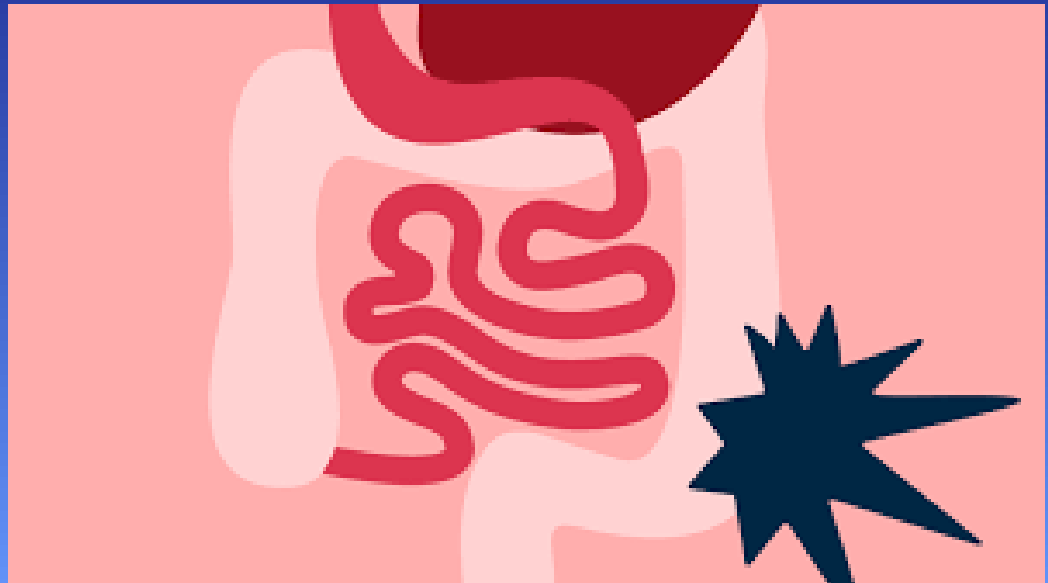


Irritable bowel syndrome (IBS)

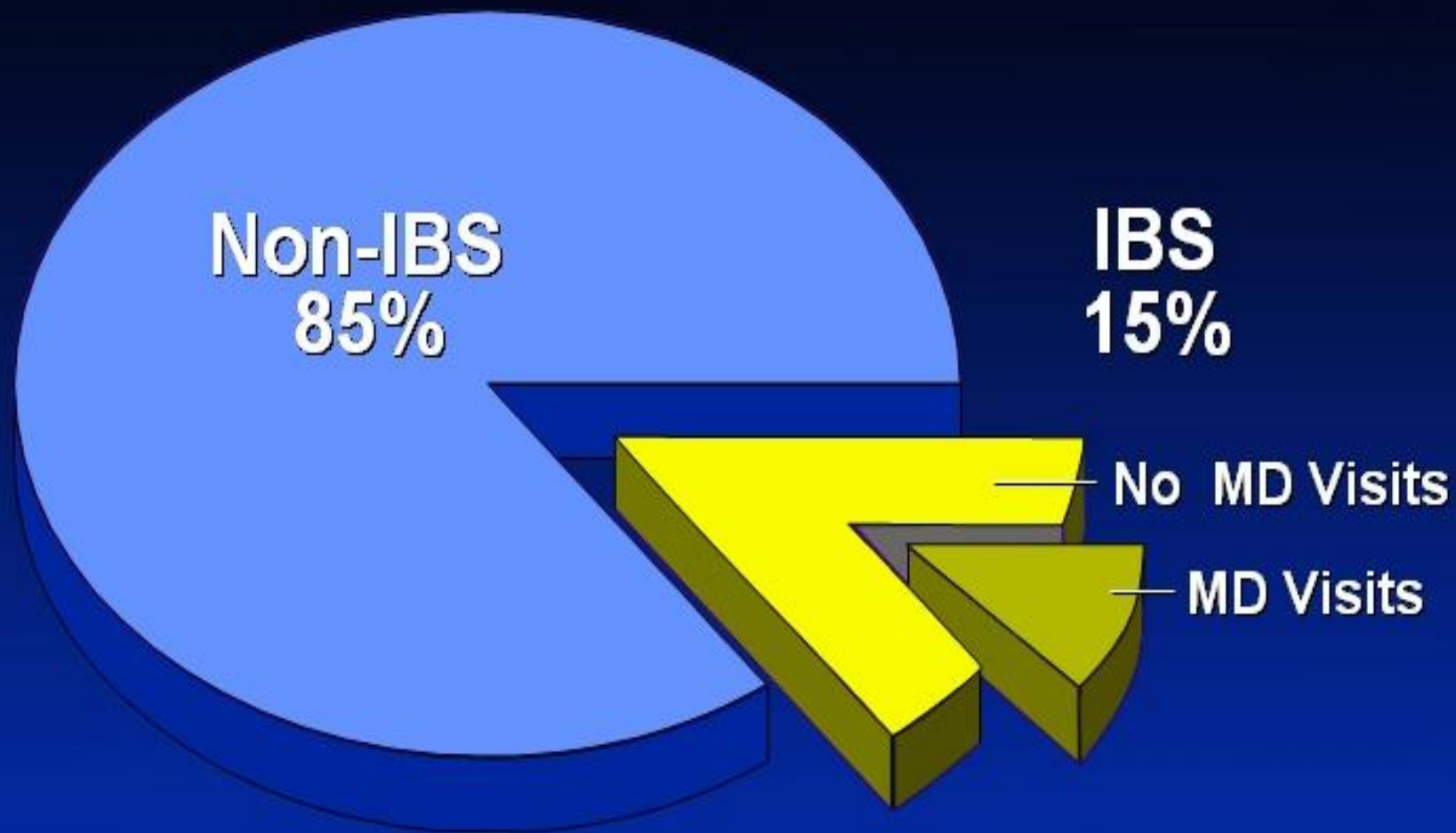
Masoodi M MD



Definition

- IBS is a functional bowel disorder characterized by symptoms of abdominal pain or discomfort that is associated with disturbed defecation
- Highly prevalent
 - In the United States, IBS accounts for 25 -50 % of all referrals to gastroenterologists
- Can be associated with significant:
 - Emotional distress
 - Impaired health-related quality of life (HRQL)
 - Disability:
 - IBS-related symptoms are often chronic and bothersome, negatively affecting patient activities of daily living (eg, sleep, leisure time), social relationships, and productivity at work or school.
 - High health care costs

Health Care Seeking



Epidemiology

- Prevalence :
 - The prevalence of IBS is greater in **women**
 - » 2:1 in the community setting
 - » 3:1 to 4:1 in the tertiary care setting
 - The first presentation of patients to a physician is between the ages of **30 and 50 years**
 - The prevalence seems to be similar in whites and blacks
- In the short term (weeks to months), the symptoms of IBS occur frequently
- Over a longer period of time (years), the symptoms of IBS wax and wane
- Females may be more likely to have constipation-predominant IBS as compared with males

Associated conditions

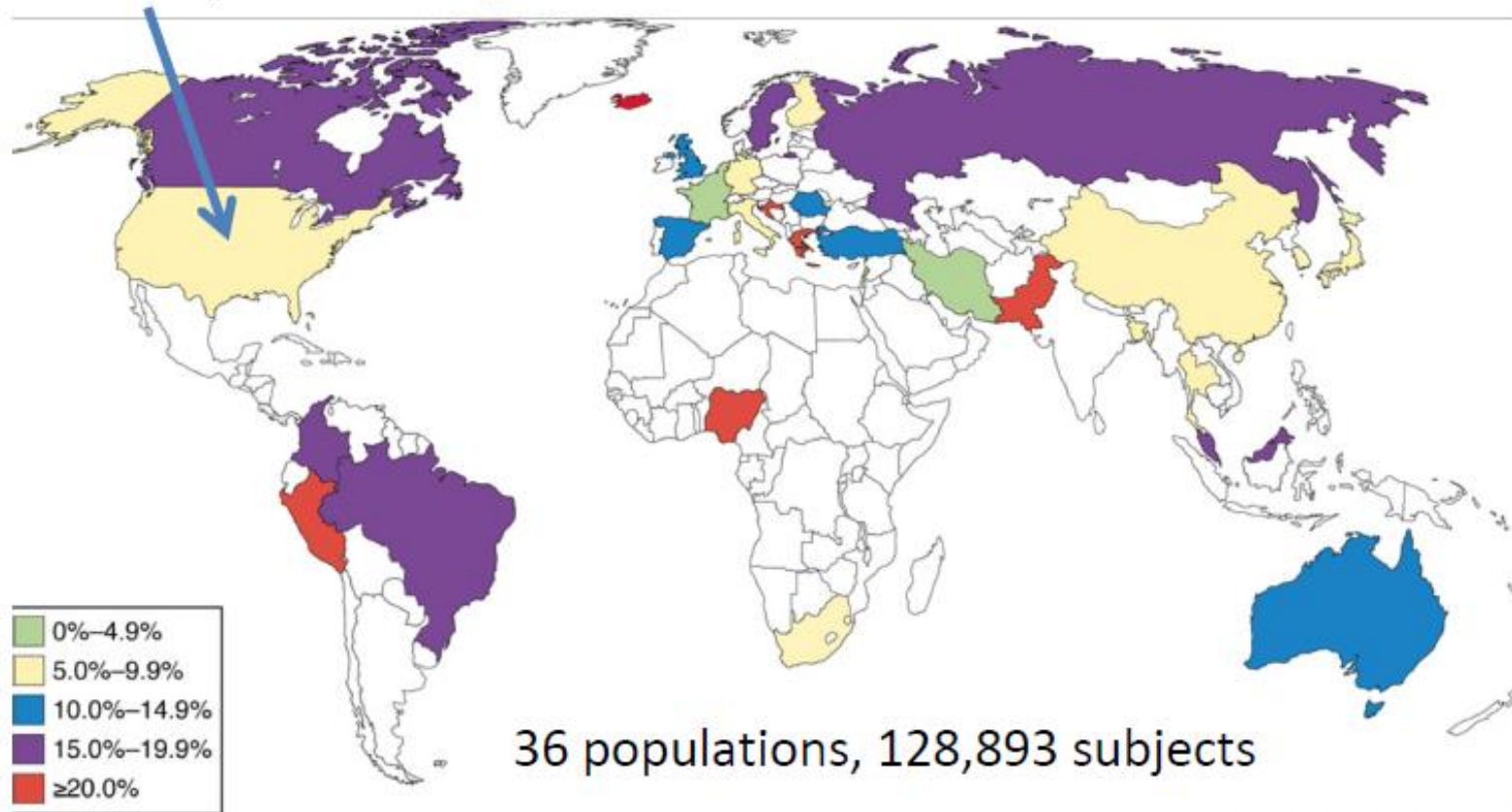
- fibromyalgia
- chronic fatigue syndrome
- gastroesophageal reflux disease
- functional dyspepsia
- non-cardiac chest pain
- psychiatric disorders including major depression anxiety, and somatization

