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# **The Effects of Common Prescription Medications on the GI System: Counseling Patients on Drug-Induced Nutrient Depletion (DIND) and Drug-Induced Microbiome Disruption (DIMD)**

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# Disclosures

- Dani Williamson is a paid consultant/speaker for Metagenics

# Objectives

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Review role of the gut and GI microbiome

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Identify common medications that cause Drug-Induced Microbiome Disruption (DIMD)

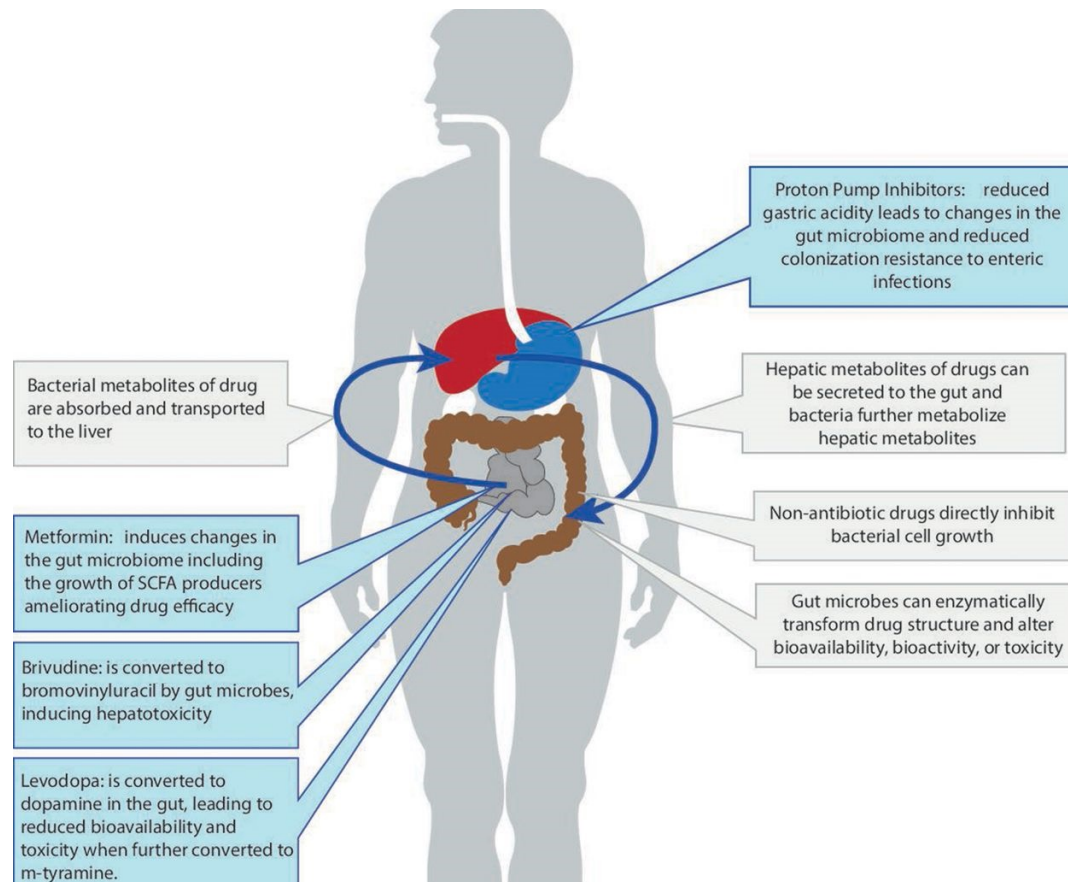
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Successful approaches to counsel patients with DIMD

# Role of the Gut and the Microbiome

- Nutrient metabolism
- Xenobiotic and drug metabolism
- Structural integrity of gut mucosal barrier
- Immunomodulation
- Protection against pathogens

# Schematic overview of different interactions between the gut microbiome and commonly used non-antibiotic drugs



- Hepatic metabolites of drugs can be secreted into the gut and bacteria further metabolize hepatic metabolites
- Non-antibiotic drugs directly inhibit bacterial cell growth
- Gut microbes can enzymatically transform drug structure and alter bioavailability, bioactivity or toxicity
- Bacterial metabolites are absorbed and transported to the liver

Weersma RK, Zhernakova A, Fu J Interaction between drugs and the gut microbiome *Gut* 2020;**69**:1510-1519.

