

Prokinetics 101

Allison Siebecker ND, MSOM, LAc

SIBO SOS™ Virtual Conference, July 2018



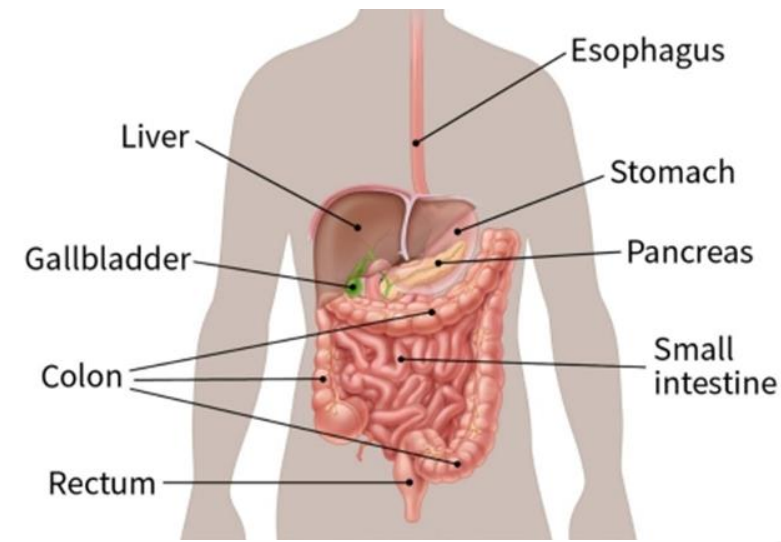
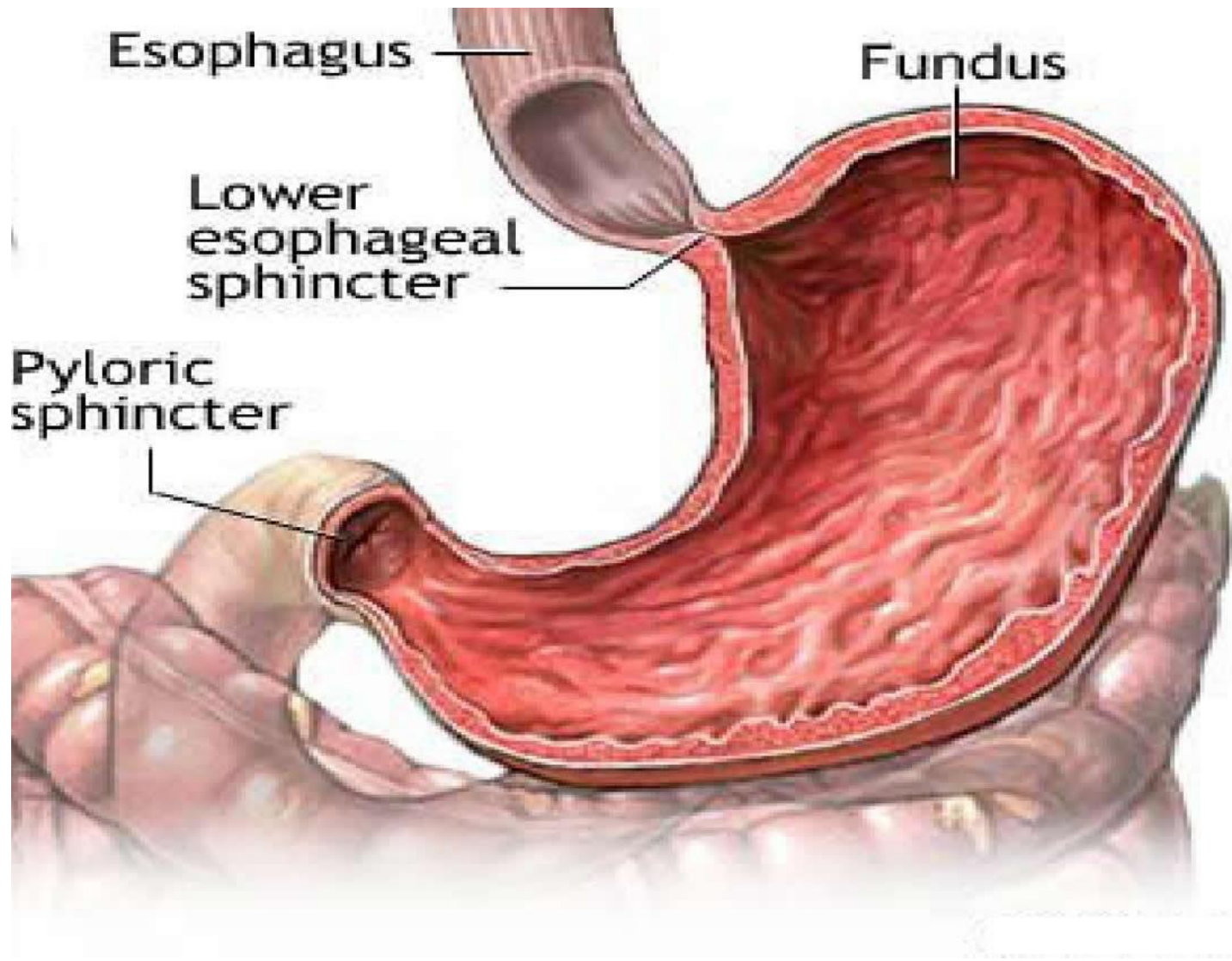
General Outline