IBS - Epidemiology

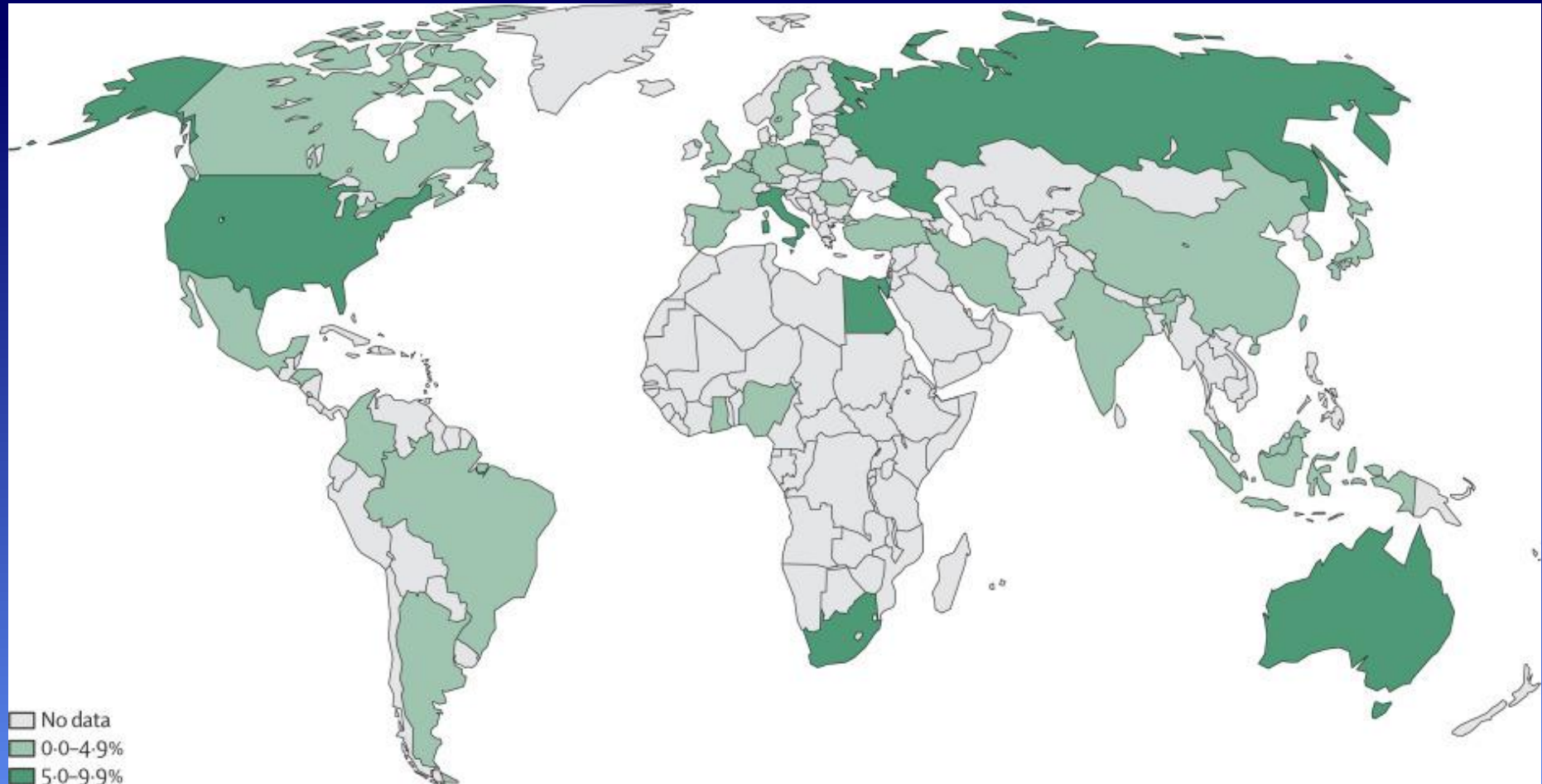


World wide prevalence of Rome II IBS

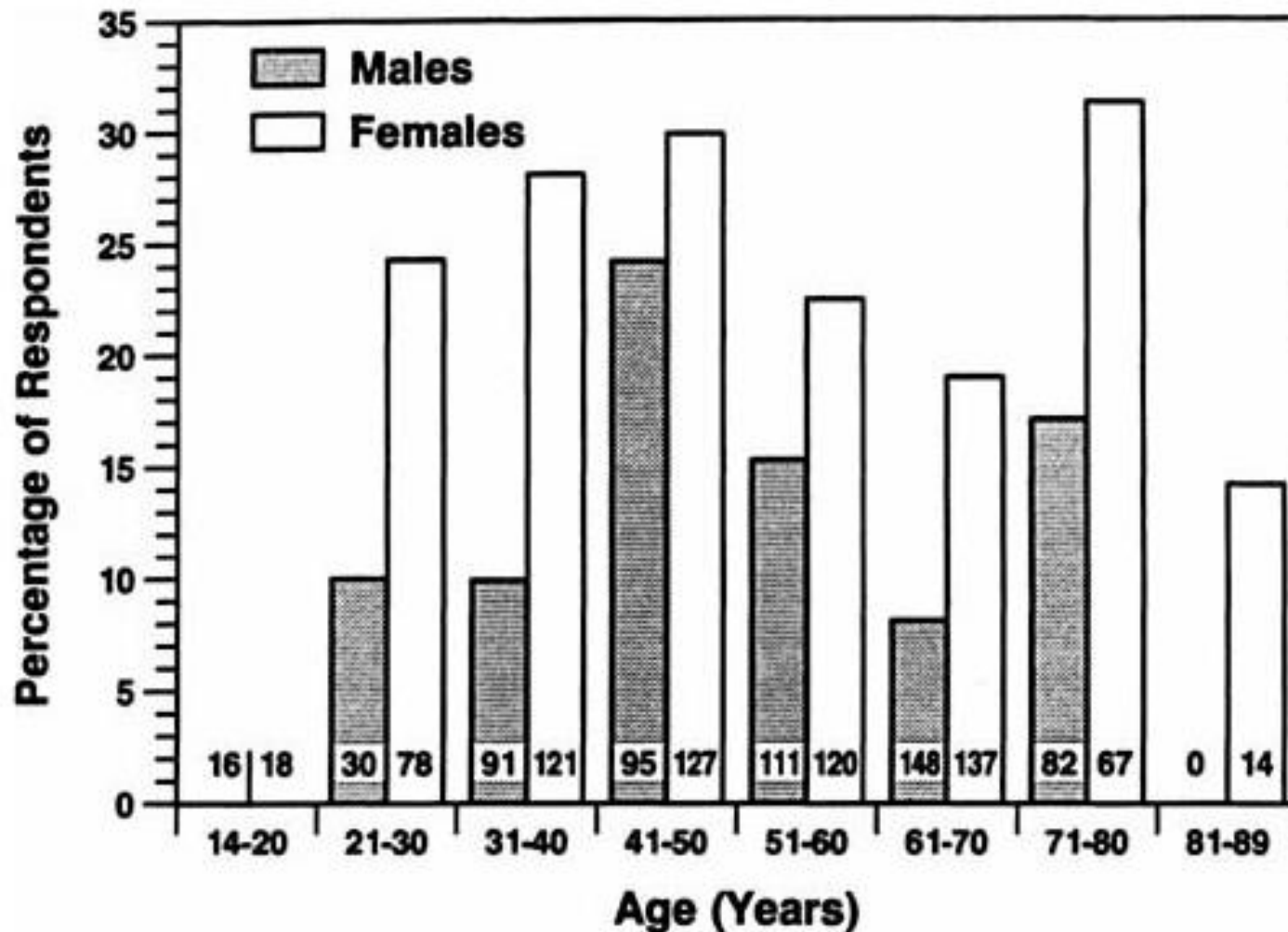
7% Rome II, 16% Manning



Global prevalence of irritable bowel syndrome according to Rome III or IV criteria



The estimated prevalence of IBS globally is approximately 11 percent, with a higher prevalence in younger individuals and in females.



Pathophysiology of IBS

A **bio psycho social** disorder

- Altered motility and enhanced visceral perception
- ~50% have psychologic symptoms
- The role of physical and sexual abuse is controversial
- Up to one third (range 7%-31%) of IBS presenters recall an antecedent gastroenteritis

Proposed mechanisms

- Abnormal motility
- Heightened visceral perception:
 - » peripheral
 - » central
- Psychologic distress
- Intraluminal factors irritating :
 - » Lactose,other sugars
 - » Bile acids,short-chain fatty acids
 - » Food allergens
- Postinfectious neuroimmune modulation of gut functions
- Central nervous system modulation