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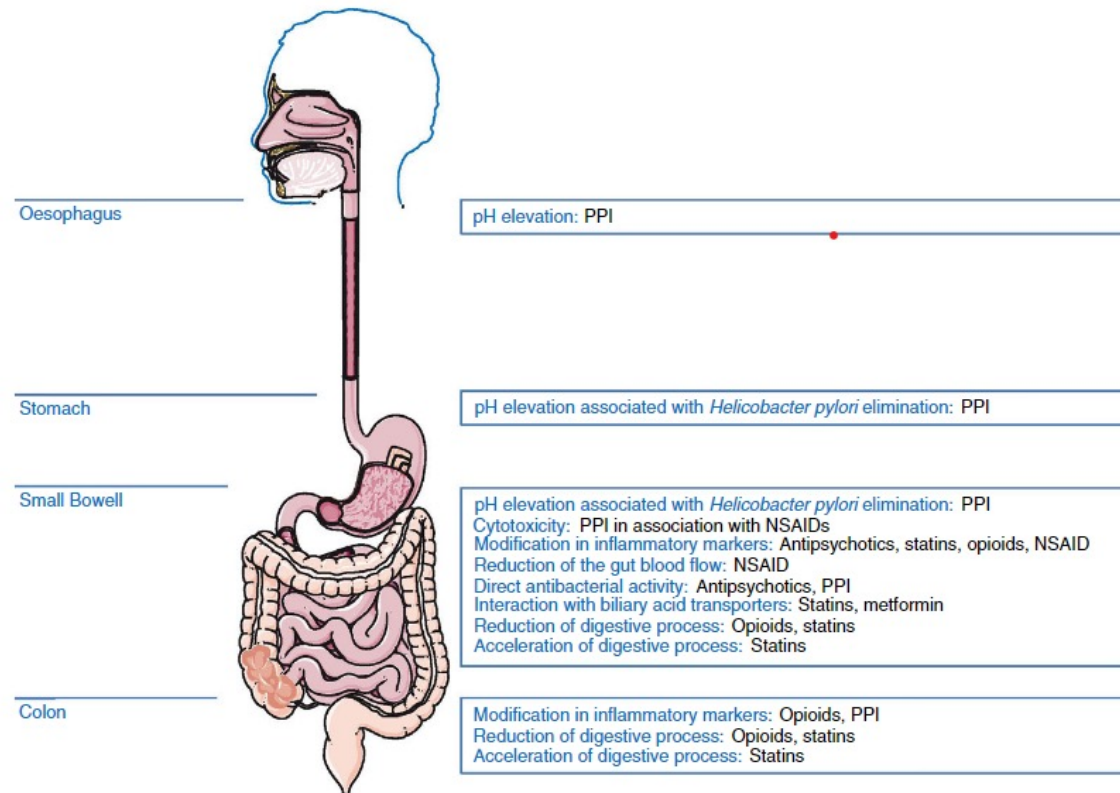
# Systematic review: human gut dysbiosis induced by non-antibiotic prescription medications

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# Proposed Mechanisms of DIMD



**FIGURE 2** Proposed mechanisms by which drugs influence the gut microbiome

# Common Drugs and their DIMD MOA

**Table 2.** Proposed mechanisms of gut microbiome alterations induced by prescription drugs

	Proposed mechanisms	References
PPI	Acid suppression in the proximal duodenum associated with ph-independent mechanisms	Freedberg et al <sup>89</sup>
Metformin	Alteration of the enterohepatic recirculation of bile acids involving modulation of gut microbiome	Napolitano et al <sup>108</sup>
NSAID	Alteration of function of small intestine, likely depending on the particular type of nsaid ingested	Rogers and Aronoff <sup>47</sup>
Opioids	Modulation of the host immune system, causing microbiome alteration	Meng et al <sup>50</sup>
Statins	Interaction with bile acids and impact upon expression of inflammatory markers known to influence microbial community structure	Nolan et al <sup>115</sup>
Antipsychotics	Directly affects the growth of organisms within the gut	Davey et al <sup>83</sup>  Morgan et al <sup>85</sup>