- Prokinetics
- Prokinetics for Digestive **Disorders**⁴⁵
- Prokinetics Digestive **Symptoms**⁴⁵
- Prokinetics for **SIBO**^{40,44,47}



Prokinetics: Definition^{25,26}

- Stimulate & Coordinate GI motility
 1. Increase transit
 2. Improve coordination of GI movement, downward
 - ❖ Amplify & coordinate GI muscular contractions
- Can have different sites of action: upper or lower GI
 - Some better for upper GIT (esophagus/stomach/Small Intestine)
 - Some better for lower GIT (Large intestine)
 - Some can effect the whole GIT



Prokinetics vs Laxatives

Prokinetics

- Metoclopramide
- Cisapride
- Domperidone (Motilium)
- Erythromycin low dose
- Prucalopride (Resolor/Resotran)
- Ginger
- Iberogast



Laxatives

- Osmotic
 - Polyethylene Glycol (Miralax)
 - Magnesium
- Stimulant
 - Senna
 - Bisacodyl
- Prosecretory
 - Linaclotide (Linzess)
 - Lubiprostone (Amitiza)



Prokinetics are Not Laxatives Laxatives are Not Prokinetics



- ❖ Prokinetics can be used in diarrhea patients
- ❖ Laxatives (i.e. secretagogues) don't stimulate MMC



Digestive Disorders & Symptoms



Esophagus

Stomach

Small Intestine

Large Intestine



Hydrochloric
Acid





Disorders



- Achalasia
- Systemic Sclerosis
- Hirschsprung's Disease

Well-defined Motility Disorders



-
- GERD/Reflux Dz
 - Functional Dyspepsia
 - Gastroparesis
 - Ehlers-Danlos Syndrome
 - SIBO
 - IBS
 - Constipation
 - Chronic Intestinal Pseudo Obstruction

Heterogeneous Disorders



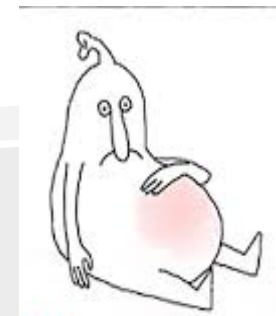
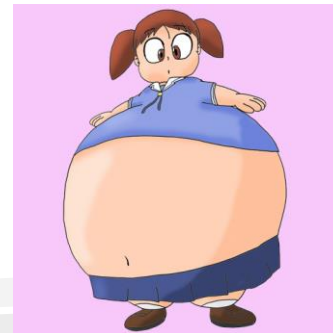
Symptoms

- Belching
- Nausea/ Morning Sickness
- Acid Reflux
- Vomiting



Upwards/Backwards
Symptoms

-
- Dysphagia
 - Food sits in stomach & won't go down/ Fullness
 - Bloating/ Gas Retention
 - Constipation
 - Abdominal Pain



Not Moving Down
Symptoms



Prokinetics: Mechanisms of Action^{25,28,99,100-102}

- Dopamine₂ Receptor Antagonist: D₂ (-)⁹⁹
- Muscarinic₃ Acetylcholine Receptor Agonist: M₃ (+)¹⁰⁰
- Muscarinic_{1/2} Acetylcholine Receptor Antagonist M_{1/2} (-)¹⁰⁰
- Acetylcholinesterase Inhibitor⁹⁹
- Serotonin₃ Receptor Antagonist: 5-HT₃ (-)^{99,102}
- Serotonin₄ Receptor Agonist: 5-HT₄ (+)⁹⁹
- Motilin Receptor Agonist⁹⁹
- Ghrelin Receptor Agonist⁹⁹
- Cholecystokinin_A Receptor Antagonist: CCK-A (-)²⁵
- Opioid Receptor Antagonist¹⁰¹

Mechanisms of Action^{25,27-28,100-102}

Table II. Prokinetic compounds: drug-receptor interaction.

