# Psychiatric Disorders in Gastrointestinal Disease

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BRIGHAM AND WOMEN'S HOSPITAL

HARVARD MEDICAL SCHOOL

# Disclosures

- I have no conflicts of interest to disclose

# Objectives

- Describe the intestinal microbiome and the gut-brain-microbiome axis and their role in the pathogenesis of psychiatric disorders in gastrointestinal disease
- Discuss psychiatric disorders in common disorders of gut brain interaction (DGBI- formerly functional disorders) and Inflammatory Bowel Disease (IBD)
- Consider treatment approaches and areas of emerging research for patients with gastrointestinal and psychiatric disorders

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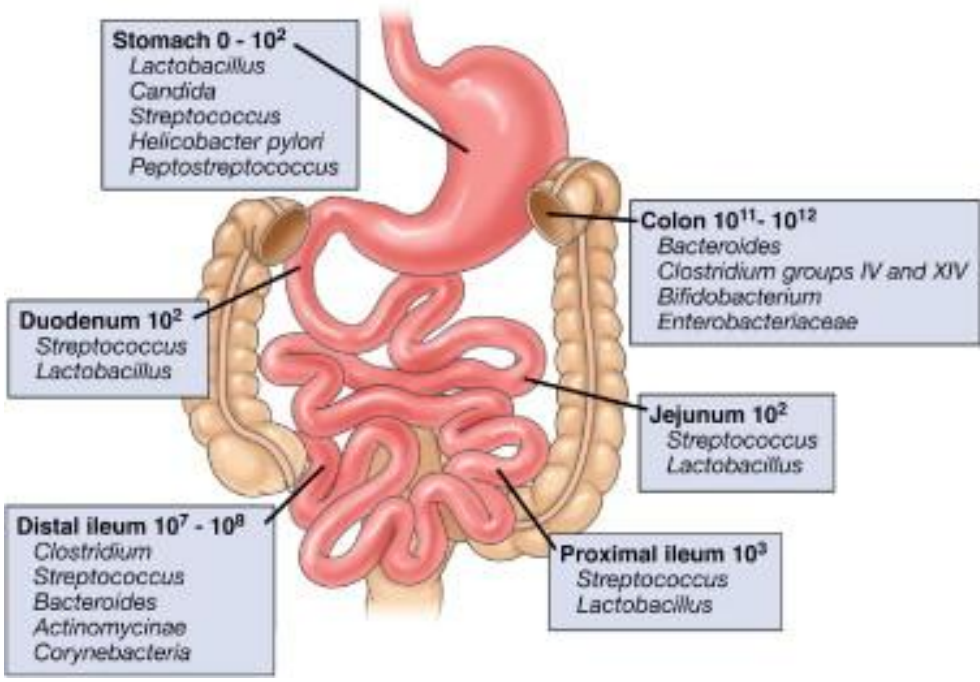
- Administrative focus: Vice Chair, Faculty Enrichment
- Research focus: Psychiatric disorders in IBD, healthcare worker burnout, digital health

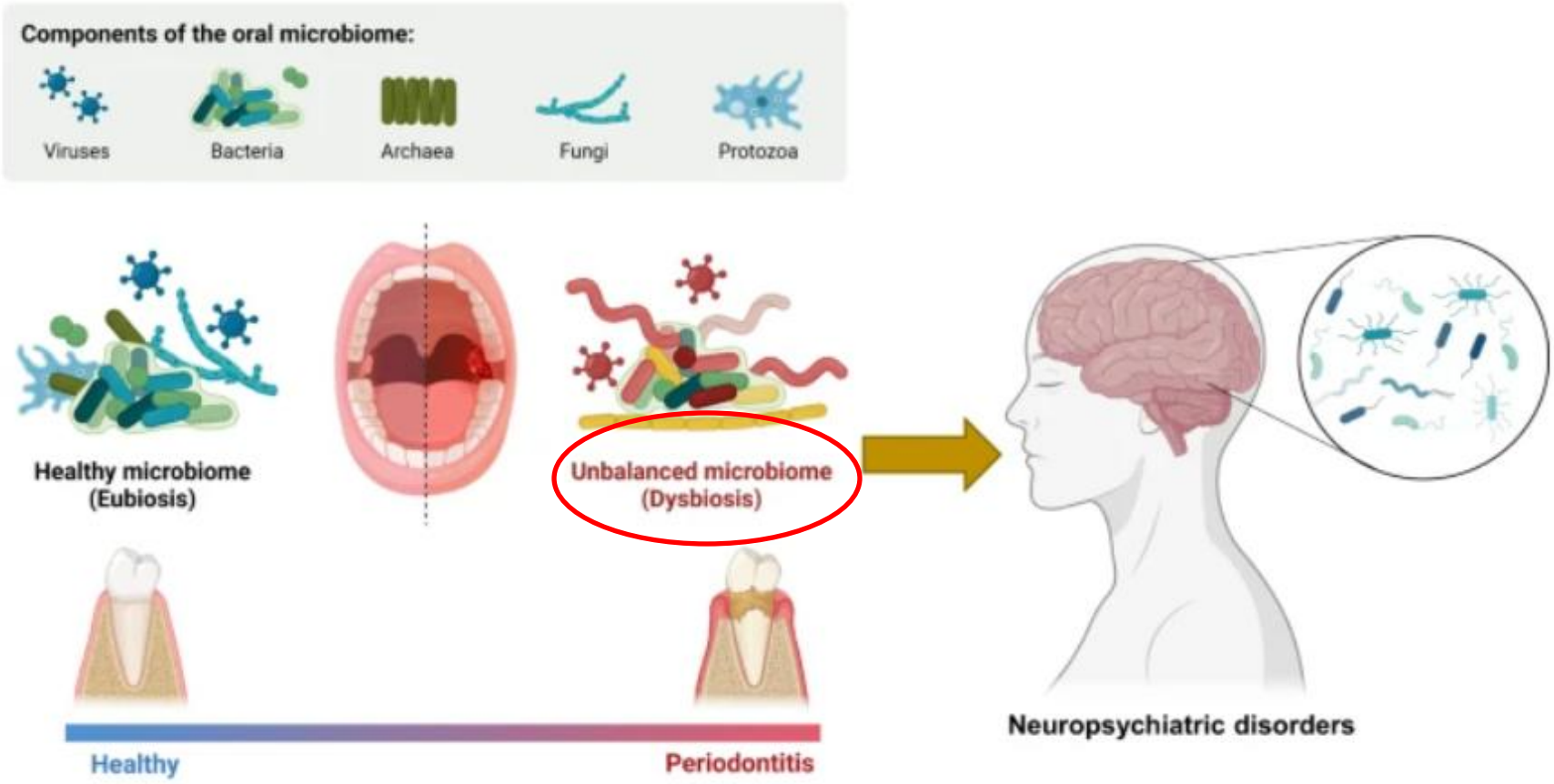
# Intestinal Microbiome

- Bacteria colonize the gut in early post-natum
- Affect the immune system, key nutrients and energy metabolism
- Change in response to environmental and developmental factors in disease



