Curr Pharm Des 2004; 10:3561-3568.

MECHANSISM OF ACTION

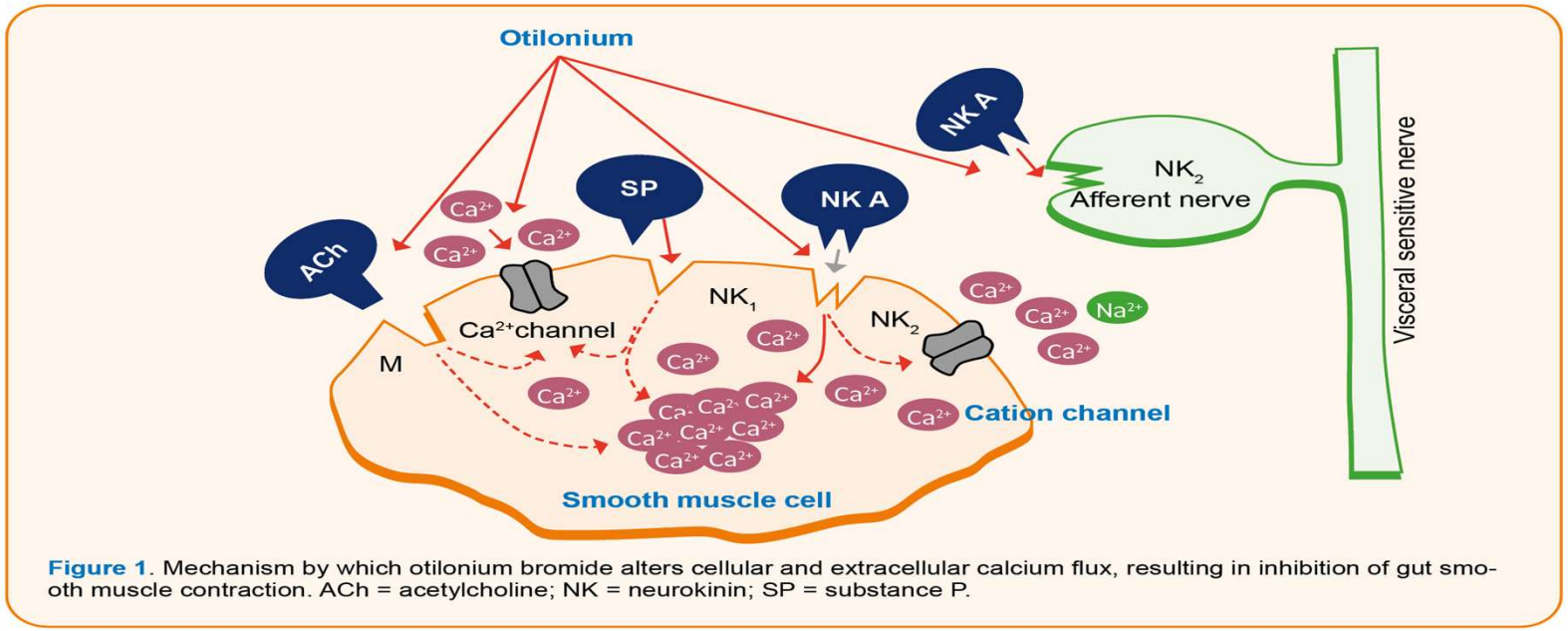


Figure 1. Mechanism by which otilonium bromide alters cellular and extracellular calcium flux, resulting in inhibition of gut smooth muscle contraction. ACh = acetylcholine; NK = neurokinin; SP = substance P.

Spinelli. Clin Drug Invest 2007;27(1):15-33.