# Antibiotics Role in DIMD

- Antibiotics decrease microbial diversity in the gut
  - Microbial diversity is a hallmark of a healthy microbiome
- Antibiotics increase LPS (lipopolysaccharide) exposure
  - LPS is one of the most potent immune triggers
- Antibiotics decrease butyrate production
  - Butyrate is highly anti-inflammatory

Angevelde P, et al. Antibiotic-Induced Lipopolysaccharide (LPS) Release from Salmonella typhi: Delay between Killing by Ceftazidime and Imipenem and Release of LPS. Antimicrob Agents Chemother. 1998;42(2):739-743

Canani RB, et al. Potential beneficial effects of butyrate in intestinal and extraintestinal diseases. World J Gastroenterol. 2011;17(12):1519-28.

# Antibiotics

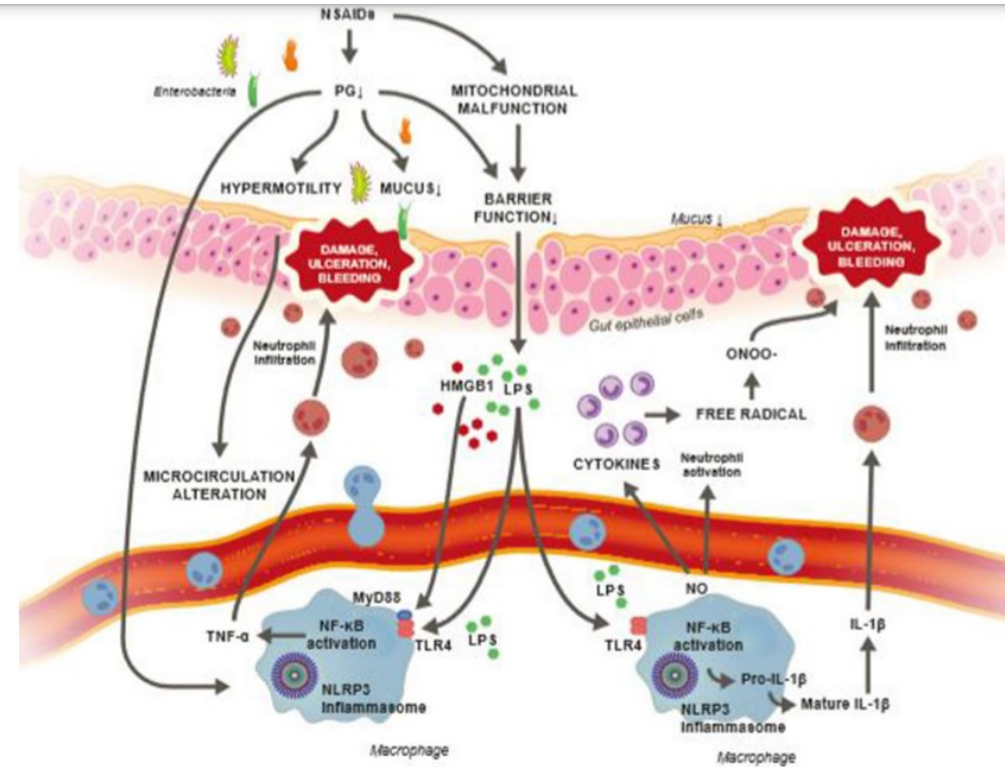
- Common Drugs: All antibiotics
- Nutrients Depleted: B vitamins, calcium, magnesium, iron, beneficial bacteria, zinc, vitamin K
- Potential Side Effects of Depletion: Dysbiosis (gas, bloating, decreased digestion and absorption of nutrients), candida, fatigue, weight gain, elevated homocysteine, C. diff
- Counseling Pearls: Broad spectrum probiotic, Timing of administration of probiotic, Duration of probiotic supplementation, Alternatives to probiotics