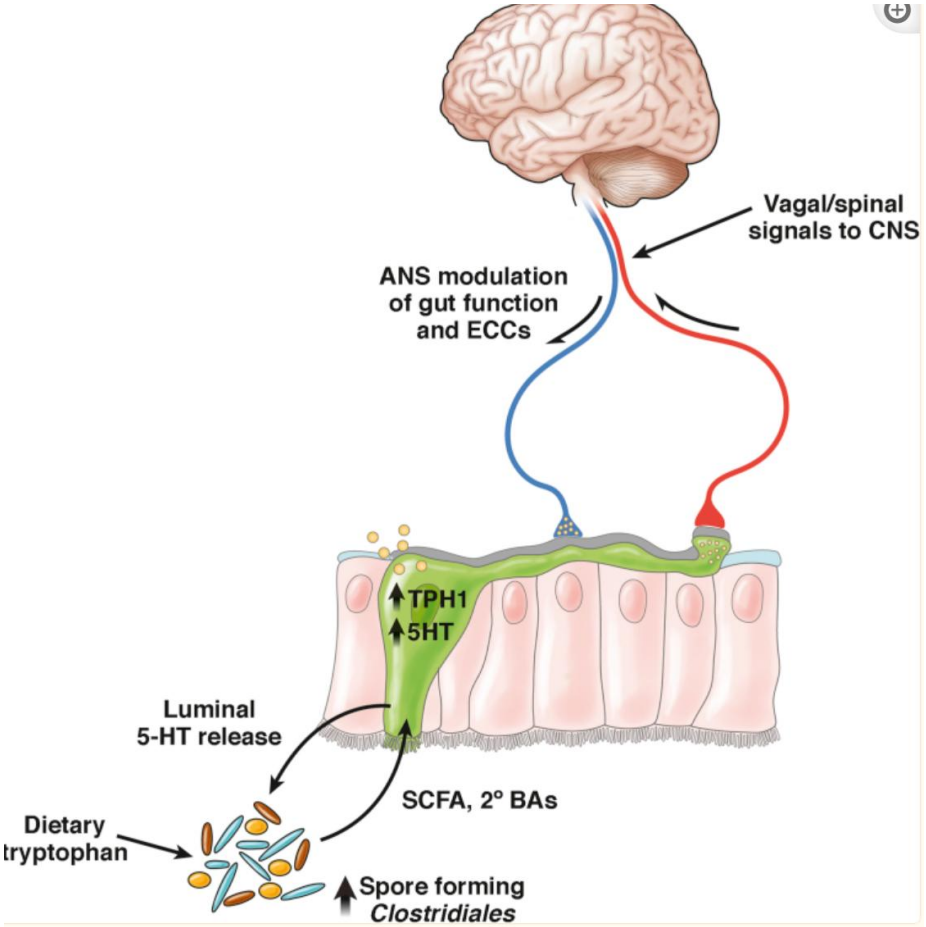

Abraham and Cho, 2009; Xavier and Podolsky, 2007; Korzenik and Podolsky, 2006

# Intestinal Microbiome- Practical Applications



# Brain-Gut-Microbiota Axis Mechanisms

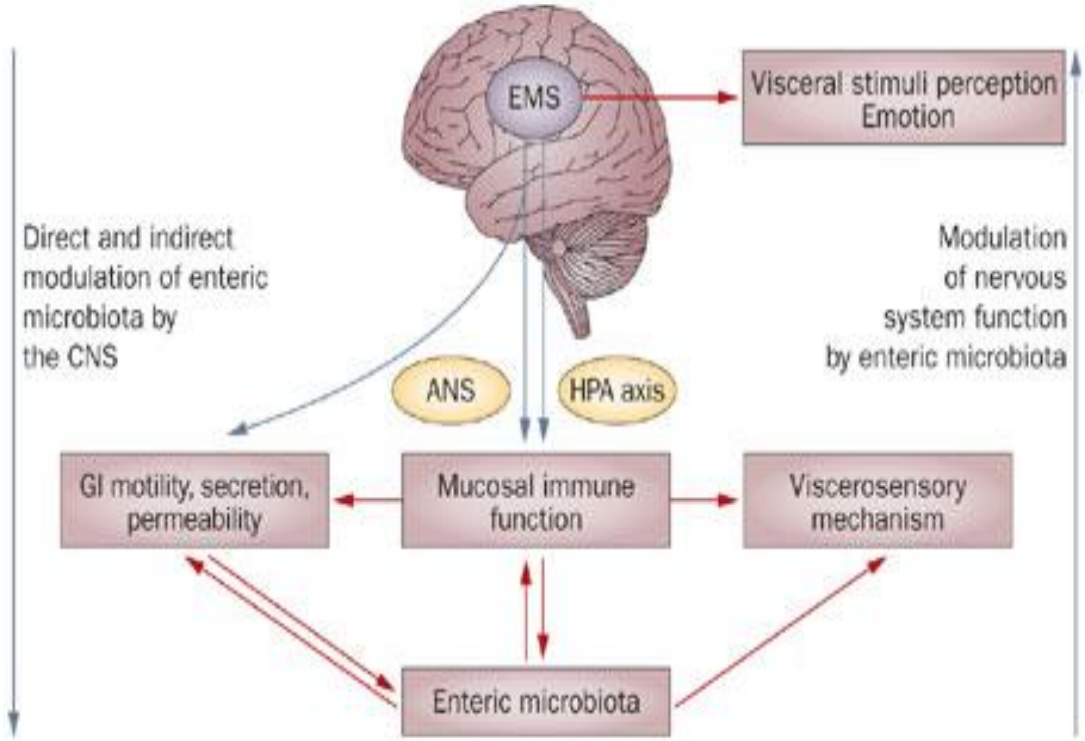
- Extrinsic plexus modulates the intrinsic plexus