For IBS relief[2]

Mechanism of action: Spasmomen® targets IBS symptoms where they start[1,2,3]

MOA: an antispasmodic that works in three ways to relieve IBS subtypes[1,2,3]

1	2	3
		
Direct blockade of calcium channels (Ca^{++})	**Antagonism of tachykinin NK_2 receptors**	**Inhibitions of acetylcholine muscarinic receptors (M3 - AChR)**
Reduces spasms	Reduces visceral pain	Reduces intestinal secretions
Extra-cellular: modulates Ca^{++} entry into the intestinal smooth muscle cells. Intracellular: inhibits Ca++ release from sarcoplasma[3]	**Tachykinins play a major role in visceral nociception. OB antagonizes the tachykinin NKA receptors on afferent nervs terminations and intestinal smooth muscle cells; inhibits intra-cellular Ca++ [2,3]**	**Inhibits Ca++ mobilization at the level of the colonic epithelium, thus exhibiting an antisecretory potential[3]**

Efficacy with **SPASMOMEN®** is the result of combined MOA (calcium channels, NK receptors and cholinergic pathways)[2,3]

1. Spinelli A. Clin Drug Investig 2007;27:15-33. 2. SPASMOMEN® corporate SmPC.
3. Triantafillidis JK, Malgarinos G. Clin Exp Gastroenterol 2014;7:75-82.

MECHANSISM OF ACTION

MOA: an antispasmodic that works in three ways to relieve IBS subtypes[1,2,3]

	NKA	
Direct blockade of calcium channels (Ca^{++})	**Antagonism of tachykinin NK_2 receptors**	**Inhibitions of acetylcholine muscarinic receptors (M3 - AChR)**
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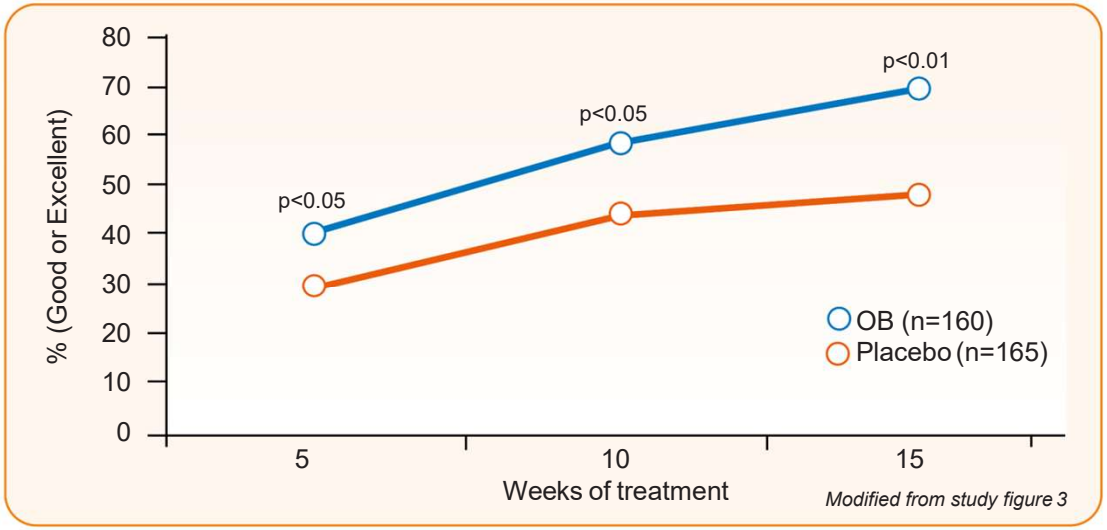
Spinelli. Clin Drug Invest 2007;27(1):15-33.

Otilonium Bromide: Assessment of treatment efficacy

According to physicians, treatment with otilonium bromide was "Good" or "Excellent" in a higher percentage of IBS patients vs placebo