Psychosocial factors

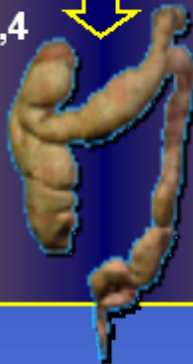


Vagal nuclei

5-HT

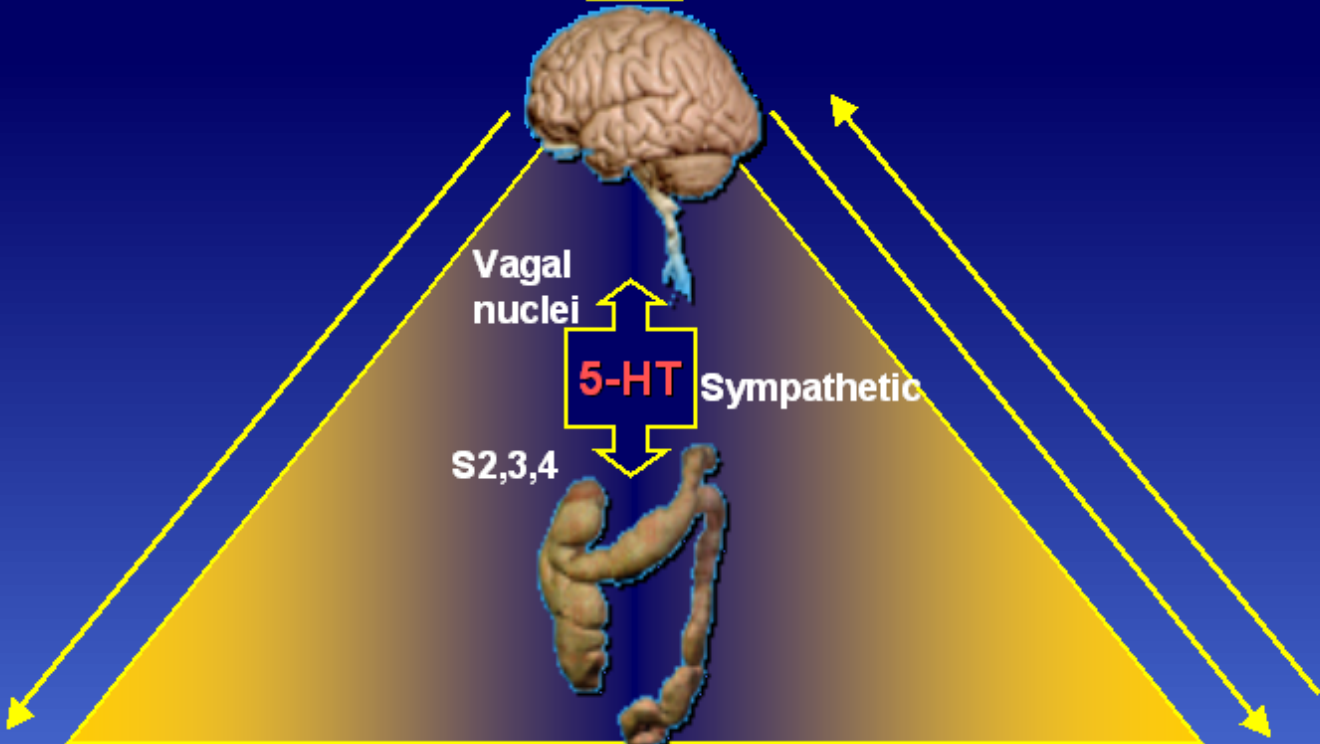
Sympathetic

S2,3,4

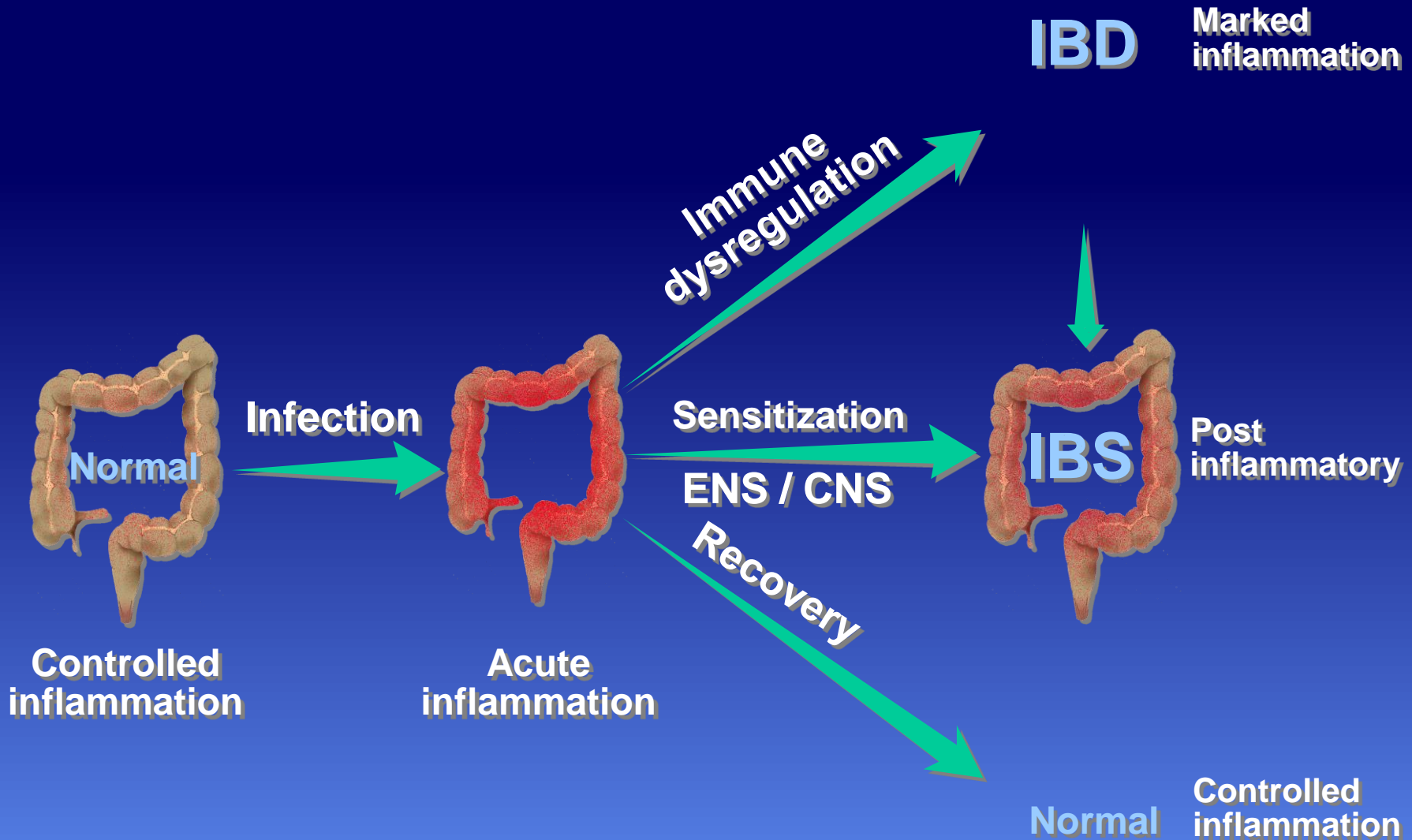


Altered motility

Visceral hypersensitivity



Post Infectious IBS



IBS - Hypersensitivity

End Organ Sensitivity

- "Silent" nociceptors

Endogenous Modulation

- Cortex
- Brainstem

Visceral Hypersensitivity

Hyperalgesia

Allodynia

Spinal Hyperexcitability

- Nitric oxide activation

Long-term Hyperalgesia

- Tonic cortical regulation
- Neuroplasticity

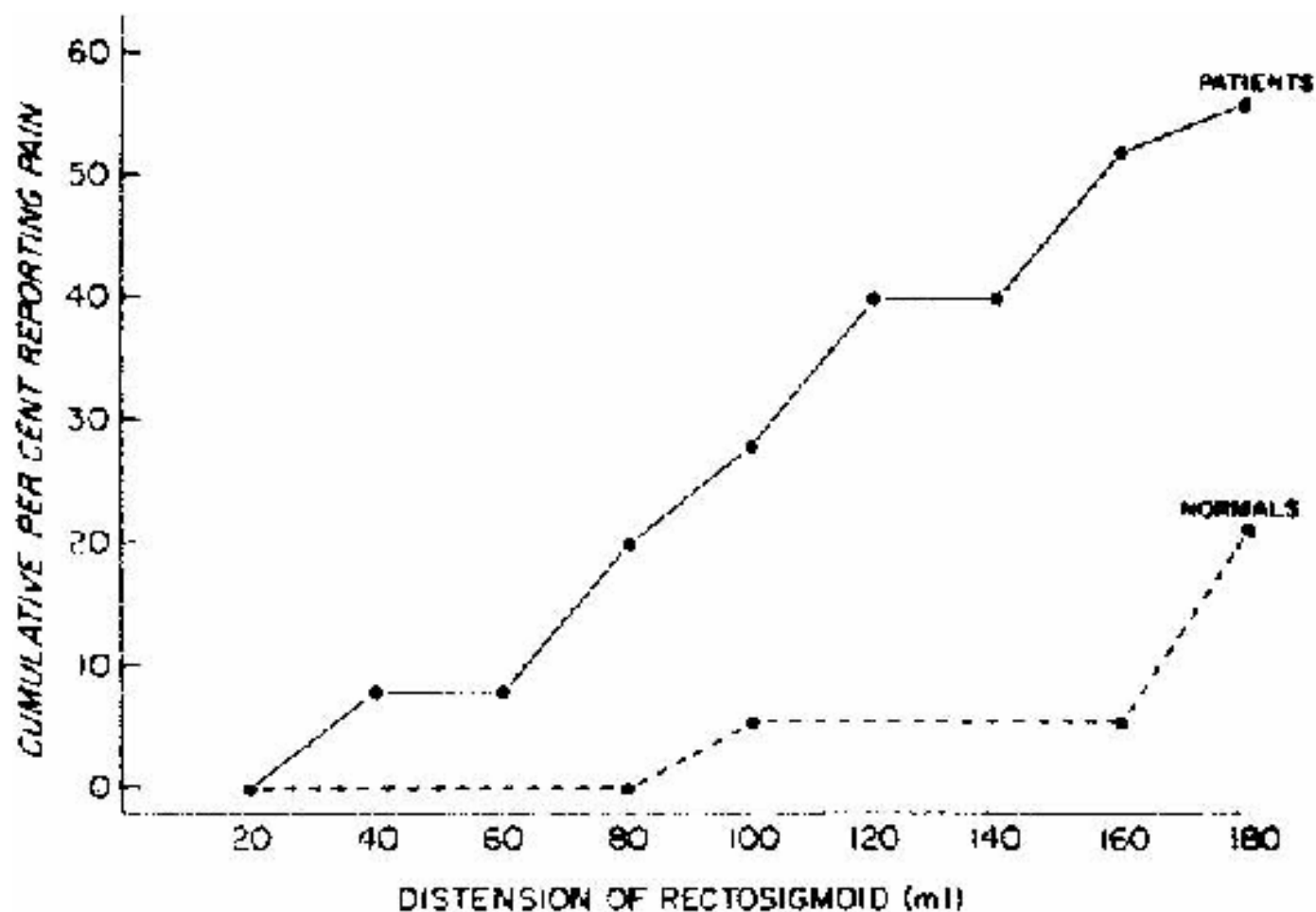
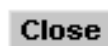
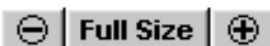


FIGURE 86-3. Perception of rectal balloon inflation is compared in healthy volunteers (*dashed line*) and patients with irritable bowel syndrome (IBS) (*solid line*). More patients with IBS reported pain with rectal distention. Furthermore, they experienced pain at much lower volumes than the healthy volunteers. (From Whitehead WE, Engel BT, Schuster

ROLE OF PSYCHOSOCIAL FACTORS IN IBS

- Psychological and sociocultural factors:
 - history of emotional, sexual or physical abuse
 - stressful life events
 - chronic social stress
 - anxiety disorder
- Psychologic stress exacerbates GI symptoms
- Psychosocial factors affect health status and clinical outcome

Serotonin

- The neurotransmitter serotonin (5-hydroxytryptamine [5-HT]) is a **predominant signaling molecule in the enteric nervous system ENS**.
- **Most (90% to 95%) of the body's serotonin is found in the gut**, and smaller amounts are found in the brain (about 3%) and in platelets (about 2%).
- In the GI tract, serotonin facilitates communication between the ENS and its effector systems (muscles, secretory endothelium, endocrine cells, and vasculature of the GI tract), thus playing a key role in normal GI tract functioning.
- In addition, serotonin plays a role in the communication between the ENS and the CNS.