Keefer and Kane, 2017;
Martin et al, 2018

# Brain-Gut-Microbiota Axis Mechanisms



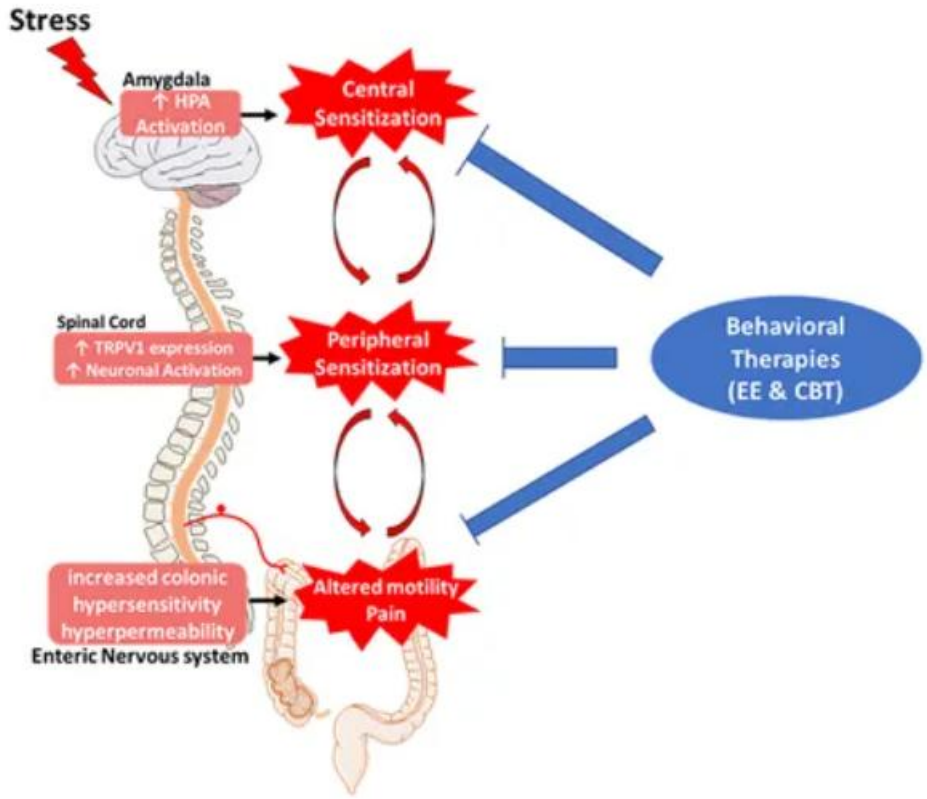

- Neuroanatomical pathways such as vagus nerve (VN) or spinal cord
- Neuroendocrine system such as the hypothalamic-pituitary-adrenal axis (HPA axis)
- Immune links mediated by cytokines
- Direct or indirect chemical pathways that may involve microbial metabolites and some specific neurotransmitters
- ***Stress changes intestinal permeability***



Keefer and Kane, 2017

# Brain-Gut-Microbiome in Psychiatric Disorders in GI Disease

Figure 1




- Dysregulation of the brain gut axis
- Stress → HPA axis activation, in turn causing CNS and ENS afferent sensitization, with increased pain and changes in motility

Orack, 2021

# Case

- A 29 y/o woman with a medical history notable for migraines, functional dyspepsia and episodic use of cannabis is admitted to the hospital for intractable vomiting. She reports she is unable to tolerate PO content. She has not recently used cannabis. She explains that she experiences intermittent episodes of vomiting which last 5 days at a time. She is insisting the medical team prescribe Ativan which they do not wish to prescribe. They consult you for help in managing her case.

# Disorders of Gut Brain Interaction (DGBI): IBS

- Recurrent abdominal pain, altered bowel habits and often bloating

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

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

- Symptom duration 3 months, symptom onset at least 6 months prior to diagnosis

# IBS and Psychiatric Disorders

- **MDD:** Prevalence 27-47% - 3x higher rate, severe GI sx, risk factor for IBS, low energy, difficulty sleeping, headaches, back and joint pain
- **GAD:** Prevalence 32% -anticipatory worries, avoidance, rumination about GI sx
- **PTSD:** 36% - close association with physical and sexual trauma; increased risk among female veterans
- **Panic d/o:** 44% - symptoms of nausea, diarrhea and abdominal discomfort

# Treatment Approach: TIC

# Treatment

- Integrated approach: Team communication
- Psychotropic approach:

→Visceral hypersensitivity: TCAs, SNRIs

→Nausea/appetite/satiety: Mirtazipine

→Bloating/epigastric discomfort: Buspar, Venlafaxine

→Motility/bloating: SSRIs – Citalopram, Paroxetine

→Refractory symptoms: Quetiapine, Olanzapine

- CBT

# IBS-D vs IBS-C

| Drug Name | Symptoms Targeted | Type of IBS |
|---|---|---|
| Amitriptyline/Nortriptyline | Pain/Loose Stools/Incomplete Defecation | IBS-D |
| Duloxetine/Venlafaxine | Pain/Loose Stools/Mood | IBS-D |
| Escitalopram/Citalopram/ Fluoxetine/Sertraline | Bloating/Pain/ Frequency/Mood | IBS-C |
| | | |

# DGBI:
# Functional Dyspepsia

1. *One or more* of the following:
    1. Bothersome postprandial fullness
    2. Bothersome early satiation
    3. Bothersome epigastric pain
    4. Bothersome epigastric burning

    AND

2. No evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms

- Symptoms symptom duration 3 months, symptom onset 6 months

# Functional Dyspepsia and Psychiatric Disorders

- Significant association with both **anxiety** (26%) and **depressive disorder** (34%), particularly in tx refractory patients (65%)
- High incidence of physical and sexual **trauma** (one study reported at high as 67%)
- Emotional distress in FD related to inability to achieve adequate food and drink intake

# Assessment and Treatment

- Assess target symptoms for psychotropic usage:
  - -Appetite changes
  - -Weight fluctuation
  - -Nausea/vomiting
  - -Pain
  - -Insomnia
- Literature focus on TCAs, some reports on Mirtazipine
- CBT

# DGBI: CVS

1. Stereotypical episodes of vomiting regarding onset (*acute*) and duration (*less than 1 week*)
2. At least three discrete episodes in the prior year and two episodes in the past 6 months, occurring at least 1 week apart
3. Absence of vomiting between episodes, but other milder symptoms can be present between cycles

- Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

# Cycle of CVS

- **Inter-episodic phase:** Symptom free
- **Pre-emesis phase:** Approach of an episode, nausea varies, can still retain PO meds
- **Emetic phase:** Intense, persistent nausea, vomiting and other symptoms
- **Recovery period:** Hunger, tolerance of oral intake and vigor return to normal

# CVS versus CHES

| Cyclical Vomiting Syndrome | Cannabinoid Hyperemesis Syndrome |
|---|---|
| Intractable vomiting with periods of being well relieved by hot showers | Intractable vomiting with periods of being well relieved by hot showers |
| No clear pattern of relationship | Prolonged, excessive use of cannabis with symptoms < 24 hours of last use |
| No clear pattern of relationship though use of cannabis can also provide relief | Complete and sustained cessation produces remission though use of cannabis can also provide relief |
| Rapid gastric emptying | Delayed gastric emptying |
| Family history of migraines | Variable history |
| Odansetron (Zofran) can help | Hallmark of odansetron not helping |

* Cannabis withdrawal symptoms – like CHES, relief with cannabis usage, but symptoms typically begin >24 hours (1-10 days) after last use and no relief with hot showers