Compound	D ₂ receptor antagonism	5-HT ₃ receptor antagonism	5-HT ₄ receptor agonism	Motilin receptor agonism	CCK-A receptor antagonism	M ₃ receptor agonism	Opioid receptor antagonism
Metoclopramide	yes	yes	no	no	no		
Domperidone	yes	no	no	no	no		
Cisapride	no	yes	yes	no	no		
Erythromycin (low dose)	no	no	no	yes	no		
Prucalopride	no	no	yes	no	no	no	no
<i>Low Dose Naltrexone</i>	no	no	no	no	no	no	yes
Iberogast	no	yes	yes	no	no	yes	yes
Ginger	no	yes	no	no	no	yes	no

Site of Action & Safety^{25,27,28,44,53,99,103}

Table III. Prokinetic compounds: comparison of activity profiles

Compound	Crossing BB barrier	Antiemetic effect	Activity on proximal gut	Activity on distal gut	Adverse effects
Metoclopramide	yes	yes	yes	no	many
Domperidone	no	yes	yes	no	some*
Cisapride	no	no	yes	yes	few *
Erythromycin (low dose)	no	no	yes	yes/no	few
Prucalopride	no	yes	yes	yes	few
<i>Low Dose Naltrexone</i>	yes	no	yes	yes	some
Iberogast		yes	yes	yes	few
Ginger		yes	yes	no	few

* But with drug-related deaths



Erythromycin



Ginger



Ginger Containing Formulas




Iberogast



Prokinetic Dosage Options

based on the effect you want

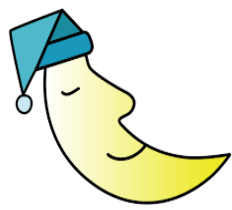
1. Before meals (30 min before)

- 
- Helps push food through faster = Gastroparesis or related sx (i.e. Erythromycin for GP)
 - Sometimes: before first meal - once a day dosing (i.e. Azithromycin for Gastroparesis)
 - Sx before meals (i.e. Ginger for Nausea to help someone to be able to eat)
 - ❖ May cause bloating if stomach emptying is normal- pushes food through too fast allowing fermentation without proper digestion.


2. After/between meals (1-2 hrs after, or when needed)

- Sx after meals (i.e. Iberogast for bloating, pain, nausea or acid reflux after eating)
- Exception: LDN is not dosed throughout the day (dosed Morning/waking &/or Bedtime)

3. Before bed

- 
- Helps stimulate MMC = SIBO relapse prevention (i.e. Prucalopride at low dose/0.5mg)
 - Helps BM in morning (at higher doses) = Constipation (i.e. Prucalopride at full dose/2-4mg for Chronic Constipation)

4. Combo – Daytime & Bedtime

- 
- For Symptom Relief and SIBO Relapse Prevention (i.e. Ginger before meals for Nausea and at bed for SIBO)




Clinical Notes



- Side effects can occur
 - Lower the dose or switch prokinetics (don't give up on the whole category)
 - Acid Reflux when start: purge LI with osmotic laxative x 2-3d
 - May be temporary (1-3 d)
- Ok to combine Prokinetics
 - Exception: Erythromycin with Domperidone or Cisapride
- Tolerance can occur
 - 2 week break may refresh effect (“drug holiday”)



Prokinetics for SIBO



Prokinetics - Use in SIBO

- SIBO Relapse Prevention^{40,44,47}
 - While treatment is in progress – between courses (Pharmaceutical/Herbal Antibiotics or Elemental Diet)
 - After successful treatment
- 1. SIBO Symptom Relief

SIBO Treatment Protocol

Third Line Therapy

Variation of the Cedars-Sinai Protocol (Pimentel 2006)¹
Drs. Siebecker (siboinfo.com) & Sandberg-Lewis (2010)²





Prokinetics - Use in SIBO Prevention


- SIBO Relapse Prevention^{40,44,47}
 - Stimulate MMC (in the small intestine) at night
 - to clear bacteria and prevent build up
 - If between rounds = hold gains made & prevent backsliding
 - If after eradication = maintain clear SI environment (maintain remission)
 - Dosed: before bed (hs)
 - Dose: low dose (applies to pharmaceuticals & some but not all herbals)
 - Not trying to effect LI/stimulate BM with this approach
 - Pk can cause BMs on an individual basis & at higher dose (less likely at low dose)
 - Switch to a different Pk if this happens and is unwanted



Prokinetics - Use in SIBO Symptoms

2. SIBO Symptom Relief

- What's different: used in *daytime* or at *higher dose*
 - vs low dose at bedtime
 - Exception: LDN is not dosed throughout the day. Dosed 1-2xd in the morning &/or evening/night, not intermittently for Symptom relief.