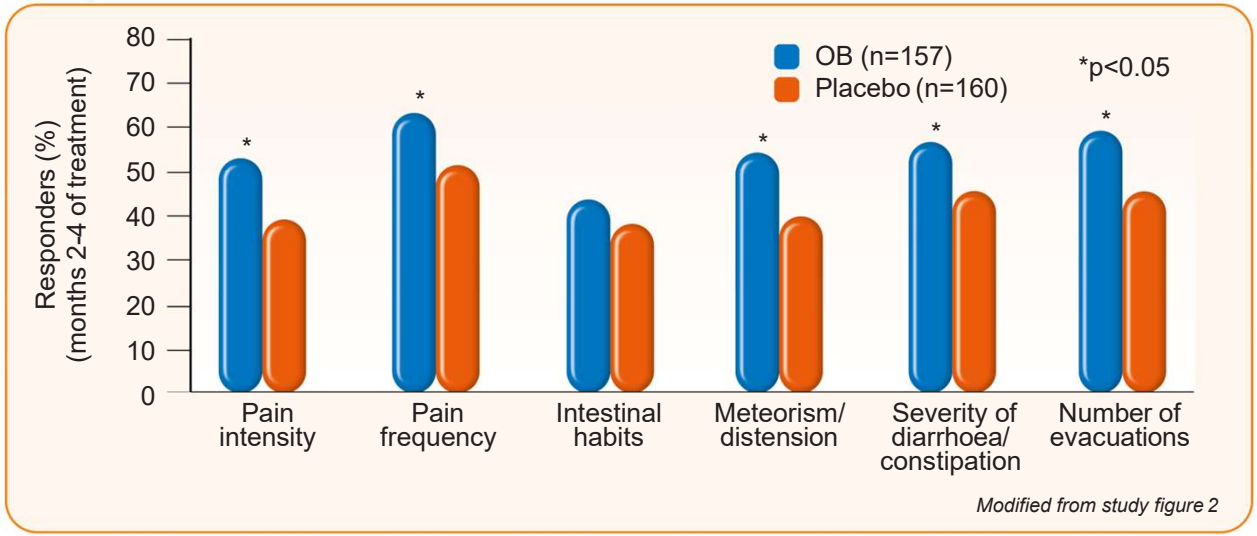


Modified from study figure 3

Double-blind, randomized, placebo-controlled, parallel-group trial. OB or placebo were assigned to 325 IBS patients for 15 weeks to evaluate the efficacy of OB (40 mg TID). Battaglia et al. Aliment Pharmacol Ther 1998;12:1003-1010.

Otilonium Bromide: 12 single efficacy endpoints

In a controlled 15 weeks trial, enrolling 378 patients, Otilonium Bromide (OB) was shown to be more active than placebo on most symptoms of the disorder (36.9% vs 22.5%; difference between groups: 14.4%, p<0.007).



Modified from study figure 2

Rates of total monthly responses in the single endpoints of IBS in months 2-4 of treatment in the ITT patients with respective baseline scores >0. *p<0.05 otilonium bromide vs placebo group.

Double-blind, placebo-controlled, parallel-group trial. 378 IBS patients was treated for 15 weeks with OB (40 mg TID) or placebo to evaluate 12 single efficacy endpoints reported by patients.
Glende et al. Eur J Gastroenterology Hepatol 2002;14:1331-1338.

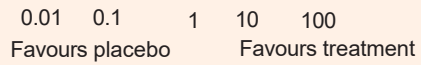
Otilonium Bromide: Comparison with other spasmolytics

Otilonium bromide appears to be effective in relieving global IBS symptoms on the basis of two high OB quality studies

Global assessment for otilonium bromide shows the highest level of significance vs placebo

Meta-analysis of 7 high quality trials

Drug	Treatment n/N	Control n/N	OR (95% CI Random)
Pinaverium Bromide	19/25	17/25	1.5 (0.4-5.0)
Cimetropium Bromide	30/48	28/47	1.1 (0.5-2.6)
Otilonium Bromide	**148/317**	**102/325**	**1.9 (1.4-2.7)**
Mebeverine	6/40	12/40	0.4 (0.1-1.2)
Hyoscine	106/182	91/178	1.3 (0.9-2.0)
Total High Quality studies	309/612	250/615	1.5 (1.2-1.9)