# Assessment and Treatment


- Lorazepam/Antiemetics/ Triptans abortive
- *Strong:* TCAs (Amitryptiline) 100mg dosage in 10mg increments po QHS can produce remission
- *Conditional:* Topomax 50mg BID in 25mg increments
- Sleep and stress management (meditation/biofeedback, healthy diet)

# Case

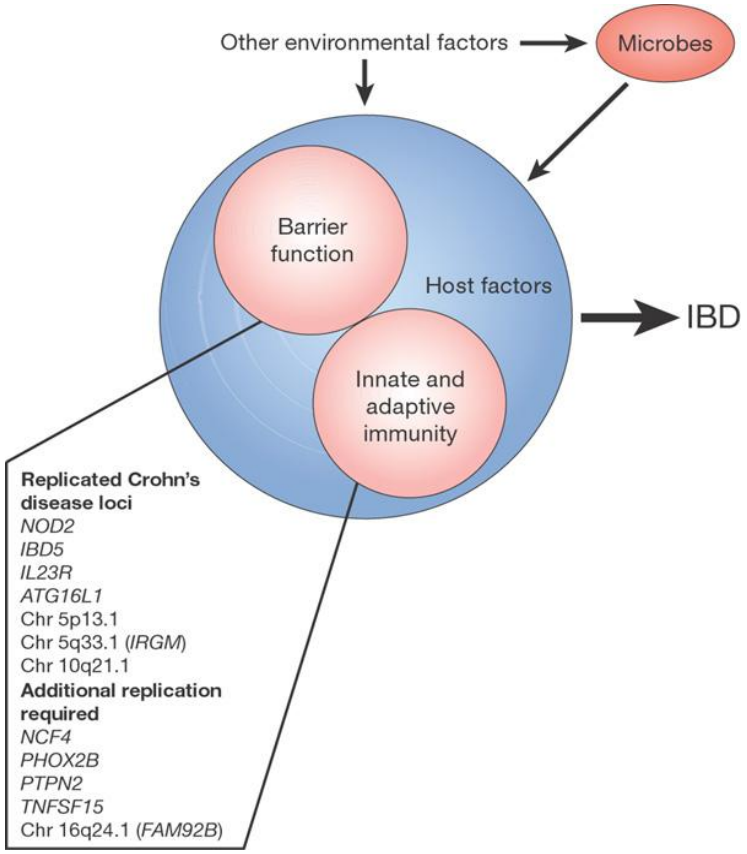
- 42 y/old woman with ileocolonic Crohn's first dx 19 years ago. Has had multiple resection surgeries (ileo-cecal, mid-jejunum, ileal) with 80 cm of small bowel remaining. Current ostomy.
- As many as 10 hospitalizations per year for fatigue, abdominal pain and diarrhea – usually placed on fluids and TPN. Dysmenorrhea correlates with Crohn's flares. **She's been hospitalized again, and you get called to address her existing depression and consult on how to decrease future ED visits.**
- Prior trials of Ustekinumab (Stelara) and Natalizumab (Tysabri). Psychiatric history of depression, anxiety and PTSD due to childhood emotional and sexual abuse. On Valium, Mirtazipine, Celexa, and Trazodone.
- Family history of Crohn's and Hodgkins. Married to a policeman with 2 children; supportive family. Got her GED and completed nursing school; on SSDI for past 5 years.
- Complains of sx of gastroparesis, pain, anxiety, insomnia and tends to catastrophize. Smokes 0.5 ppd.

# Inflammatory bowel disease

- 3.1 million Americans
- Peak onset 15 to 30 years
- Interaction of genetic and nongenetic factors –

  -Twin studies indicate 5-fold risk with one relative

  -Diet, antibiotic usage, intestinal colonization have a role




Abraham and Cho, 2009; Xavier and Podolsky, 2007; Korzenik and Podolsky, 2006

# IBS vs IBD

## IBS

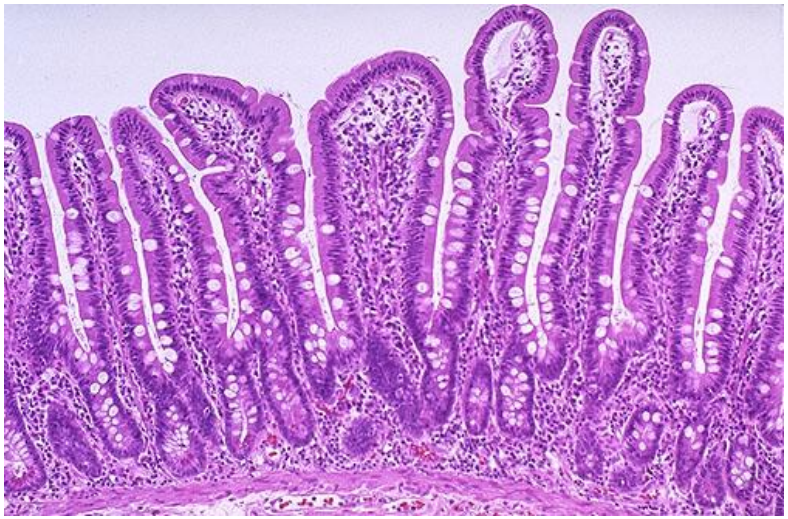
- Functional
- Syndrome
- No inflammation
- No permanent harm to intestines
- Higher current, lifetime mood d/o prevalence

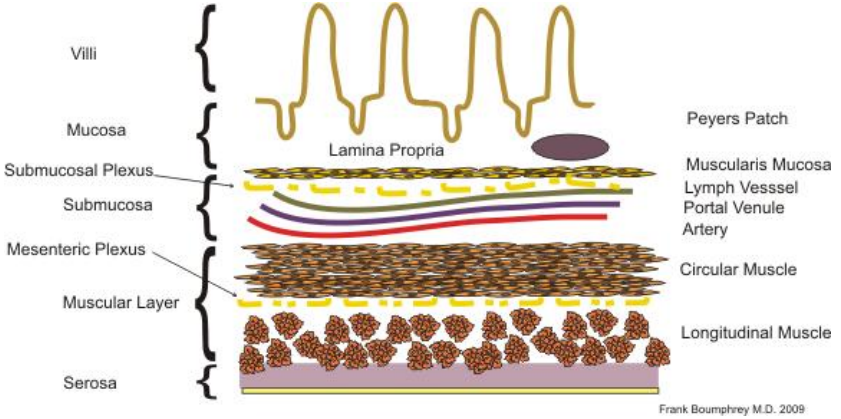
## IBD

- Structural
- Genetic ←→ environment
- Disease
- Inflammation on scope
- Intestinal bleeds, elevated colon cancer risks