# Probiotic Considerations During/After Antibiotics

- In order to reestablish microbiome balance, mitigate risk of infections during use, and create a healthy environment for immune function:
  - Prioritizing a multi-strain probiotic, featuring a spectrum of the phylogenetic tree
  - Probiotic supplementation 1 hour before or 2 hours after antibiotic use
    - Consider probiotics containing *S. Boulardii* during antibiotic usage
  - Probiotic supplementation until course complete

# NSAIDs Role in DIMD

- NSAIDS negatively impact microbial diversity in the gut
- Diversity is a hallmark of health



**Fig. 1** Mechanism underlying the pathophysiology of NSAID-induced intestinal damage. *PG* prostaglandins, *HO-1* heme oxygenase-1, *ONOO-* peroxynitrite, *NO* nitric oxide, *iNOS* inducible nitric oxide synthase, *NF- $\kappa$ B*

nuclear factor- $\kappa$ B, *NLRP3* pyrin domain-containing 3, *TLR4* Toll-like receptor 4, *LPS* lipopolysaccharide, *TNF $\alpha$*  tumor necrosis factor  $\alpha$ , *IL-1 $\beta$*  interleukin-1 $\beta$

# NSAIDs

- Common Drugs: Ibuprofen, naproxen, ketoprofen, meloxicam
- Nutrients Depleted: Vitamin C, folic acid, iron, B5, calcium
- Potential Side Effects: High homocysteine, anemia, diarrhea, mouth sores, cardiovascular disease, increased risk of Crohn's, heartburn/GERD, ulcers/bleeding
- Counseling Pearls: Address inflammation at the root (diet), Alternatives to NSAIDs (turmeric, CBD, fish oil, SPMs, MVI, SBIs)

# Nutrient Alternatives to NSAIDs

- CBD oil – every cell in the body has an endocannabinoid receptor (except the brainstem) when your endocannabinoid system is out of balance, contributes to pain, CBD works as a systemic anti-inflammatory blocking pain receptors
- Fish oil – omega 3 fatty acids like the ones found in fish, are anti-inflammatory. Fish oils contain specialized pro resolving mediators (SPMs for short), which block the pain receptors and resolve the inflammatory response. Decades of research from Harvard backs this up. We make them naturally but patients with chronic pain have lower levels.

# Nutrient Alternatives to NSAIDs

- Multivitamin – full spectrum multivitamin will help decrease inflammation and also help offset the other nutrient depletions caused by their NSAIDs as well as other meds the patient may be on. A good multivitamin is a good insurance policy for every single patient
- Turmeric – MOA by which curcumin shows anti-inflammatory effect is by attenuating inflammatory response of TNF- $\alpha$  stimulated human endothelial cells by interfering with NF- $\kappa$ B
  - Inhibits COX-1 and COX-2

# Considerations for NSAID Damage Repair

- Probiotics- may help in preserving the functionality of the enteral mucosa in patients treated with NSAIDs. *Bifidobacterium breve*, *Lactobacillus gasseri*, *Lactobacillus plantarum* are a few of the strains that have been shown to decrease NSAID induced enteropathy.



# Considerations for NSAID Damage Repair

- Serum Derived Immunoglobulins(SBI)- Immunoglobulins bind microbes and toxins in the GI tract and eliminate them prior to immune system activation. Building a stronger barrier to the external environment.
- Diet – Anti-inflammatory