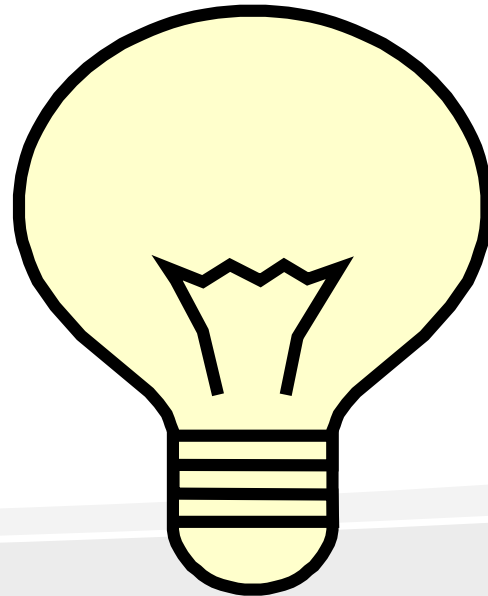
Prokinetics - Use in SIBO


Bedtime	Daytime	Bed & Day	Higher Dose Bed &/or Day
Relapse Prevention	Symptom Relief	Relapse Prevention & Symptom Relief	Adds both effects Esp Sx Relief



Key Points

- Relapse Prevention is a key part of SIBO treatment
 - Diet & Prokinetics are essential preventions





Prokinetics For SIBO Relapse Prevention

Dosed: before bed (hs) to stimulate MMC overnight (or hs & am/mid-afternoon)

- Pharmaceutical

- **Low Dose Erythromycin (LDE)** 50-62.5 mg hs^{25,26,40,49,65,99,103,111-116}
- **Low Dose Prucalopride (LDP)** 0.5 mg hs (up to 2 mg as needed)^{25,99,103,111,61,64,68}
- **Low Dose Naltrexone (LDN)** 2.5- 5 mg hs or bid^{44,117-119,62,65,60,69}
 - 2.5 mg/d- diarrhea, 5 mg/d- constipation, titrated up from 0.5/1 mg

- Herbal

- **Iberogast** 30-60 drops hs^{48-52,54}

(Iberis, Angelica, Milk Thistle, Caraway, Lemon Balm, Celandine, Licorice, Peppermint, Chamomile)

- **Ginger Root** 1000 mg hs^{46,53,63,100,102,104-108}

- **Motil Pro** 2-3/hs (5Htp, Acetyl L Carnitine, *Ginger*, Vit C, B6)
- **Prokine** 2-3/hs (5Htp, *Ginger*, Peppermint, Chamomile, Cinnamon, Gentian, B1, B6, Methyl B12/Folic)
- **Motility Activator**¹⁰⁴ 2-3/hs (Artichoke, *Ginger*)
- **SIBO-MMC** 2-3/hs (5Htp, *Ginger*, B6, Prickly Ash, Jujube, Flax Oil)

Ginger Containing Prokinetic Formulas



104



Iberogast^{48-52,54}
9 Herbs (No Ginger)



Pharmaceutical Pk Logistics

- Prucalopride
 - US: obtained through Canadian Pharmacies
 - 1 or 2mg pill is Cut= 0.5 mg dose
- Erythromycin (LDE)
 - 250 mg pill is Cut into quarters= 62.5 mg dose. (It can be cut)
 - Compounded into 50 mg dose
- LDN
 - Compounding necessary
 - Often started low 0.5-1 mg & ramped up to avoid sleep side effects
 - Prescribe a lower dose, then change prescription to full dose ongoing



How To Choose Pk



- ❖ When you need strongest effect: Prucalopride or Erythromycin
 - LDE: need effectiveness, Gastroparesis, possibly if underweight
 - Pruc: need effectiveness, (+)vinc/CdtB Ab, w/constip (OK for diarr too)
 - LDN: inflammation, auto-immunity/(+)vinc/CdtB Ab, depression
 - Iberogast: want natural, broad sx relief, nausea/dyspepsia
 - Ginger/Combo: want natural, nausea/Gastroparesis, caution w/GERD (except Motility Activator- altered shogals/no ginger burn)
 - Motil Pro/Prokine/SIBO-MMC: depression/sleep issues due to the 5-HTP
- ❖ PARQ patient & ask their input



When To Start

- Soon after Antimicrobial Tx
 - Day after finish Tx, to prevent rapid relapse
 - Con: hard to assess Tx effect when starting new med (pt could react to Pk)
 - Con: Possible false (+) if Retest on Pk
 - Wait a few days (3-5) days to assess Tx effect & Retest
 - Con: Patient may relapse

❖ Plan ahead

- Give Pk plan with Abx/HAbx/ED Tx- since it's started soon after Tx



Duration

1. Short Term x 3-6 month, then a trial removal (Pimentel)
 - 1/3 non-chronic or Short duration of SIBO (< 1 yr)
 2. Long Term/Ongoing
 - 2/3 chronic - SIBO \geq 5 yr - If relapse when stop Pk
- Ok to do a trial removal at any time: only risk= relapse
 - When Stopping: Cut down slowly to catch possible relapse
 - Every other day x 2 wk, then every 3rd day x 2 wk...
 - If Sx return: go back to full dose Pk- this may stop the relapse
 - But if Sx continue: 1. 3-7 d Tx 2. Or full Tx course may be needed.