Serotonin

- In the gut, serotonin is synthesized by and stored in the enterochromaffin cells, which are located within the mucosa of the intestinal wall.
- When material passes through the lumen and the mucosa is stimulated, enterochromaffin cells release serotonin, which then binds to its receptors (primarily 5-HT_{1P} receptors) on intrinsic primary afferent neurons, initiating peristalsis and secretion.
- Serotonin also binds to 5-HT₄ receptors on interneurons, which augments the transmission of signals to motor neurons, resulting in enhanced peristaltic activity.
- In transgenic mice lacking 5-HT₄ receptors, colonic motility is abnormally slow.
- By binding to 5-HT₃ receptors on efferent sensory innervations coming from the vagus and the spinal nerves, serotonin mediates signaling between the ENS and the CNS and, thus, modulates pain perception.

Serotonin

- To regulate the signaling process, **excess serotonin must be removed**; this is accomplished by the SERT molecule expressed by intestinal epithelial cells
- Serotonin levels may also be affected by altering the amount or function of SERT

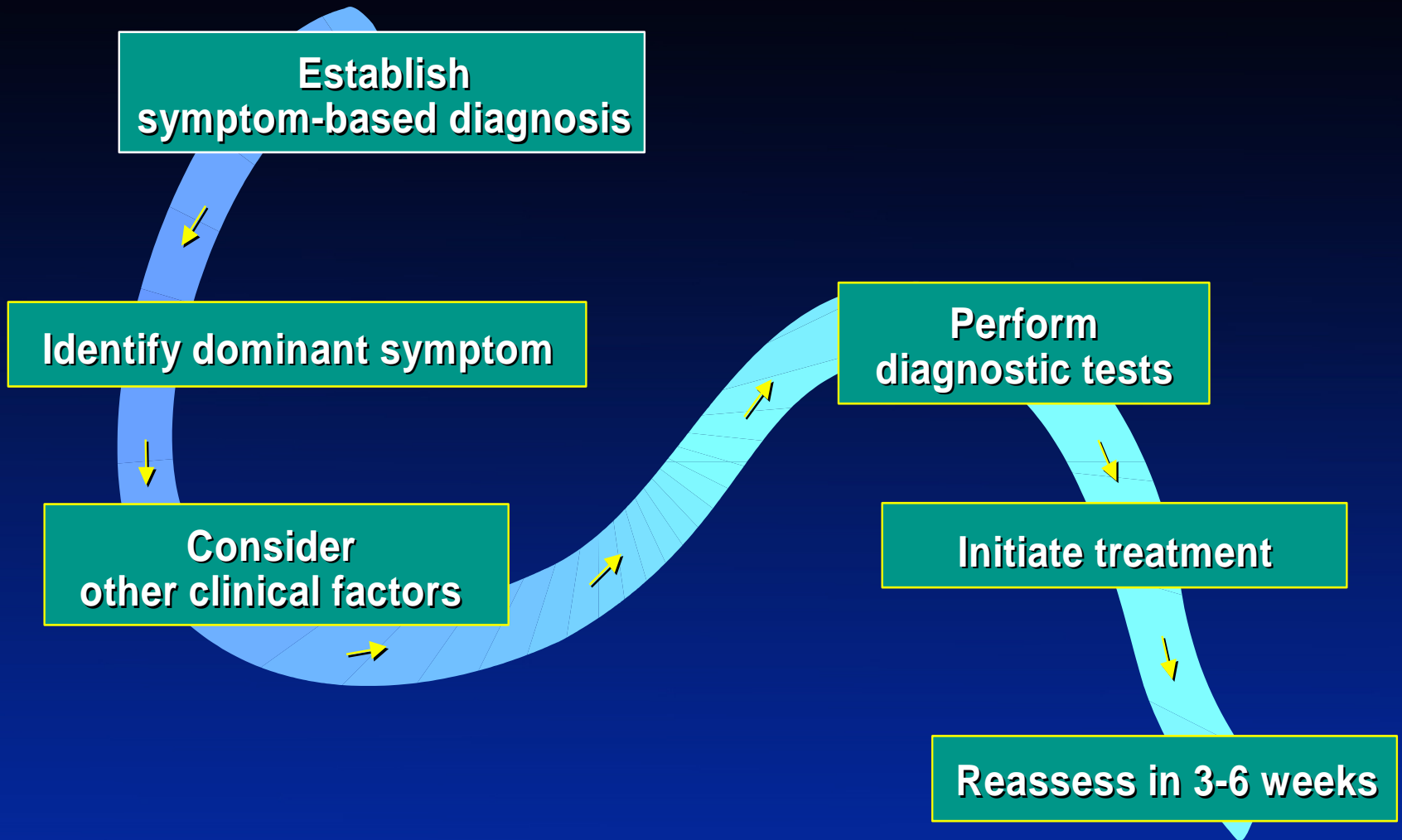
Serotonin

- Impairment or **imbalance in serotonergic signaling**, which can affect GI motility, secretion, and visceral sensitivity, may be affected by defects or deficiencies in serotonin production, specific serotonin receptors, or proteins such as SERT.

IBS Can Lead to Impaired HRQL

- Patients with functional GI disorders have poorer functional status than those with organic GI diagnoses
- Patients with IBS have significantly poorer HRQL than the general population or of patients with GERD

IBS - Diagnostic Approach



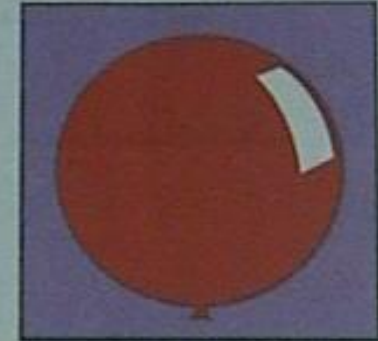
Dominant Symptoms

- Pain
- Diarrhea
- Constipation

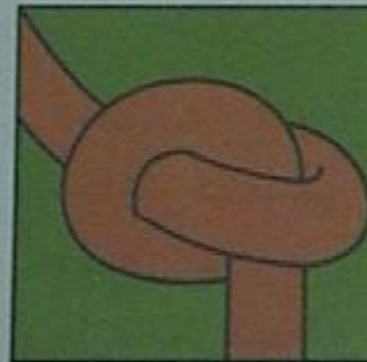
نشانه‌های تیپیک بیماری
IBS (سندم روده تحریک پذیر)



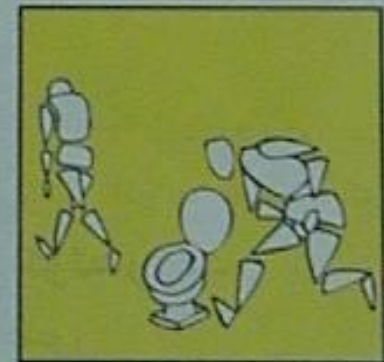
اسپاسم دردناک



نفخ شکم



دل پیچه



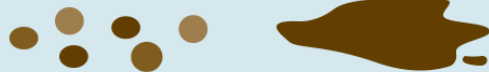
یبوست، اسهال

IBS subtypes

- **IBS with predominant constipation**
 - Patient reports that abnormal bowel movements are usually constipation (type 1 and 2 in the BSFS)
- **•IBS with predominant diarrhea**
 - Patient reports that abnormal bowel movements are usually diarrhea (type 6 and 7 in the BSFS)
- **•IBS with mixed bowel habits**
 - Patient reports that abnormal bowel movements are usually both constipation and diarrhea (more than one-fourth of all the abnormal bowel movements were constipation and more than one-fourth were diarrhea)
- **•IBS unclassified**
 - Patients who meet diagnostic criteria for IBS but cannot be accurately categorized into one of the other three subtypes.

IBS-Constipation

≥ 25% Hard or lumpy
< 25% Loose or watery

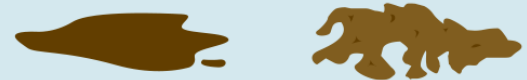


≥ 25% Hard or lumpy
≥ 25% Loose or watery

IBS-Mixed Pattern

IBS-Diarrhea

≥ 25% Loose or watery
< 25% Hard or lumpy



< 25% Hard or lumpy
< 25% Loose or watery

IBS-Unspecified

Stool type
& frequency

Rome I Criteria

Symptoms >3 months

Abdominal pain/discomfort

– Relieved with defecation
and/or



– With change
in stool frequency
and/or



– With change
in stool consistency



Two or more at least
1/4 of the time

– Δ in stool frequency

– Δ in form

– Difficult passage

– Mucous

– Bloating

Rome II Diagnostic Criteria for Irritable Bowel Syndrome^{3†}

At least 12 weeks, which need not be consecutive, in the preceding 12 months of abdominal discomfort or pain that has 2 of 3 features:

1. Relieved with defecation; and/or
2. Onset associated with a change in frequency of stool; and/or
3. Onset associated with a change in form (appearance) of stool.

Symptoms that cumulatively support the diagnosis of IBS:

1. Abnormal stool frequency (for research purposes, 'abnormal' may be defined as greater than 3 bowel movements per day and less than 3 bowel movements per week);
2. Abnormal stool form (lumpy/hard or loose/watery stool);
3. Abnormal stool passage (straining, urgency, or feeling of incomplete evacuation);
4. Passage of mucus;
5. Bloating or feeling of abdominal distention.

The diagnosis of a functional bowel disorder always presumes the absence of a structural or biochemical explanation for the symptoms.

NOTE. Evaluation also includes a complete physical examination, sigmoidoscopy, and additional testing when indicated. Other studies may include examination of the stool (ova and parasites, occult blood, laxatives), complete blood count, sedimentation rate, and serum chemistries. In certain cases, imaging studies (eg, upper gastrointestinal series, colonoscopy with rectal biopsy) will be needed).

Rome II Criteria

At least 12 weeks in preceding 12 months
of abdominal discomfort or pain and 2 of following:



**Pain
relieved
with
defecation**

and / or

**Onset
associated
with change
in frequency
of stool**

and / or

**Onset
associated
with change
in form
of stool**

Rome III

Recurrent abdominal pain or discomfort* at least 3 days per month in the last 3 months associated with 2 or more of the following:

- (1) Improvement with defecation
 - (2) Onset associated with a change in frequency of stool
 - (3) Onset 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 diagnosis.
 - Discomfort means an uncomfortable sensation not described as pain.
 - In pathophysiology research and clinical trials, a pain/discomfort frequency of at least 2 days a week during screening evaluation for subject eligibility

Rome II and III criteria

- Whereas the **Rome II criteria** require symptoms to be present for at least 12 weeks in the past 12 months, the **Rome III criteria** require symptoms to originate for 6 months prior to diagnosis, and be currently active (ie, patient meets criteria) for 3 months.
- It is hoped that the less restrictive symptom timeframe requirements of the Rome III guidelines will make them more clinically practical than the previous iterations.