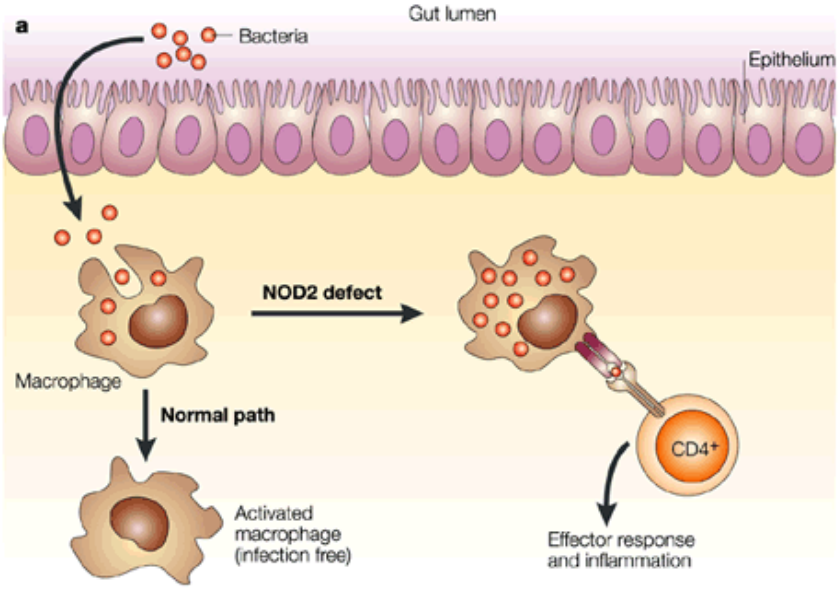
# Inflammatory Response

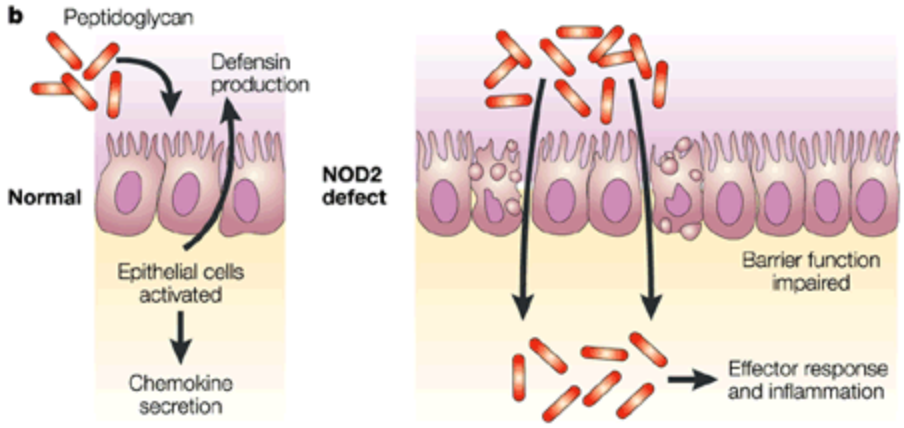
- Hallmark of active IBD is activation of innate immune cells (neutrophils, macrophages, natural killer T cells) and adaptive immune cells (B and T cells) in the intestinal mucosa
- Activation of these cells activate inflammatory markers like TNF-a, interleukin 1-B, interferon-y and cytokines of the interleukin-23-Th17 pathway





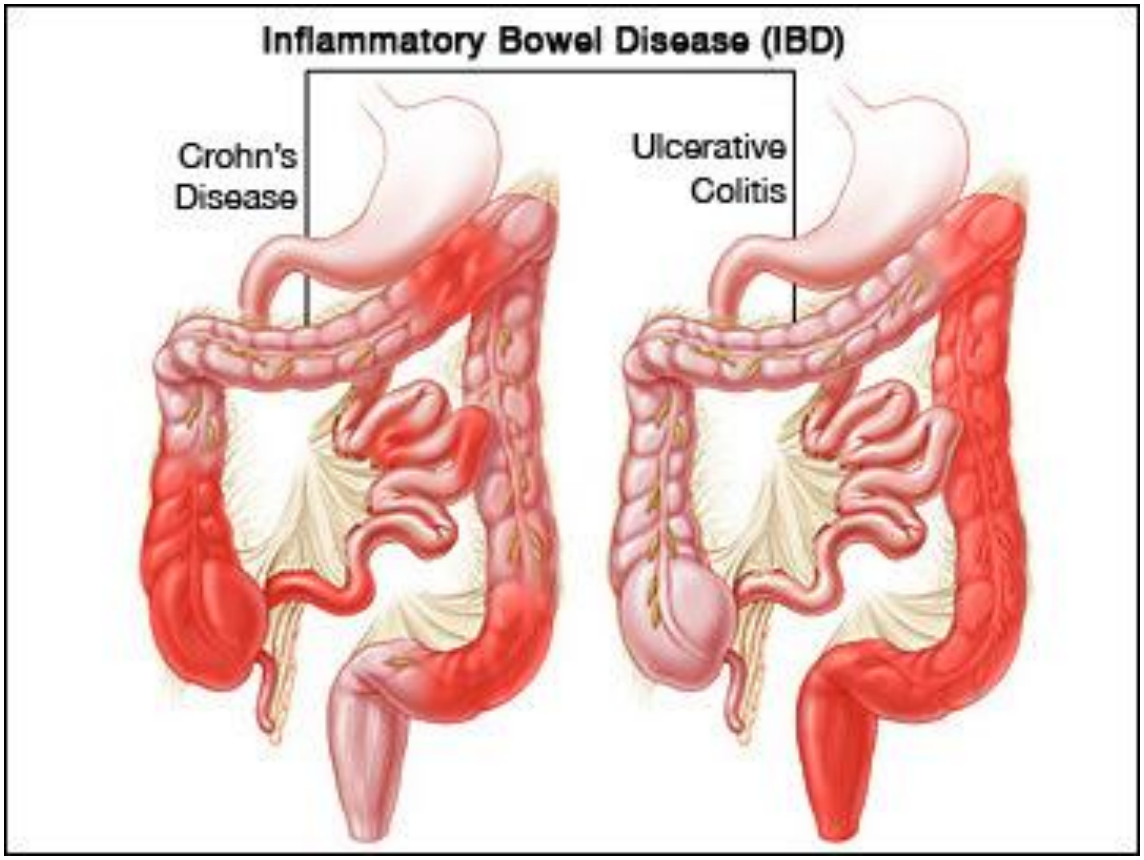
# IBD pathophysiology




Abraham and Cho, 2009; Xavier and Podolsky, 2007; Korzenik and Podolsky, 2006

# Crohn’s vs Ulcerative Colitis




Abraham and Cho, 2009; Xavier and Podolsky, 2007; Korzenik and Podolsky, 2006

# Treatment

- Monoclonal antibodies against TNF-a and interleukin-23
- Infliximab (Remicade), Vedolizumab (Entyvio), Nataluzimab (Tysabri), Adalimubab (Humira)
- Aminosalicylates, corticosteroids, antibiotics reduce inflammation and promote mucosal healing