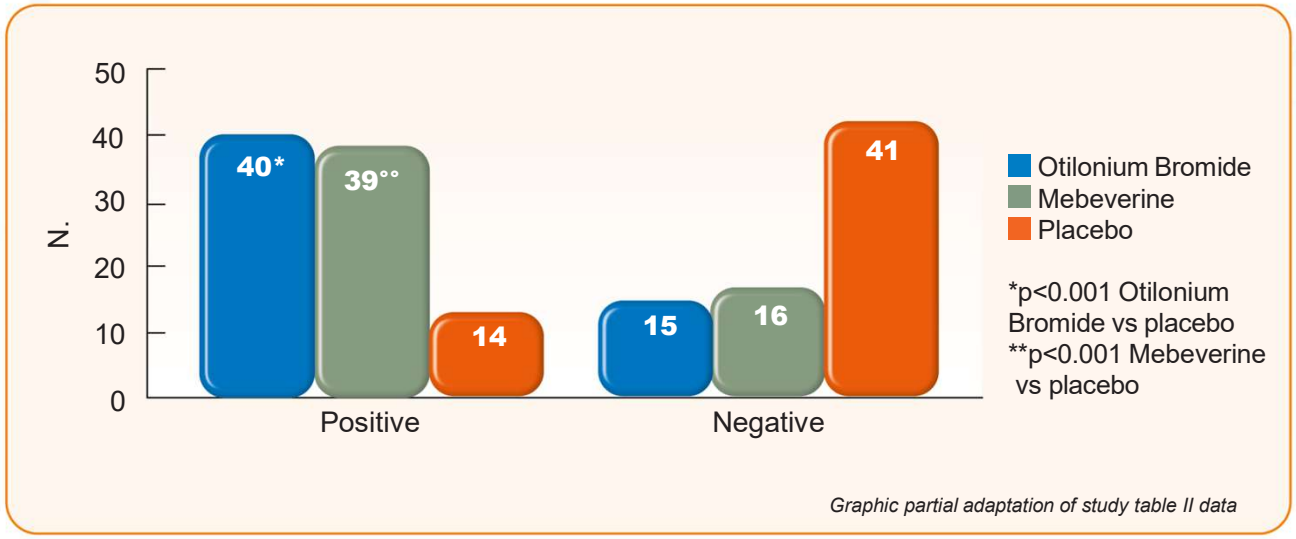
Modified from study figure 2 (b)

Meta-analysis of 51 double-blind clinical trials using bulking agents, prokinetics, anti-spasmodics, alosetron, tegaserod and antidepressants to evaluate therapies on IBS. In this figure are shown only the high quality clinical trials (n=7), which used global assessment as an efficacy outcome to evaluate spasmolytic treatment.
Lesbros-Pantoflickova et al. Aliment Pharmacol Ther 2004;20:1253-1269.

Otilonium Bromide: Head-to-head comparison

Mebeverine

Response to treatment with Otilonium Bromide, Mebeverine or placebo overall evaluation



Graphic partial adaptation of study table II data

Otilonium Bromide is as active as Mebeverine, but better tolerated

Single-blind, cross-over trial which lasted for six week. 60 IBS patients received mebeverine (135mg TID), OB (40mg TID) or placebo to compare the effect on symptoms.
Capurso et al. Clinical Trials Journal 1984;21:285-290.

OTILONIUM BROMIDE
SAFETY AND TOLERABILITY

Otilonium Bromide performs its pharmacological effect directly on the intestinal wall, because the systemic absorption following oral administration is low

At therapeutic doses, the drug is well tolerated

- Safety findings were superimposable to those of placebo
- No particular overdosage-related problems in humans
- Neither acute nor chronic toxicity in animals
- No teratogenic, embryotoxic or mutagenic effects in animals

OTOLONIUM BROMIDE: CONCLUSION

Clinical trials demonstrated that **Otilonium Bromide** reduces abdominal pain in patients with IBS

In controlled clinical trials, **Otilonium Bromide**
shows to have a favorable tolerability profile

Most IBS patients can be treated effectively and with a good tolerability profile

In summary

- We following ROME IV consensus guidelines
  - No universal biomarker
- 5 distinct categories of disease
  - Chronicity, variable, no red flags, pathological screens are negative
- Don't do exhaustive investigations
- Remember IBS is pain first and foremost
- Make a positive diagnosis
- Endoscopy is based on age and red flag symptoms
- Multi-disciplinary team approach is paramount as no medical therapy alone alters disease course

THANK YOU