SIBO Tx - Prokinetic Points

- Pk don't clear/Tx SIBO
 - Don't expect Sx relief in most (unless used at higher dose & in the day/meals)
 - ❖ Educate Pt- they may d/c it if they can't feel it working
- OK to continue during multiple courses but not necessary
 - Important to be on between courses- to keep gains made & prevent backslide
- OK to Retest SIBO while on Pk, but stop it 2 nights before test (24hr $\frac{1}{2}$ Life)
- Natural Pk & LDN are not strong enough for some (esp tough cases)
 - If you want to be sure - erythromycin, prucalopride
- OK to combine Pk's since MoA are different (taken together or AM&PM)



Reference Slides



Other Prokinetics

- Azithromycin (gastroparesis, SIBO)⁴⁹ 100-400 mg qd before 1st meal (200mg standard).
No CYP_{3A4} interactions like LDE, less cardiac risk
- Not studied for SIBO, studies on prokinetic effect
 - Triphala (mild prokinetic, laxative)^{29,30,31}
 - Japanese Daikenchuto^{32,33,34} (processed Ginger 5g + Ginseng 3g + Sichuan Pepper 2g)
 - Bitter Orange (immature/fructus auranti /Zhi Shi)(poncirus fructus)^{35,36,37,38}
- Not studied for SIBO, questionable prokinetic effect but in use as such
 - D-Limonene (“Some researchers believe d-limonene may support healthy peristalsis”)^{108,109}
 - Pbx: L acidophilus, B bifidus
 - 5HTP
 - 6 Gentlemen Formula
 - Fat (Try CLO hs or upon arising)
- Decrease stress (sympathetic ns)



Pk: Pregnancy, Lactation

- There are no category listing for the low Rx Pk doses used
 - LDE (Cat B at reg Abx dose)⁶⁵
 - Prucalopride is analogous to US Cat B (at 2-4mg dose)⁶⁴
 - Safe: LDN⁶², Iberogast^{48,54}, Ginger (max 2g/d)^{53,63}



Pk: Pediatrics

- Pediatric Doses:
 - LDE 25mg⁶⁷
 - LDN 0.1 mg/kg body weight or ½ adult dose^{60,69}
 - Prucalopride 0.01mg/kg⁶¹ (use adult dose if > 50kg)⁶⁸
 - Iberogast 10-30 gtts⁵⁴
 - Ginger 250mg




Erythromycin^{25,26,40,49,65,99,103,111-116}

- Dose:
 - Gastroparesis = 250 mg tid, 30 min before/with meals (range 150-500 mg)
 - SIBO relapse prevention (low dose) = 50 or 62.5 mg hs (bedtime)⁴⁰
 - Sx Relief (low dose) = 50 or 62.5-100 mg 30 min before/with meals or between meals
 - 50mg= compounding 62.5mg = cut a 250mg pill into quarters
 - Peds: 25 mg (Liquid Rx or cut a 150 mg pill into quarters = 37.5mg if older child)
- Pro: well-studied/effective, inexpensive, easily available, low side effects, no/low antibiotic effects at low dose.
- Con: tolerance possible, long-term antibiotic/low-dose Antibiotic, CYP_{3A4} interactions, can prolong QT waves (increased risk of sudden cardiac death when Abx dose is co-administered with other CYP_{3A4}).
- Contraindicated: pre-existing heart conditions.
- Note: Many drug interactions due to CYP_{3A} metabolism - check before prescribing.



Prucalopride^{25,99,103,111,61,64,68}

- Dose:
 - Constipation/Other GI disorders = 2 mg hs (range 0.5-4 mg)
 - SIBO relapse prevention (low dose) = 0.5 mg hs (range 0.25-1 mg)
 - Sx Relief = 0.5-2 mg
 - Peds: 0.01 mg/kg
- Pro: well-studied/very effective for wide array of GI disorders & sx, safe (no QT/CYP450), low side effects, neuroprotective-may heal MMC nerve damage over time.
- Con: tolerance possible, expensive, US: 2-3 wks to get in mail/not FDA approved yet.




LDN_{44,117-119,62,65,60,69}

- Dose:
 - IBS = 0.5 mg qd
 - SIBO relapse prevention = 2.5mg hs: diarrhea / 2.5mg bid or 4.5 hs: constipation
 - IBD = 4.5 mg qd
 - Sx relief: 0.5-5 mg
 - Peds: 0.01 mg/kg
- Pro: anti-inflammatory, used for pain, Auto Immune Dz & depression, natural MoA (stimulates endogenous opioids, CNS anti-inflammatory), safe, safe in peds /preg/ lactation.
- Con: not strong enough for some (1/3+: technically not a prokinetic), side effects are dose dependent: neurological (including sleep disturbance) & GI, compounding necessary.
 - Titrate dose up slowly from 0.5 or 1mg to lessen side effects.