Rome IV criteria for IBS

According to the Rome IV criteria, IBS is defined as recurrent abdominal pain, on average, at least one day per week in the last three months, associated with two or more of the following criteria :

- Related to defecation
- Associated with a change in stool frequency
- Associated with a change in stool form (appearance)

Diagnosis

- Historically IBS was long considered a "diagnosis of exclusion," leading to excessive testing of patients with characteristic symptoms.
- Fortunately, advances in research have led to the development of **symptom-based approaches**, aimed at standardizing IBS patient subgroups, and the development of consensus guidelines advocating a **positive diagnosis of IBS** based primarily on the pattern and nature of symptoms, without the need for excessive laboratory testing
- No symptom-based criteria have ideal accuracy for diagnosing IBS and need limited evaluation

Evaluation

Physical examination

- Exclude findings not consistent with IBS :
 - » enlarged liver
 - » abdominal mass
 - » signs of bowel obstruction
- A pelvic examination :
 - » For lower abdominal/pelvic symptoms
 - » Is a change in menstrual pattern
- A rectal examination:
 - » Identify a lax sphincter or paradoxical pelvic floor muscle contraction.

IBS - Diagnosis

Physical

Abnormal exam
Fever
Positive occult stool

Historical

Weight loss
Onset in older patients
Nocturnal awakening
Family Hx CA / IBD

Initial Labs

↓ *Hgb*
↑ *WBC*
↑ *ESR*
Abnormal chemistry



Red Flags

Diagnosis

The presence of **alarm features** potentially indicative of organic disease necessitates further evaluation.

- Abnormal P/E : Mass ,arthritis
- Rectal bleeding
- Family history of colon cancer or IBD
- Nocturnal symptom
- Progressive abdominal pain
- Weight Loss
- Age >50
- Anemia/iron deficiency
- High ESR
- Elevated CRP or fecal calprotectin/lactoferrin
- Leukocytosis
- Abnormal TFT

Diagnosis

In all patients with suspected IBS, we perform a CBC and age-appropriate colorectal cancer screening.

In patients with diarrhea, we perform the following:

- Fecal calprotectin or fecal lactoferrin
- Stool testing for giardia
(antigen detection or nucleic acid amplification assay)
- Serologic testing for celiac disease
- CRP levels, only if fecal calprotectin and fecal lactoferrin cannot be performed

- The diagnostic role of **antibodies to cytolethal distending toxin B (CdtB) and vinculin** requires confirmation before they can be used in the evaluation of patients with suspected IBS .
- Anti-CdtB were significantly higher in IBS diarrhea as compared to patients with IBD, healthy controls, celiac disease, and IBS constipation.
- The of anti-CdtB for IBS diarrhea:
 - specificity 92%
 - sensitivity 44%
- Anti-vinculin had a sensitivity and specificity of 33 and 84 percent, respectively

Other tests - In addition, we perform a limited number of studies guided by the clinical presentation. These include the following:

- Age-appropriate colorectal cancer screening in all patients.
- In IBS patients with **constipation**, abdominal radiograph to assess for stool accumulation and determine the severity.
- We perform physiologic testing (anorectal manometry and balloon expulsion testing) to rule out dyssynergic defecation in patients with severe constipation that is refractory to management with dietary changes and osmotic laxative therapy.

Patients without alarm features

In patients who meet diagnostic criteria for IBS and have no alarm features, **we do not routinely perform any additional testing** beyond the initial evaluation.

This limited diagnostic approach rules out organic disease in over **95 percent** of patients

Patients with alarm features

- The diagnostic evaluation is based on the clinical presentation and usually includes endoscopic evaluation in all patients and imaging in selected cases.
- In patients with diarrhea, we perform **colonoscopy** to evaluate for the presence of IBD and **perform biopsies** to exclude microscopic colitis .
- We reserve colonic imaging (eg, **abdominal CT scan**) if there is a clinical suspicion for a structural lesion . The imaging modality is guided by the clinical presentation. As an example, if pain, bloating, early satiety and constipation are of recent onset in a postmenopausal female, then we perform a pelvic imaging with an **ultrasound** and/or abdominal CT scan .

There is no role for colonoscopy in IBS, other than in those with:

- Age-appropriate colorectal cancer screening
- Alarm symptoms or signs
 - More than minimal rectal bleeding
 - Weight loss
 - Unexplained iron deficiency anemia
 - Nocturnal symptoms
 - Family history of selected organic diseases including colorectal cancer, inflammatory bowel disease, or celiac sprue
- Symptoms suggestive of IBS with diarrhea who have atypical features and/or relevant risk factors that increase the likelihood of them having microscopic colitis
 - (female sex, age ≥ 50 years, coexistent autoimmune disease, nocturnal or severe, watery, diarrhea, duration of diarrhea < 12 months, weight loss or use of potential precipitating drugs including NSAID, PPI, etc)

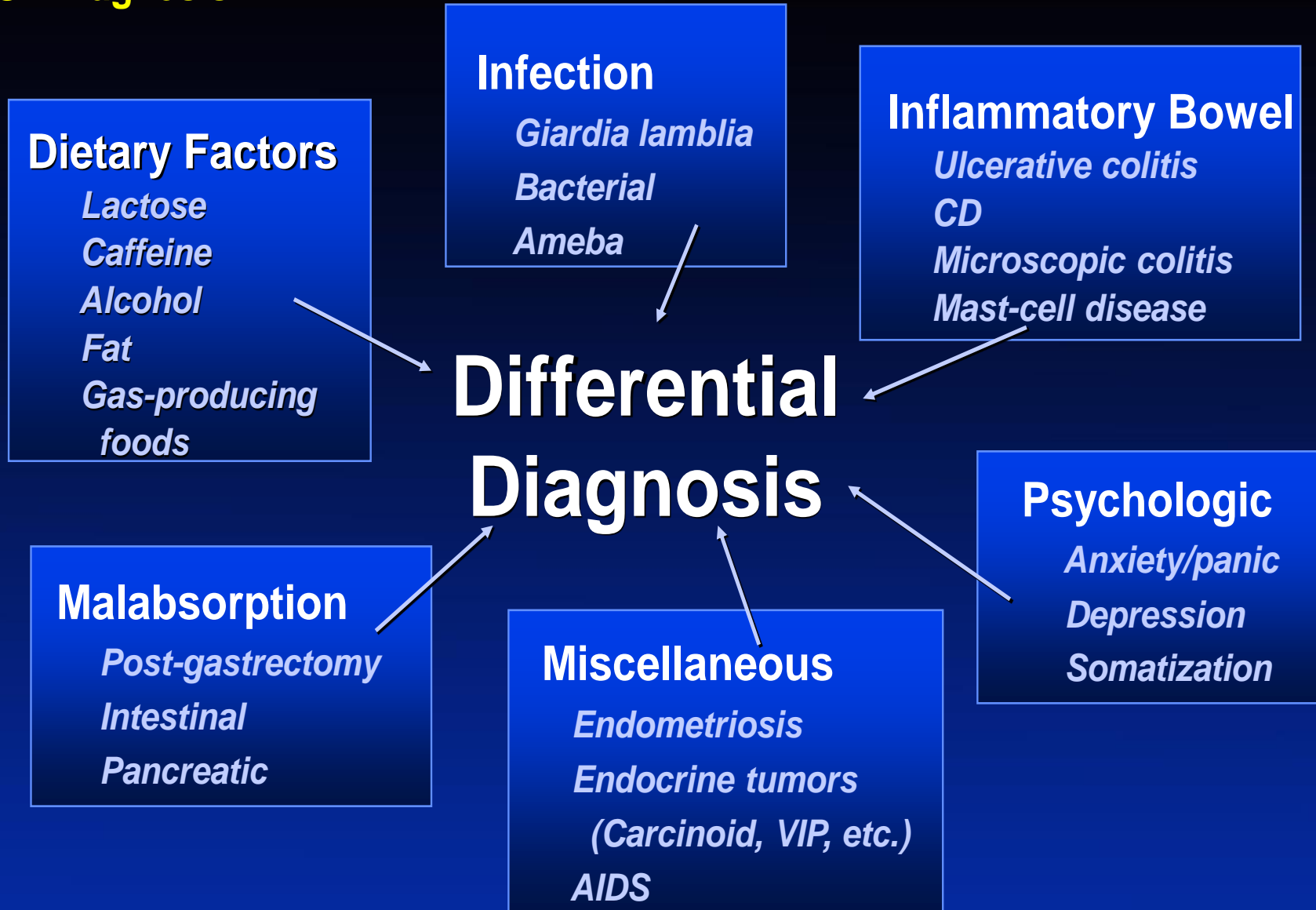
IBS and celiac disease

- In a systematic review the **pretest probability of IBD, colorectal cancer, or infectious diarrhea was found to be less than 1%** in patients meeting symptom-based criteria for IBS.
- However, one exception is **celiac disease**: the pretest probability of celiac disease in patients meeting symptom-based criteria for IBS was **10 times higher than that in the general population.**
- Recently, testing for celiac disease in patients with suspected IBS with diarrhea (IBS-D) has been shown to be most financially feasible in areas in which the prevalence of celiac disease is at least 8%

IBS and celiac disease

- Data to support testing for celiac disease are conflicting
- In a meta-analysis met diagnostic criteria for IBS, 4 percent of patients had celiac disease
- Although more than 7 percent of non-constipated IBS patients had celiac disease associated antibodies suggesting gluten sensitivity, the prevalence of biopsy proven celiac disease was similar to controls