# Mood Disorders in IBD

- Depression and/or anxiety

-30-35% in remission

-80% during relapse

- IBD patients twice as likely to experience depressive disorder compared to general population
- Risk factors

-Severe and active disease

-Corticosteroid usage

# Mood Disorders in IBD

**Depression**

- More frequent IBD relapse
- Earlier IBD relapse
- Increased disease activity
- Interference with remission from Infliximab
- Reduced med adherence in geriatric patients

# IBD ←→ Depression

# The bi-directional association between IBD and depression

## Risk of New-Onset Depression by IBD status

| Group | Adjusted OR for Depression[a] |
|---|---|
| IBD patients | 9.43 (95% CI, 6.43–13.81; *P* <.001) |
| Unaffected siblings | 1.82 (95% CI, 1.14–2.91; *P* =.013) |
| Control group | Reference |

OR, odds ratio; IBD, inflammatory bowel disease

[a]Adjusted for age, sex, monthly income, urbanization, Charlson comorbidity index, medical comorbidities, and all-cause clinical visits.

- Patients with depression were also at risk for IBD development

  25,552 patients with depression, 26,147 unaffected siblings, and 104, 588 healthy controls without depression.
- The adjusted odds ratio for IBD among patients with depression and their unaffected siblings were 1.87 (95% CI, 1.07–3.26; *P* =.028) and 1.69 (95% CI, 1.05–2.69; P = 0.029), respectively

# Controversies on Depression in IBD

- *Relapse or Remission?*
- *Crohns vs Colitis?*
- *Frequency higher than other medical illnesses?*
- *Before or after IBD dx?*

- Subset of patients with IBS-like sx have higher rates of depression during remission
- Higher rate of lifetime psychiatric illness in CD pts due to more severe somatic sx
- Frequency equal to other medical conditions (e.g. ~30%)
- Increasing evidence of a bidirectional relationship between depression and IBD

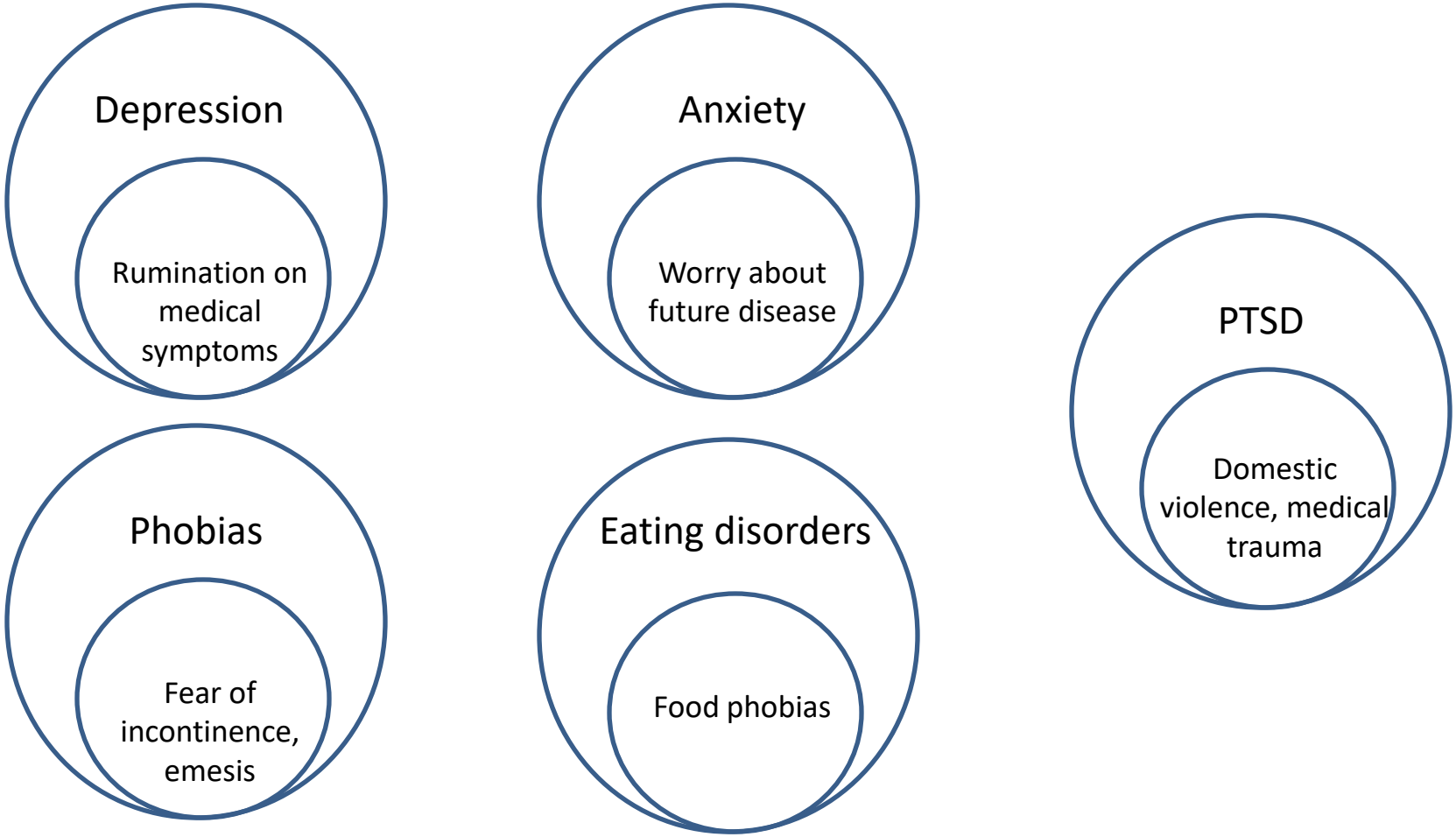
# Depressive Subtypes

- 75%:  Mild depression, with prominent symptoms being fatigue, irritability, and depressed feelings
- 20%: Somatic depression, with prominent features including anhedonia, change in appetite, fatigue, physical complaints, irritability, and depressed feelings
- 5%:  Cognitive despair, morbid and suicidal ideation, weeping, hopelessness, fatigue, and feelings of sadness



Szigethy et al, 2014

# Clinical Presentation



# Other Pathologies

- PTSD (32%)
- Specific phobia
- Panic Disorder (8%)
- Social Anxiety Disorders (6%)
- Personality Types
- Substance Use Disorders

# Treatment Approach

- Interview (IBS, visceral hypersensitivity, insomnia, fatigue, cognitive dysfunction)
- Psychoeducation
- Objective disease disproportionate to sx
- Treatment options (pharm and/or therapy)
- Malnutrition, anemia, vitamin def
- Smoking cessation