Iberogast^{48-52,54}

- Dose:
 - IBS/Dyspepsia = 20 gtts with meals x 1 mo
 - SIBO relapse prevention = 60 gtts hs (30-60 gtts range)
 - Sx = 20-30 gtts tid-qid (see ‘dosing options’) or PRN for occasional help
 - Peds: 10-20 gtts tid-qid
- Pro: natural, well-studied/effective for a wide array of GI disorders & sx (*including diarrhea), safe in peds/preg/lactation, no side effects in studies. Great for the medicine cabinet.
- Con: not strong enough for many, individual side effects possible.



Ginger^{46,53,63,100,102,104-108}

- Dose:
 - General: 1000-2000 mg qd (up to 6g qd), commonly as 500-1000 mg/dose
 - SIBO relapse prevention: 1000-2000 mg hs
 - Peds: 250 mg
- Pro: well-studied/effective for stomach prokinesis, anti-nausea, anti-inflammatory, anti-neuroinflammatory, gastroprotective
- Con: not strong enough for many, tolerance possible, side effects: GERD/Ginger Burn (exception Motility Activator)(lots of water helps)



The End



Keep updated -

Join my Newsletter at SIBOInfo.com ; Welcome



References

25. Scarpignato C, Pelosini I. What are the mechanisms responsible for the efficacy of cisapride in treatment of reflux esophagitis?. In: Giuli R, Galmiche J, Jamieson G, Scarpignato C., ed. *The Esophogastric Junction*. 1st ed. Gazelle Distribution Trade; UK eFd. edition; 1998. Available at: http://www.hon.ch/OESO/books/Vol_5_Eso_Junction/Articles/art171.html. Accessed August 4, 2017.
26. Acosta A, Camilleri M. Prokinetics in Gastroparesis. *Gastroenterology Clinics of North America*. 2015;44(1):97-111. doi:10.1016/j.gtc.2014.11.008.
27. Manabe N, Rao A, Wong B, Camilleri M. Emerging Pharmacologic Therapies for Irritable Bowel Syndrome. *Current Gastroenterology Reports*. 2010;12(5):408-416. doi:10.1007/s11894-010-0124-1.
28. Simmen U, Kelber O, Okpanyi S, Jaeggi R, Bueter B, Weiser D. Binding of STW 5 (Iberogast®) and its components to intestinal 5-HT, muscarinic M₃, and opioid receptors. *Phytomedicine*. 2006;13:51-55. doi:10.1016/j.phymed.2006.03.012.
29. Mukherjee P, Rai S, Bhattacharyya S, Paul P. Clinical Study of 'Triphala' – A Well Known Phytomedicine from India. *Iranian Journal of Pharmacology and Therapeutics*. 2006;5:51-54.



References

30. Jirankalgikar YM, Ashok BK, Dwivedi RR. A comparative evaluation of intestinal transit time of two dosage forms of *Haritaki* [*Terminalia chebula* Retz.]. *Ayu*. 2012;33(3):447-449. doi:10.4103/0974-8520.108866.
31. Tamhane MD, Thorat SP, Rege NN, Dahanukar SA. Effect of oral administration of *Terminalia chebula* on gastric emptying: an experimental study. *J Postgrad Med*. 1997 Jan-Mar;43(1):12-3. PubMed PMID: 10740705.
32. Tominaga K, Arakawa T. Kampo medicines for gastrointestinal tract disorders: a review of basic science and clinical evidence and their future application. *Journal of Gastroenterology*. 2013;48(4):452-462. doi:10.1007/s00535-013-0788-z.
33. Nagano T, Itoh H, Takeyama M. Effect of Dai-kenchu-to on levels of 3 brain-gut peptides (motilin, gastrin and somatostatin) in human plasma. *Biol Pharm Bull*. 1999 Oct;22(10):1131-3. PubMed PMID: 10549871.
34. Mochiki E, Yanai M, Ohno T, Kuwano H. The effect of traditional Japanese medicine (Kampo) on gastrointestinal function. *Surgery Today*. 2010;40(12):1105-1111. doi:10.1007/s00595-010-4388-8.
35. Qiu X, Huang X, Chen Z et al. Pharmacokinetic study of the prokinetic compounds meranzin hydrate and ferulic acid following oral administration of Chaihu-Shugan-San to patients with functional dyspepsia. *Journal of Ethnopharmacology*. 2011;137(1):205-213. doi:10.1016/j.jep.2011.05.009.
36. Jiang Y, Bai X, Zhu X, Li J. The effects of Fructus Aurantii extract on the 5-hydroxytryptamine and vasoactive intestinal peptide contents of the rat gastrointestinal tract. *Pharmaceutical Biology*. 2014;52(5):581-585. doi:10.3109/13880209.2013.854396.
37. Kim B, Kim H, Lee G et al. Poncirus trifoliata fruit modulates pacemaker activity in interstitial cells of Cajal from the murine small intestine. *Journal of Ethnopharmacology*. 2013;149(3):668-675. doi:10.1016/j.jep.2013.07.017.
38. Shim W, Back H, Jung S et al. An aqueous extract of Poncirus fructus activates the prokinetic activity of 5-HT receptor subtype 4 without hERG interaction. *Journal of Ethnopharmacology*. 2010;132(1):328-333. doi:10.1016/j.jep.2010.08.042.