IBS - Diagnosis



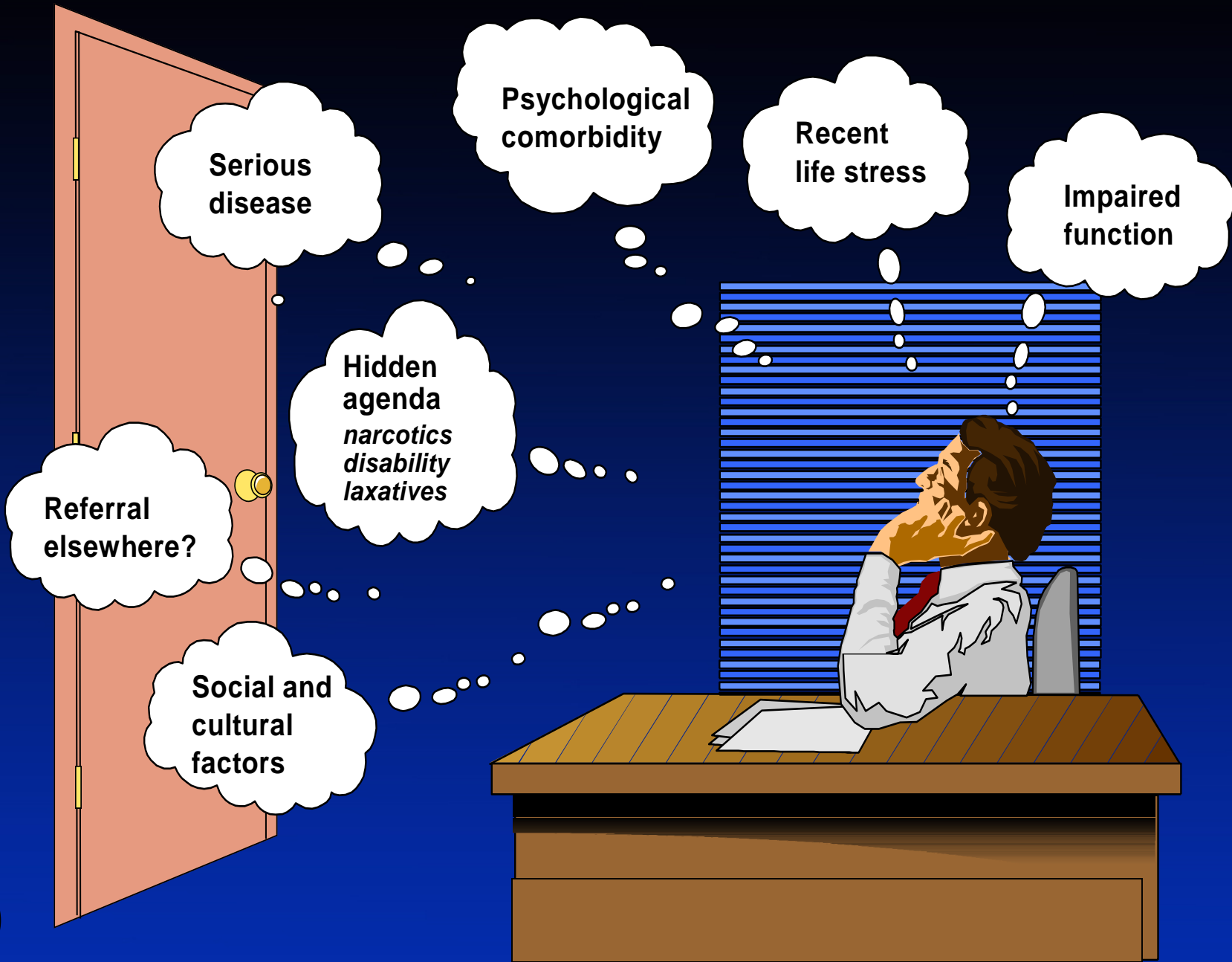
DISEASE COURSE

- Most patients have chronic symptoms that vary in severity over time
- Symptoms:
 - remained unchanged in 30-50%
 - progressed in 2-18 %
 - improve in 12 -38 %
- IBS subtype may change over time with the most frequent change being from predominant constipation or diarrhea to mixed bowel habits
- 2 -5 % of patients were diagnosed with an alternate gastrointestinal disease

IBS - Patient's Agenda



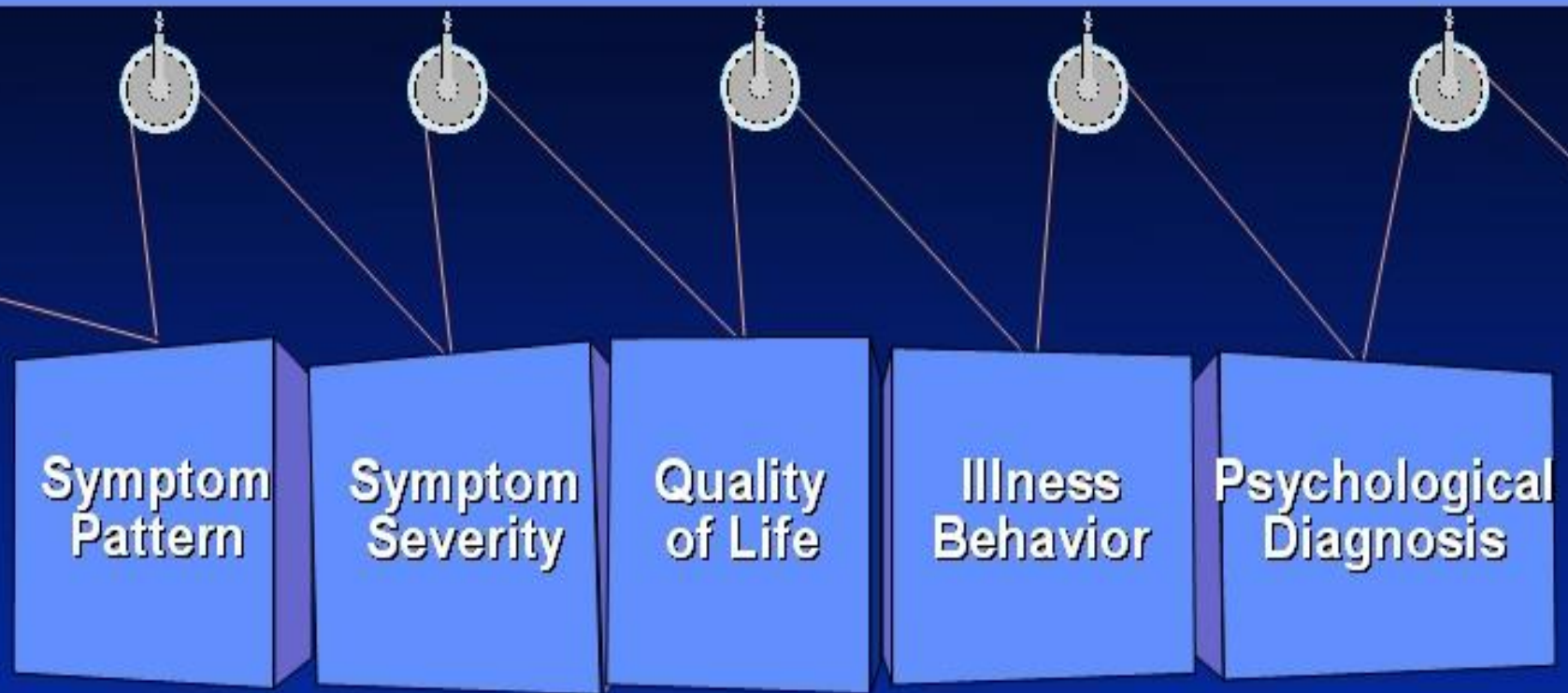
IBS - Doctor's Agenda



Management guide for IBS

- Make a positive diagnosis
- Listen to the patient
- Explanation and reassurance
- Healthy lifestyle advice
- Dietary advice
- Psychological consideration and treatment
- Pharmacological approach

TREATMENT



Treatment of IBS

- The threshold to treat the patient with IBS should be based on the patients assessment of their symptoms.
- In many cases, the therapeutic trial can be undertaken before further diagnostic studies are done and will depend on the symptom
- Goals of IBS treatment :
 - » Improved global IBS symptoms:
 - Abdominal discomfort
 - Bloating
 - Alter bowel habits

GENERAL PRINCIPLES

- Therapeutic relationship (the most important)
- Patient education (mechanisms of IBS)
- Reassurance
 - Patients should also be counseled that although IBS does not increase their risk of malignancy, it is a chronic disorder.
 - Involve the patient in treatment decisions
- Dietary modification (No specific diet ?)
 - Decreased caffeine, tea or cola, alcohol , milk, fatty foods
 - Increased intake of fiber if bloating is not a major factor (Lubrication-Bulking-Binding)

BEHAVIORAL THERAPY

- An integral part of the treatment of many IBS patients
- Improvement in IBS symptoms is frequently correlated with improvement in anxiety-depression

BEHAVIORAL THERAPY

- **Biofeedback** is one example of a noninvasive, behavioral intervention that may help patients with IBS achieve symptom relief.
- In this approach, sensors are strategically placed at specific positions on patients, and a computer and video monitor are used to illustrate (via sounds or line graphs) body functions of which patients are normally not aware. This information can be used to help patients recognize and modify (eg, increase, decrease, coordinate) their physiologic responses to various stressful stimuli (eg, stress-related motility)
- The value of biofeedback and other behavioral therapies cannot be discounted in the management strategy for IBS and should be considered in the overall treatment plan.

Physical activity

- Increased physical activity composed 20 to 60 minutes of moderate to vigorous activity three to five days per week

Constipation

- In patients with IBS with constipation (IBS-C) who have failed a trial of soluble fiber (eg, psyllium/ispaghula), we suggest polyethylene glycol (PEG).
- We treat patients with persistent constipation despite treatment with PEG with:
 - lubiprostone
 - linaclotide
 - plecanatide
- We use tenapanor in patients who fail other therapies for constipation.

Lubiprostone

- Lubiprostone is a locally acting chloride channel activator that enhances chloride-rich intestinal fluid secretion. We use lubiprostone in patients with IBS with persistent constipation despite PEG.
- The approved dose for IBS-C (8 micrograms twice daily in women) is lower than the approved dose for treatment of chronic idiopathic constipation
- The most common adverse event was nausea

Guanylate cyclase agonists

- Linacotide and plecanatide are guanylate cyclase agonists that stimulates intestinal fluid secretion and transit.
- Dose of 290 micrograms daily
- Patients also demonstrated a significant improvement in secondary endpoints of abdominal pain/discomfort, bloating, straining, stool consistency, number of CSBMs (complete and spontaneous bowel movements) and spontaneous bowel movements per week
- Diarrhea was the most common side effect

Sodium/hydrogen exchanger 3 (NHE3) inhibitor

- Tenapanor, reduces the absorption of sodium and phosphate and enhances intestinal fluid volume and transit.
- Improvement in both average weekly complete spontaneous bowel movements and abdominal pain as compared with placebo .
- Diarrhea, abdominal distension, flatulence, and dizziness were the most frequent side effects

5-hydroxytryptamine (serotonin) 4 (5HT₄) receptor agonists

- Tegaserod has been **withdrawn from the market** but has been demonstrated to reduce abdominal pain in IBS and improve constipation
- A history of ischemic colitis, intestinal ischemia, bowel obstruction or adhesions, symptomatic gallbladder disease, and suspected sphincter of Oddi dysfunction are some of the contraindications to the use of tegaserod.

TEGASEROD

- The 5HT₄ receptor agonist
- Effective in relieving global IBS symptoms in female IBS patient with constipation
- Increases colonic activity
- Dose :2-6mg b.i.d
- Use for short-term treatment of women with IBS-C and for men and women younger than 65 years of age with chronic idiopathic constipation.

TEGASEROD adverse effects

- The adverse effects
 - headache (15% and 12%)
 - diarrhea (9% and 4%)
- In most cases, diarrhea was mild, occurred as a single episode during the first week of therapy, and resolved with continued treatment.
- Clinically significant diarrhea (resulting in hospital admission, hypovolemia, hypotension, and need for intravenous fluid) occurred in a minority (4 of 10,000) of patients in clinical trials.
- A long-term, open-label safety study showed that tegaserod was safe and well tolerated in patients receiving 6 mg twice daily for up to 1 year
- Small number (0.11 percent) of **cardiovascular events** (myocardial infarction, unstable angina, or stroke) were reported.