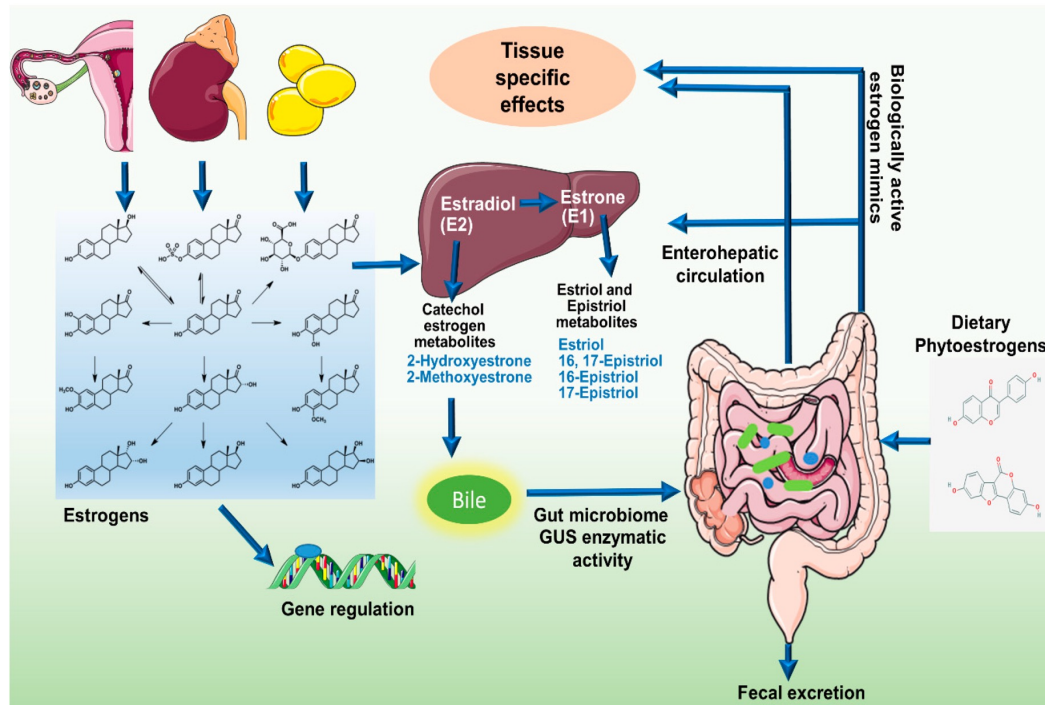
# Corticosteroids

- Common Drugs: methylprednisolone, prednisone, dexamethasone
- Nutrient Depletion: calcium, vitamin D, magnesium, zinc, vitamin C, B6, B12, folic acid, selenium, chromium
- Potential Side Effects: gastritis, peptic ulcer disease, abdominal distention, dyspepsia, elevated blood sugar, weight gain, osteoporosis
- Counseling Pearls: Anti-inflammatory alternatives (diet, turmeric, fish oil, capsaicin, vitamin D)

# Oral Contraceptives/ Hormone Replacement Therapy

- Common Drugs: All estrogen-containing hormone drugs used for contraception and menopause (Yaz, Ortho Tri-Cyclen, FemHRT, Premarin)
- Nutrient Depletion: beneficial flora, magnesium, zinc, most minerals, B vitamins, vitamin C
- Potential Side Effects: heart disease, fatigue, candida, irritable bowel syndrome, lowered immunity, depression, sexual dysfunction, anemia, infertility
- Counseling Pearls: Supplement what's being depleted (MVI, magnesium, probiotics), Get to root of hormonal imbalances (if not being used as contraception)

# Estrogen and the Gut



Schematic representation of modulation of estrogens and its metabolites in circulation by the estrobolome. The C-18 steroid hormones, Estrogens (E1, E2, and E3) circulate in the blood stream either in free or protein bound form exerting diverse biological effects. Hepatic metabolism of parent estrogens E2 and E1 irreversibly hydroxylates the C2, C4, or C16 positions of the steroid ring producing estrogen metabolites with varying hormone potency, bioavailability, and half-life. Estrogens and their metabolites are then conjugated in the liver through glucuronidation and sulfonation to allow biliary excretion. While most of the conjugated estrogens are excreted in urine or feces, a significant proportion is reabsorbed into the circulation. Gut bacteria possessing  $\beta$ -glucuronidase activity can deconjugate the conjugated estrogens leading to reabsorption into the circulation. In addition, enteric microbes synthesize estrogen-like compounds or estrogen mimics from dietary sources.

# Oral Contraceptives

- Estrogens alter the microbiome diversity.
- Estrogens alter intestinal permeability.

Chen KLA, et al. Long-Term Administration of Conjugated Estrogen and Bazedoxifene Decreased Murine Fecal  $\beta$ -Glucuronidase Activity Without Impacting Overall Microbiome Community. *Sci Reports*. 2018;8(1):8166.

Rhodes JM, Cockel R, Allan RN, Hawker PC, Dawson J, Elias E. Colonic Crohn's disease and use of oral contraception. *Br Med J (Clin Res Ed)* 1984;288(6417):595–6.