# Psychopharmacology

- Differences in side effects guide choices
- E.g. Zoloft, Venlafaxine vs Paroxetine
- Bupropion in case studies
- SSRIs and GI bleeds
- Clonidine
- TCAs
- Psychotherapy

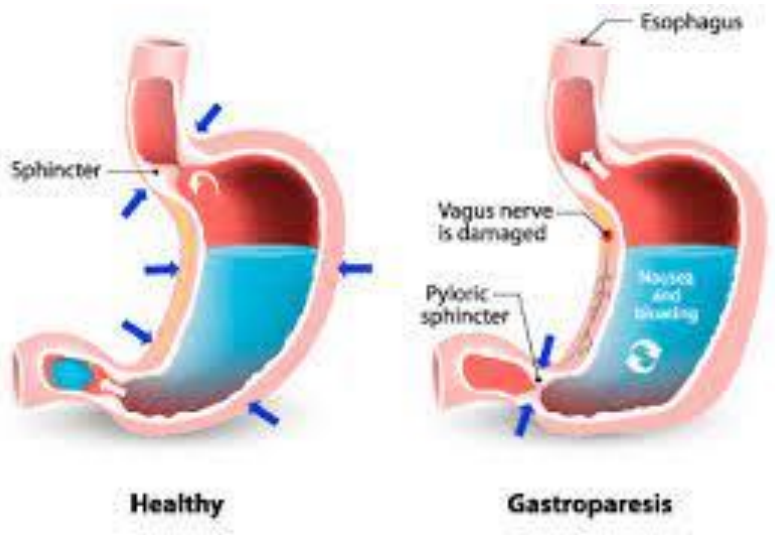
# Psychopharmacology: Microscopic Colitis

- Collagenous vs lymphocytic
- Zoloft and Clozapine (higher risk)
- Duloxetine and Paroxetine (intermediate risk)
- Lexapro (lower risk)

Lucendo, 2017

# Psychopharmacology: Gastroparesis

- Partial paralysis of the stomach
- Nausea, early satiety, reduced appetite
- Buspar, Mirtazipine

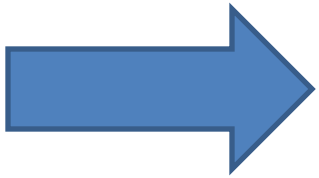


# Psychopharmacology: Fatigue

- Physical, cognitive behavioral fatigue
- Sleep, mood, anemia, nutritional deficiencies, inflammation
- Acupuncture, CBT, biologics, Modafinil

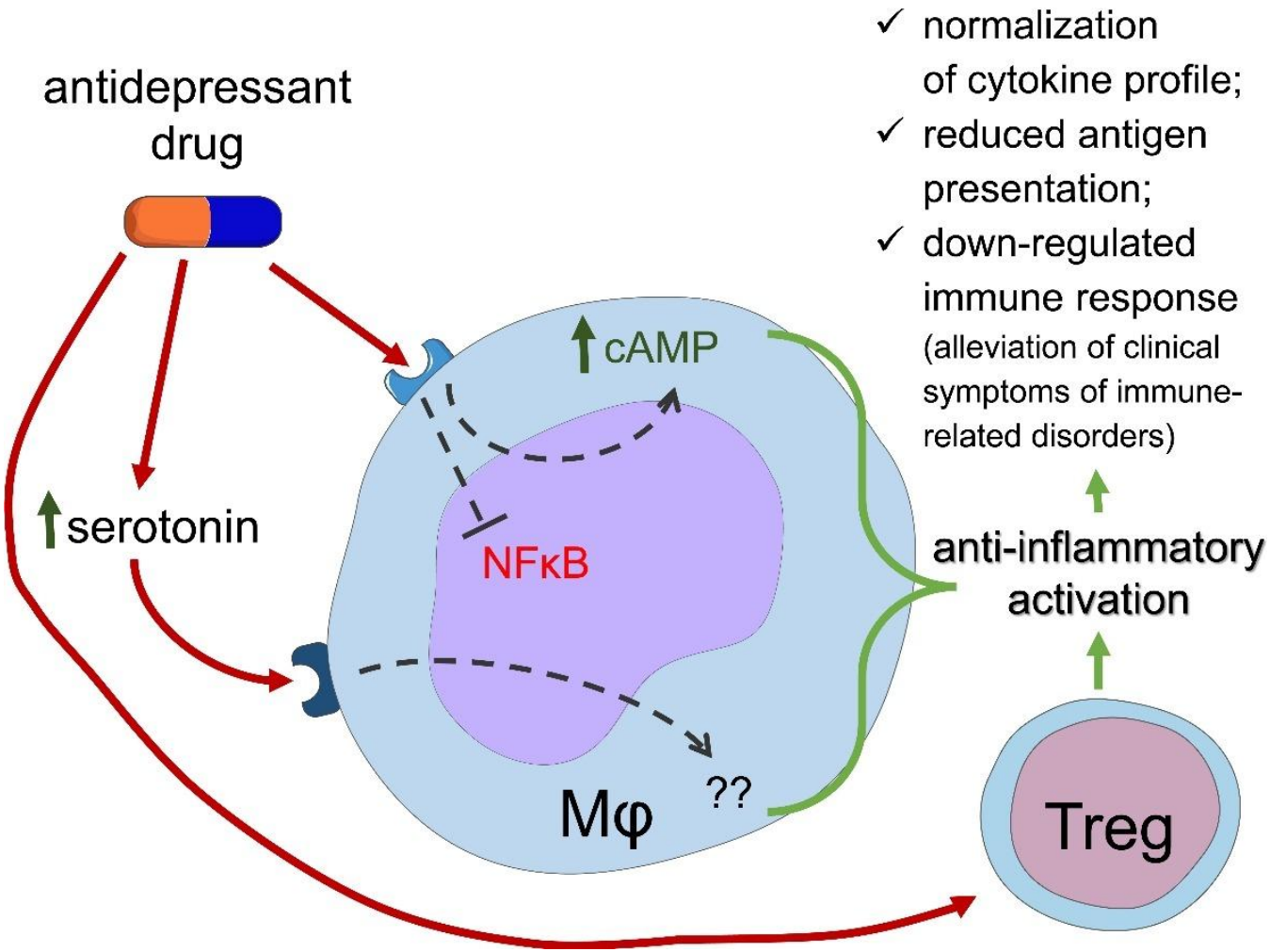
# Psychiatric Treatment

Antidepressants
(SSRIs, SNRIs,
TCAs, Mirtazipine)



- Psychiatric diagnoses
- Inflammation
- Appetite
- Weight
- Pain
- Nausea
- Insomnia
- Fatigue
- Cognitive dysfunction
- IBS overlay