Prucalopride

- Is a serotonin receptor agonists
- Has not been evaluated in patients with IBS

- **Bulking supplements:**

- » The proposed mechanisms:

- Bulking of the stool

- Lubrication

- Binding of agents such as bile

Diet

- Diarrhea-predominant IBS subjects may respond better to an elimination diet
- Patients with IBS may benefit from exclusion of gas-producing foods; a diet low in fermentable oligo-, di-, and monosaccharides and polyols (FODMAPs); and in select cases, lactose avoidance
به عنوان مثال، غذاهای حاوی فروکتوز، از جمله عسل، شربت ذرت با فروکتوز بالا، سیب، گلابی، انبه، گیلاس، یا الیگوساکاریدها، از جمله گندم
- Exclude foods that increase flatulence
 - Beans, Onion, Celery, Carrots, Raisins, Banana, Apricots, Prunes

لوبیا، پیاز، کرفس، هویج، کشمش، موز، زردآلو، آلو، کلم بروکسل، جوانه گندم، چوب شور، و نان شیرینی، الکل و کافئین

Low FODMAP

- Low FODMAP dietary education should be provided by a trained dietician to avoid unnecessary dietary over-restriction and a nutritionally replete diet .
- Low FODMAP education consists of initially eliminating FODMAPs from the diet for six to eight weeks and then, following symptom resolution, gradual reintroduction of foods high in fermentable carbohydrates to determine individual tolerance to specific fermentable carbohydrates

Lactose-restricted diet

- Patients with known lactose intolerance should be placed on a lactose-restricted diet.
- We also suggest an empiric trial of a lactose-free diet in patients who complain of persistent abdominal bloating despite exclusion of gas-producing foods
- As improvement of symptoms does not necessarily imply lactose maldigestion, the diagnosis of lactose intolerance can be confirmed with breath testing

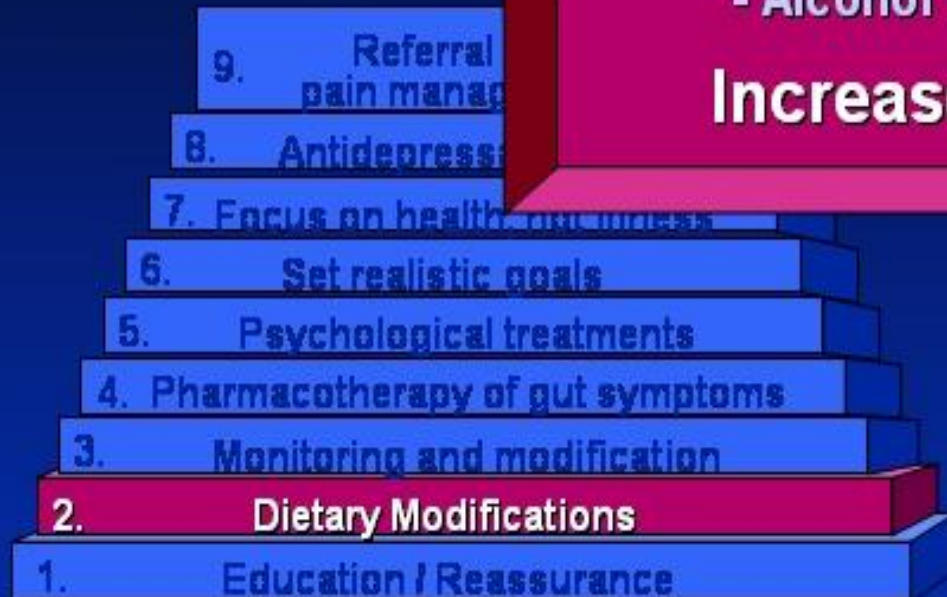
IBS - Treatment Approach

Dietary Modifications

Eliminate offending items

- Lactose
- Caffeine
- Fatty foods
- Alcohol
- Sorbitol gum
- Large meals
- Food sensitivity
- Gas producing foods

Increase fiber (constipation)



Diarrhea

- In patients with diarrhea-predominant symptoms, we use antidiarrheals (eg, loperamide) as initial treatment
 - loperamide 2 mg 45 minutes before a meal on regularly scheduled doses. (maximum daily dose 16 mg/day).
- **Bile acid sequestrants**
(eg, cholestyramine, colestipol, colesevelam) as second-line therapy

Effectiveness of antidiarrheals in the management of irritable bowel syndrome

Loperamide

- Is an effective agent for the treatment of diarrhea, reducing stool frequency, and improving stool consistency.
- Not more effective than placebo at reducing pain, bloating, or global symptoms of IBS,
- Safety and tolerability data on loperamide are lacking.

DRUGS (Diarrhea)

- Anticholinergic agents:
 - Dicyclomin (20mg qid)
 - Hyoscyamine (0.125-0.25mg PO or SL Tid or Qid)
- Antidepressants
 - Analgesic properties independent of their mood improving effects (TCA or SSRIs)
 - Low doses should initially be administered
 - Onset of action is after 3-4 weeks
- Antidiarrheal agents
 - Loperamide (PRN)
 - Diphenoxylate

5-HT₃ receptor antagonists

- More effective than placebo at relieving global IBS symptoms and relief of abdominal pain and discomfort in male and female **IBS patients with diarrhea**.
- Potentially serious **side effects** including constipation and colon ischemia.
- The benefits and harms balance for alosetron is most favorable in women with severe IBS and diarrhea who have not responded to conventional therapies.

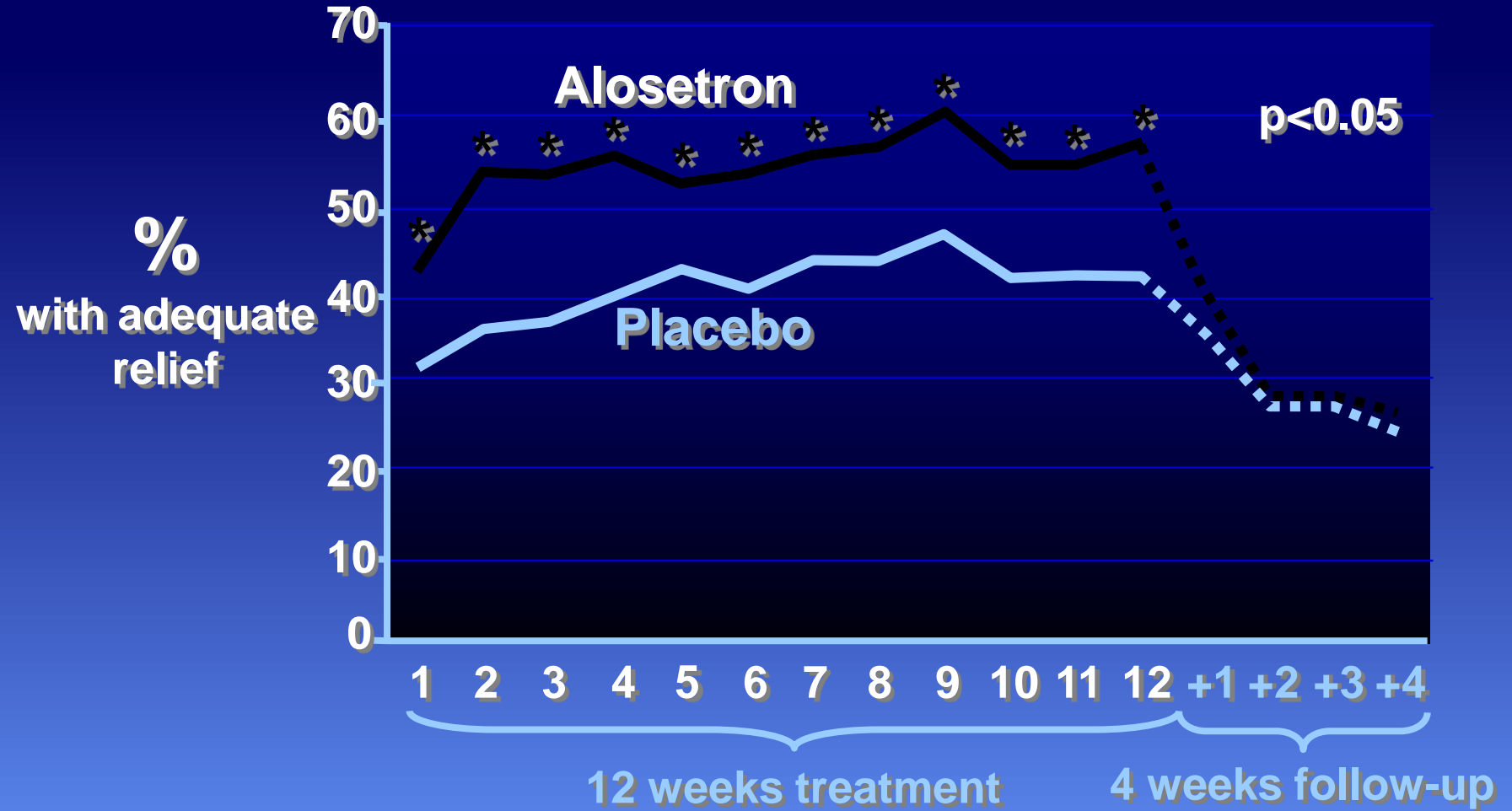
DRUGS (ALOSETRON)

- 5HT₃ receptor antagonist
- Modulates visceral afferent activity from GI
 - decreasing colonic motility and secretion
- Indicated only for women with:
 - Severe diarrhea-predominant IBS
 - No response to conventional therapy
 - Chronic IBS symptoms lasted for six months
- Dose: 1-4mg bid
- Discontinue if :
 - Constipation
 - Abdominal pain
 - Rectal bleeding (ischemic colitis) or bloody diarrhea

DRUGS (ALOSETRON)

- The most frequently reported adverse effects during clinical trials, for alosetron and placebo, respectively, were
 - constipation (29% vs 6%)
 - Constipation generally occurred as single episodes during the first month of treatment and resolved either on its own or after an interruption in treatment.
 - abdominal pain/discomfort (7% vs 4%)
 - nausea(6% vs 5%)
 - Ischemic colitis and serious complications related to constipation

Diarrhea-Predominant Females



Ondansetron

- Ondansetron significantly improved stool consistency, frequency, and urgency but was not associated with a significant improvement in abdominal pain