Khalili H, Higuchi LM, Ananthakrishnan AN, Richter JM, Feskanich D, Fuchs CS, et al. Oral contraceptives, reproductive factors and risk of inflammatory bowel disease. *Gut*. 2013;62(8):1153–9

# Considerations During Treatment with Oral Contraceptives/HRT

- Magnesium
  - Essential nutrient for individuals on hormone therapy due to its involvement with normal blood clotting activity
  - Study showed that females taking oral contraceptives (OC) had significantly lower serum magnesium levels than control group, possibly increasing risk of thromboembolic event
  - Another study showed relationship between magnesium and estrogen
    - Higher estrogen levels may alter normal blood mineral levels leading to increased risk of thrombosis
- Vitamin C
  - OC decrease vitamin C concentration in platelets and blood plasma, decreasing bioavailable vitamin C

# Considerations During Treatment with Oral Contraceptives/HRT









- B vitamins
  - Literature indicates birth control pills alter levels of B vitamins in the body
- Coenzyme Q10 (CoQ10)
  - 2006 study examined blood samples from 15 women using OC for at least 6 months had significantly lower serum levels of CoQ10 possibly impacting future antioxidant status in women on OC
- Zn/Cu Balance
  - OC users typically have elevated levels of copper which is highly reactive and may lead to oxidative damage
  - Study of 24 women taking OC compared Zn and Cu levels vs. control group and Zn levels were significantly lower in OC group and Cu levels were significantly higher

# Testing Considerations

- Serum lab testing for inflammation and microbiome health:
  - Homocysteine, hsCRP, vitamin D, omega 3/inflammation, LPS, Zonulin, Histamine and DAO
- Testing for microbiome health
  - Stool analysis
    - Calprotectin, Candida, Dysbiosis, *H.Pylori*, Vegetable fibers etc



# Diet and Lifestyle

	Mediterranean	Traditional Diet (Weston A. Price)	Paleo	Specific Carbohydrate Diet	Ketogenic Diet	Autoimmune Protocol
 Pastured Meat	✓ • Specifically lean meat	✓ • Emphasis is placed on organic, pastured meat • Organ meats encouraged for adequate fat soluble vitamins and minerals	✓ • Emphasis is placed on organic, pastured meat • Organ meats encouraged for adequate fat soluble vitamins and minerals	✓	✓ • Moderate meat consumption as to avoid gluconeogenesis	✓ • Emphasis is placed on organic, pastured meat • Organ meats encouraged for adequate fat soluble vitamins and minerals
 Vegetables	✓	✓ • Fermented vegetables included for probiotic content	✓ • Fermented vegetables included for probiotic content	✓ • Fermented vegetables included for probiotic content • Starches, tubers, and mucilaginous vegetables are avoided	✓ • Low carbohydrate varieties are allowed	✓ • Fermented vegetables included for probiotic content • Nightshades are excluded due to saponin content
 Fruits	✓	✓	✓	✓	✓ • Only low carbohydrate varieties are allowed	✓
 Nuts & Seeds	✓	✓ • Nuts and seeds are permitted as long as they have been soaked or sprouted	✓	✓	✓	✗
 Unrefined Grains	✓	✓ • All grains are acceptable as long as they have been soaked, sprouted, or fermented	✗	✗	✗	✗
 Legumes	✓	✓ • All beans are encouraged after proper soaking in an acidic environment	✗	✓ • White/navy/lima/black/kidney beans, lentils, split peas	✗	✗
 Eggs	✓	✓	✓	✓	✓	✗
 Dairy	✓	✓ • Dairy is acceptable only if it is raw, non-homogenized, and grassfed • Fermented dairy products encouraged for probiotic content	✗	✓ • Fermented versions, 30-day aged cheeses, butter, dry curd cottage cheese	✓ • High-fat versions are prioritized	✗
Clinical Considerations	• Anti-inflammatory • Healthy patients	• Healthy patients • Kids	• Metabolic syndrome • Early stages autoimmunity	• Crohn's • Ulcerative colitis • Autism	• Neurological conditions • Seizures • MS • Alzheimer's • Parkinson's • Cancer	• Severe autoimmune patients, especially joint involvement • Rheumatoid arthritis