References

39. Kharrazian D. *Why Isn't My Brain Working?*. 1st ed. Carlsbad, CA: Elephant Press; 2013.
40. Pimentel M, Morales W, Lezcano S, Sun-Chuan D, Low K, Yang J. Low-dose nocturnal tegaserod or erythromycin delays symptom recurrence after treatment of irritable bowel syndrome based on presumed bacterial overgrowth. *Gastroenterol Hepatol (N Y)*. 2009 Jun;5(6):435-42. PubMed PMID: 20574504; PubMed Central PMCID: PMC2886395.
41. Brown K, Scott-Hoy B, Jennings L. Response of irritable bowel syndrome with constipation patients administered a combined quebracho/conker tree/M. balsamea Willd extract. *World Journal of Gastrointestinal Pharmacology and Therapeutics*. 2016;7(3):463. doi:10.4292/wjgpt.v7.i3.463.
42. Subapriya R, Nagini S. Medicinal properties of neem leaves: a review. *Curr Med Chem Anticancer Agents*. 2005 Mar;5(2):149-6. Review. PubMed PMID: 15777222.
43. Mullin G. SIBO (Small Intestinal Bacterial Overgrowth). *FXMED Podcast*. 2011. Available at: http://www.designsforhealth.com/ResearchEducation_ClinicalRounds.html.
44. Ploesser J, Weinstock LB, Thomas E. Low dose naltrexone: side effects and efficacy in gastrointestinal disorders. *Int J Pharm Compd*. 2010 Mar-Apr;14(2):171-3. PubMed PMID: 23965429.
45. Sheptulin AA, Belousova IB. Modern Prokinetics And Their Role In The Treatment Of Gastroenterological Pathology. *Klin Med (Mosk)*. 2016;94(3):178-82. Review. Russian. PubMed PMID: 27522721.
46. Micklefield GH, Redeker Y, Meister V, Jung O, Greving I, May B. Effects of ginger on gastroduodenal motility. *Int J Clin Pharmacol Ther*. 1999 Jul;37(7):341-6. PubMed PMID: 10442508.
47. Pimentel M. *A New IBS Solution: Bacteria - The Missing Link In Treating Irritable Bowel Syndrome*. 1st ed. Sherman Oaks: Health Point Press; 2006.



References

48. Ottillinger B, Storr M, Malfertheiner P, Allescher H. STW 5 (Iberogast®)—a safe and effective standard in the treatment of functional gastrointestinal disorders. *Wiener Medizinische Wochenschrift*. 2012;163(3-4):65-72. doi:10.1007/s10354-012-0169-x.
49. Larson JM, Tavakkoli A, Drane WE, Toskes PP, Moshiree B. Advantages of azithromycin over erythromycin in improving the gastric emptying half-time in adult patients with gastroparesis. *J Neurogastroenterol Motil*. 2010;16(4):407.
50. Raedsch R, Hanisch J, Bock P, Sibaev A, Vinson B, Gundermann KJ. [Assessment of the efficacy and safety of the phytopharmakon STW 5 versus metoclopramide in functional dyspepsia—a retrospective cohort study]. *Z Gastroenterol*. 2007;45(10):1041-1048. doi:10.1055/s-2007-963357.
51. Rösch W, Vinson B, Sassin I. A Randomised Clinical Trial Comparing the Efficacy of a Herbal Preparation STW 5 with the Prokinetic Drug Cisapride in Patients with Dysmotility Type of Functional Dyspepsia. *Zeitschrift für Gastroenterologie*. 2002;40(6):401-408. doi:10.1055/s-2002-32130.
52. Madisch A, Holtmann G, Plein K, Hotz J. Treatment of irritable bowel syndrome with herbal preparations: results of a double-blind, randomized, placebo-controlled, multi-centre trial. *Aliment Pharmacol Ther*. 2004 Feb 1;19(3):271-9. PubMed PMID: 14984373.
53. Thompson HJ, Potter PJ. Review: ginger prevents 24 hour postoperative nausea and vomiting. *Evid Based Nurs*. 2006 Jul;9(3):80. PubMed PMID: 16865831.
54. Iberogast [product information sheet]. Darmstadt, Germany; Steigerwald; 2015. Available at: <https://iberogast.com.au/static/documents/iberogast-oral%20liquid-pi.pdf>
55. XIFAXAN™ (rifaximin) Tablets(zuh FAX in). *Dailymed.nlm.nih.gov*. 2006. Available at: <https://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=1905>. Accessed July 28, 2017.
56. Adachi J, DuPont H. Rifaximin: A Novel Nonabsorbed Rifamycin for Gastrointestinal Disorders. *Clinical Infectious Diseases*. 2006;42(4):541-547. doi:10.1086/499950.