# Psychiatric Treatment



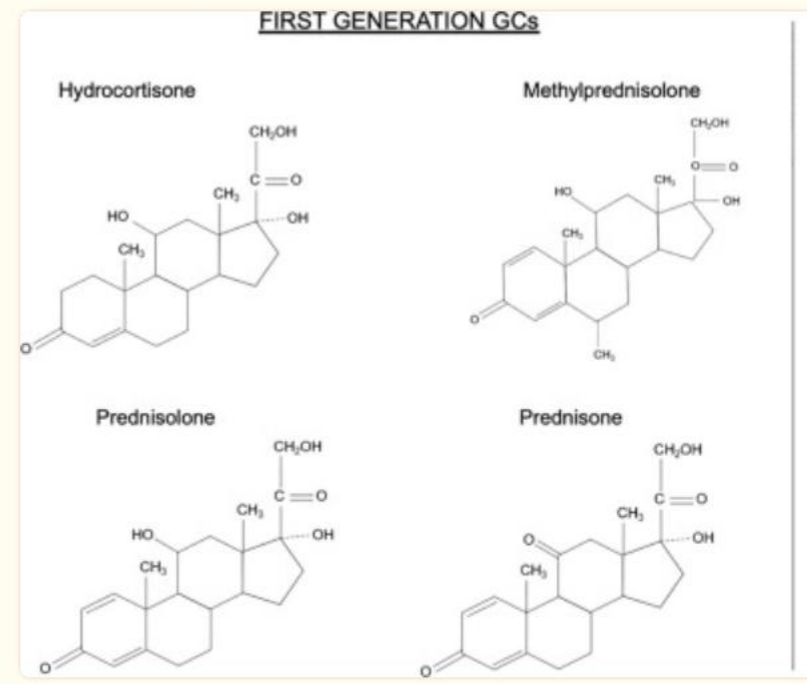

Nazimek et al, 2017

# Adverse Effects of Glucocorticoids

- Possible neuropsychiatric effects include:
  - -Anxiety, depression
  - -Insomnia
  - -Mania, hypomania
  - -Psychosis
  - -Cognitive decline
- Dose dependent onset:
  - -Risk of development minimal (1.3%): < 40 mg
  - -Risk of development high (18.4%): > 80mg

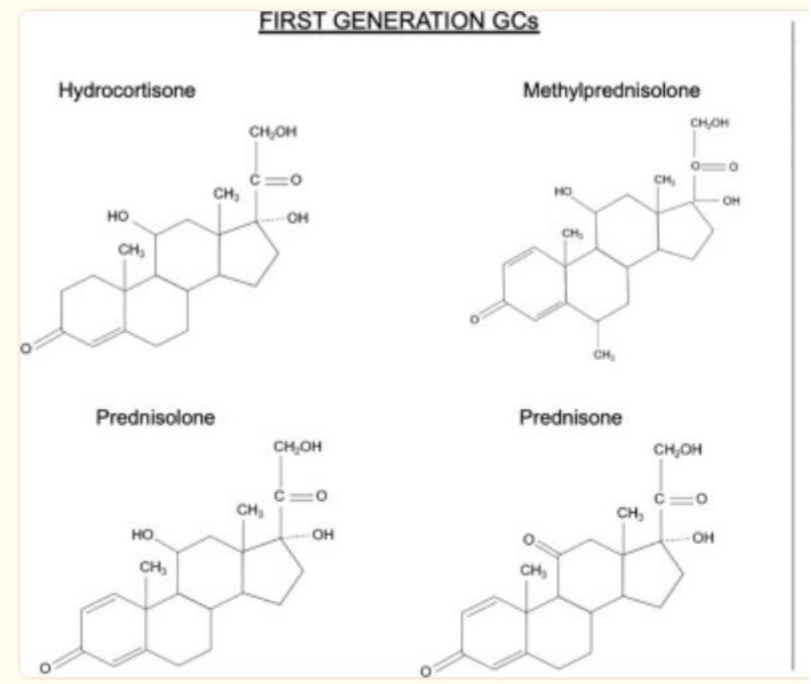
# Adverse Effects of Glucocorticoids

- Cohort of 53 patients monitored with BDI
- 49% of IBD patients (26/53) prescribed a high dose of 40mg prednisone for 2 weeks or more experienced mood changes
- 25/26 cases experienced mania
- Symptoms included irritability, inability to focus and poor sleep quality, impulsivity, rapid thought process, over-activity, feeling “sped up” inside or restlessness



# Adverse Effects of Glucocorticoids

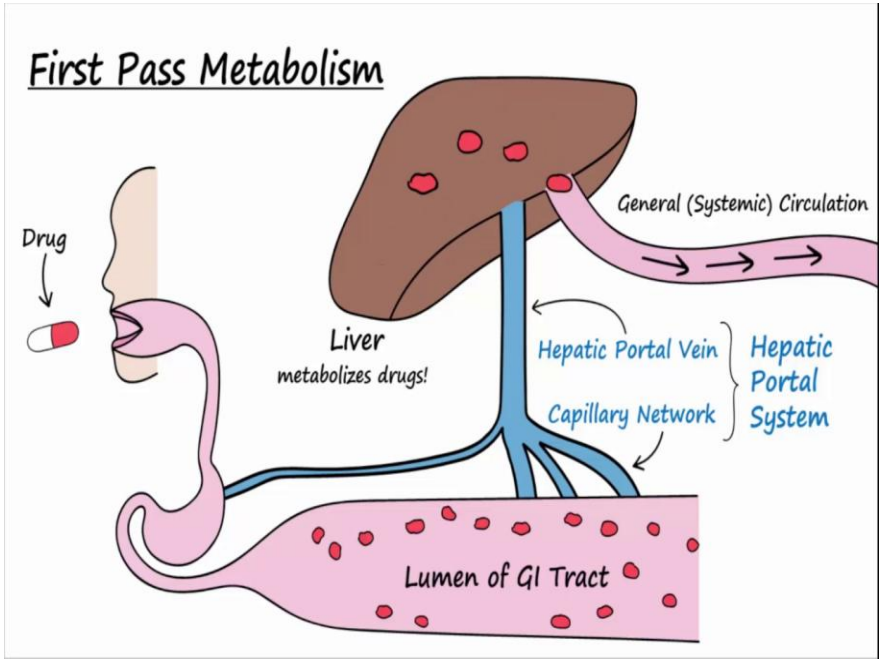
- Onset 2-3 weeks after beginning prednisone
- Younger age and female gender associated with neuropsychiatric effects
- IBD diagnosis, presence of psychiatric condition, type of maintenance therapy, initial disease activity score, duration of prednisone before mood reassessment, and positive response to treatment not associated
- Tapering prednisone reduced symptoms without further psychiatric intervention



# IBD medications and mental health

**Corticosteroids**

- 2nd generation corticosteroids (Budesonide)
  - high efficacy,
  - fewer adverse events




**Biological agents**

- Not associated with increased risk of anxiety, depression, psychiatric illness



Bruscoli et al, 2021; Mawdsley and Rampton, 2005

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