# Protect the Barrier from Damage

## NUTRIENT SUPPORT FOR INTESTINAL PERMEABILITY

Nutrient	Dosing	Mechanism of Action
L-glutamine	4 g/day for 30-90 days	An amino acid used as a primary fuel source for enterocytes to maintain the gut barrier
IgG	<b>SBI</b> 2 g/day for 60 days <b>Colostrum</b> 2 g/day for 30 days	Binds and eliminates pathogens Contains growth factors that rebuild and repair the intestinal lining
Probiotics	100 billion/day for 30-90 days	Maintains healthy gut flora, immune function
Turmeric (45-55% Curcuminoids, 3-8% Volatile Oil, 2-6% Turmerin Protein)	1 g	Decreases inflammation
Vitamin D	5,000-10,000 IU/day	Contributes to proper immune function and barrier integrity

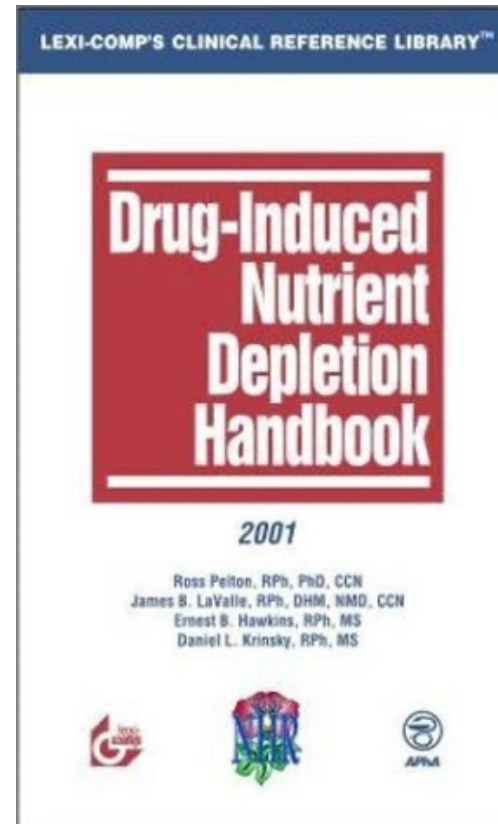
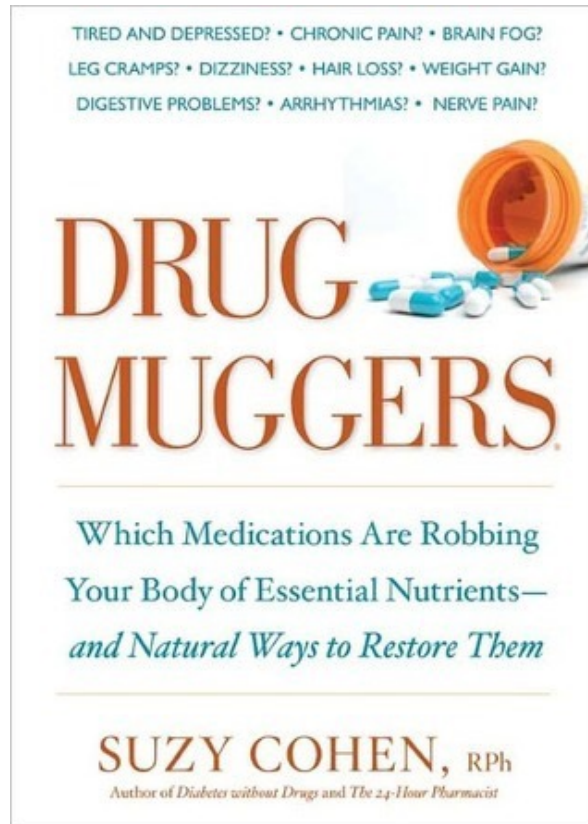
# Take-Aways

Pharmacists are front-line and can impact the most patients through addressing drug induced nutrient depletions.

A well-stocked supplement shelf can be a valuable resource for the patients in your community.

Ripple effect

# Pharmacist/Patient References & Resources



# References & Resources

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