Eluxadoline

- Combines a mu-opioid receptor agonist and a delta-opioid receptor antagonist
- Eluxadoline should only be used in **selected** patients with severe IBS-D that is refractory to **all other agents**
- **It is associated with a high incidence of severe acute pancreatitis** (0.3 percent)
- A history of biliary disorders, pancreatitis, severe liver impairment (Child-Pugh Class C), and heavy alcohol use are contraindications to its use. Eluxadoline is contraindicated in patients who do not have a gallbladder due to a high incidence of severe acute pancreatitis

DRUGS

- Prokinetic drugs (only for short-term use)
- Benzodiazepines:
 - Anxiolytic agents
 - Decrease serotonin by GABA
- Kappa agonists: Kappa opioids (fedotozine)
 - Inhibit somatic pain through a peripheral mechanism of action

Treatment of bloating

- No medication has been shown to be beneficial
- Bloating associated with constipation may respond to treatment of constipation
- Consider fiber reduction
- In patients with moderate to severe IBS without constipation, particularly those with bloating, who have failed to respond to other therapies, we suggest a two-week trial of rifaximin

DRUGS

- Peppermint oil eg. **Colpermin**
 - » The active principle is menthol
 - » Cyclic monoterpen with a Ca^{++} -channel blocking activity
- The capsule's enteric coating that active ingredient is **peppermint oil**
- In large intestine the active ingredient, peppermint oil, is slowly released for maximum effect and relief
- The selective inhibition of gastrointestinal smooth muscle by antispasmodics and peppermint oil reduce stimulated colonic motor activity and may be beneficial in patients with postprandial abdominal pain, gas, bloating, and fecal urgency

Diet and irritable bowel syndrome

- Patients often believe that certain foods exacerbate their IBS symptoms.
- There is, however, **insufficient evidence** that food allergy testing or exclusion diets are efficacious in IBS and their routine use outside of a clinical trial is not recommended.

Effectiveness of dietary fiber, bulking agents, and laxatives in the management of IBS

- Studies suggests that **soluble** (eg, ispaghula husk/psyllium,oat) but not insoluble (eg, wheat bran,corn) fiber has a significant effect for the treatment of IBS symptoms
- **Psyllium** hydrophilic mucilloid (ispaghula husk) is moderately effective and can be given a conditional recommendation.
- A single study reported improvement with **calcium polycarbophil**.
- **Wheat bran or corn bran** is no more effective than placebo in the relief of global symptoms of IBS and cannot be recommended for routine use.
- **Polyethylene glycol (PEG)** laxative was shown to improve stool frequency - but not abdominal pain in adolescents with IBS-C.

Effectiveness of antispasmodic agents in the management of IBS

- hyoscine
- cimetropium
- pinaverium
- peppermint oil
- May provide short-term relief of abdominal pain / discomfort in IBS.
- Evidence for long-term efficacy is not available.
- Evidence for safety and tolerability is limited.

Antispasmodic agents

- Antispasmodics should be administered on an as-needed basis and/or in anticipation of stressors with known exacerbating effects
- Directly affect intestinal smooth muscle relaxation (eg, mebeverine and pinaverine)
- Act via their anticholinergic or antimuscarinic properties (eg, dicyclomine and hyoscyamine)

Effectiveness of antibiotics in the management of irritable bowel syndrome

- A short-term course of a nonabsorbable antibiotic is more effective than placebo for global improvement of IBS and for bloating.
- There are no data available to support the long-term safety and effectiveness of nonabsorbable antibiotics for the management of IBS symptoms.

Rifaximin

- Given the modest benefit and relatively short-term follow-up demonstrated in the trials of rifaximin, we suggest NOT using antibiotics routinely in patients with IBS.
- However, in patients with moderate to severe IBS without constipation (particularly those with bloating) who have failed to respond to all other therapies, including a low carbohydrate diet and elimination of fermentable oligo-, di-, and monosaccharides and polyols (FODMAPs), it is reasonable to consider two-week trial of rifaximin.
- Patients with a response to rifaximin, who develop recurrent symptoms, can be retreated with rifaximin

Effectiveness of probiotics in the management of irritable bowel syndrome

- Probiotics are **not routinely recommended** in patients with IBS. Although they have been associated with an improvement in symptoms, the magnitude of benefit and the most effective species and strain are uncertain
- In single organism studies, lactobacilli do not appear effective for patients with IBS; bifidobacteria and certain combinations of probiotics demonstrate some efficacy.

Antidepressants

- Antidepressants have analgesic properties independent of their mood improving effects
- antidepressants should be started at low doses
- Due to the delayed onset of action of antidepressants, three to four weeks of therapy should be attempted before increasing the dose
- Amitriptyline, nortriptyline, desipramine, and imipramine can be started at a dose of 10 to 25 mg at bedtime.

SSRIs/SNRIs

- Given the lack of consistent high-quality evidence demonstrating an improvement in symptoms, **we do not use** SSRIs/SNRIs for the treatment of IBS .
- For patients with IBS in whom depression is a cofactor, SSRIs/SNRIs can also be used

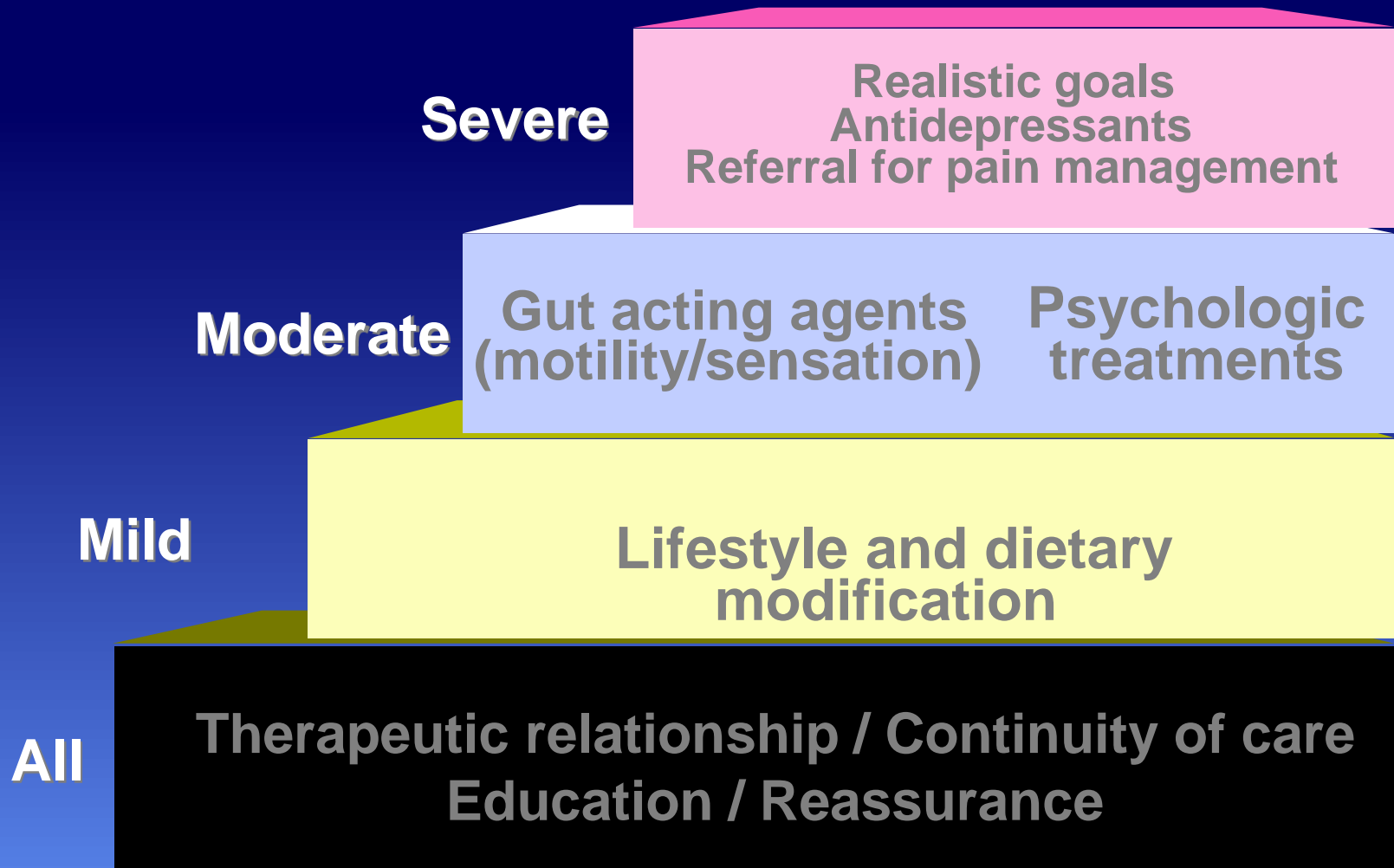
Effectiveness of psychological therapies

- Psychological therapies, including cognitive therapy, dynamic psychotherapy, and hypnotherapy, but not relaxation therapy, are more effective than usual care in relieving global symptoms of IBS.

Effectiveness of herbal therapies and acupuncture

- Available randomized controlled trials mostly tested unique Chinese herbal mixtures, and appeared to show a benefit. It is not possible to combine these studies into a meaningful meta-analysis, however, and overall, any benefit of Chinese herbal therapy in IBS continues to potentially be confounded by the variable components used and their purity. Also, there are significant concerns about toxicity, especially liver failure, with use of any Chinese herbal mixture.
- A systematic review of trials of acupuncture was inconclusive because of heterogeneous outcomes.
- Further work is needed before any recommendations on acupuncture or herbal therapy can be made.

Summary



Pharmaceutical Agents

Pain

Diarrhea

Constipation

Antispasmodics

- Anticholinergics
- Peppermint oil

- Loperamide
- Cholestyramine
- Alosetron

- Fiber
- Osmotic laxatives
- Tegaserod
- Misoprostil
- PEG solution

Opioid-like Agents

- Dextromethorphan
- Trimebutine

**New
Therapeutic
Options**

5-HT₃ antagonist

**Alosetron
Cilansetron**

**NK
antagonist**

**Anti-
depressants
TCAs
SSRIs / SNRIs**

**5-HT₄
agonists
Tegaserod**

**CCK
antagonists
Dexloxiglumide**

**κ opioid
Asimadoline**

**α-2 adrenergic
agonist
Clonidine**

Abstract

- IBS is a **highly prevalent** gastrointestinal motility disorder broadly characterized by abdominal pain/discomfort associated with altered bowel habits.
- The **chronic and bothersome** nature of IBS symptoms often negatively affects patient **quality of life and activity level** and places a substantial **economic burden** on patients and the healthcare system.
- Advances in research have led to a greater understanding of the underlying pathophysiology of IBS, particularly regarding the role **serotonin** plays in the gastrointestinal tract
- The development of stepwise, **symptom-based diagnostic** strategies that allow for a diagnosis of IBS to be made **without the need for extensive laboratory** testing
- The development of **treatment options targeting underlying pathophysiologic** mechanisms that provide relief of the multiple symptoms associated with IBS.