References

57. Neomycin Sulfate - FDA prescribing information, side effects and uses. *Drugscom*. 2017. Available at: <https://www.drugs.com/pro/neomycin-sulfate.html#ID264>. Accessed July 28, 2017.
58. FLAGYL- metronidazole tablet, film coated. *Labelingpfizercom*. 2017. Available at: <http://www.labeling.pfizer.com/ShowLabeling.aspx?id=570>. Accessed July 28, 2017.
59. Plummer N, Quilt P. *Plant Antimicrobials: The New Cornerstone Of Dysbiosis Therapy*. 1st ed. Bellevue, WA: Pharmax; [Publication date unknown, 2003-10].
60. Eichaar G, Maisch N, Augusto L, Wehring H. Pediatrics Efficacy and Safety of Naltrexone Use in Pediatric Patients with Autistic Disorder. *Annals of Pharmacotherapy*. 2006;40(6):1086-1095. doi:10.1345/aph.1g499.
61. Winter H, Di Lorenzo C, Benninga M et al. Oral Prucalopride in Children With Functional Constipation. *Journal of Pediatric Gastroenterology and Nutrition*. 2013;57(2):197-203. doi:10.1097/mpg.0b013e318292f9ea.
62. Fertility Care | LDN Research Trust - Low Dose Naltrexone. *Ldnresearchtrust.org*. 2017. Available at: <https://www.ldnresearchtrust.org/content/fertility-care>. Accessed September 15, 2017.
63. Thomson M, Corbin R, Leung L. Effects of Ginger for Nausea and Vomiting in Early Pregnancy: A Meta-Analysis. *The Journal of the American Board of Family Medicine*. 2014;27(1):115-122. doi:10.3122/jabfm.2014.01.130167.
64. European Medicines Agency - Find medicine - Resolor. *Emaeuropa.eu*. 2017. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/001012/human_med_001030.jsp&mid=WCOb01ac058001d124. Accessed September 15, 2017.
65. Erythromycin Use During Pregnancy | Drugs.com. *Drugscom*. 2017. Available at: <https://www.drugs.com/pregnancy/erythromycin.html>. Accessed September 20, 2017.
66. Briggs G, Freeman R, Yaffe S. *Drugs in Pregnancy and Lactation*. 9th ed. Philadelphia: Wolters Kluwer Health; 2014:1017.



References

67. Rosas-Blum E, Imseis E, McCallum R. Update in Pediatric Gastroparesis. *Practical Gastroenterology*. 2015;39(5).
68. Mugie S, Korczowski B, Bodi P et al. Prucalopride Is No More Effective Than Placebo for Children With Functional Constipation. *Gastroenterology*. 2014;147(6):1285-1295.e1. doi:10.1053/j.gastro.2014.09.005.
69. Smith J, Field D, Bingaman S, Evans R, Mauger D. Safety and Tolerability of Low-dose Naltrexone Therapy in Children With Moderate to Severe Crohn's Disease. *Journal of Clinical Gastroenterology*. 2013;47(4):339-345. doi:10.1097/mcg.0b013e3182702f2b.
70. NEEM: Uses, Side Effects, Interactions and Warnings - WebMD. *Webmdcom*. 2017. Available at: <http://www.webmd.com/vitamins-supplements/ingredientmono-577-neem.aspx?activeingredientid=577&>. Accessed September 20, 2017.
71. Min BR, Solaiman S, Shange R, Eun JS. [Gastrointestinal Bacterial and Methanogenic Archaea Diversity Dynamics Associated with Condensed Tannin-Containing Pine Bark Diet in Goats Using 16S rDNA Amplicon Pyrosequencing](#). *Int J Microbiol*. 2014;2014:141909. doi: 10.1155/2014/141909. Epub 2014 Jan 2.
72. Oh S, Shintani R, Koike S, Kobayashi Y. [Ginkgo fruit extract as an additive to modify rumen microbiota and fermentation and to mitigate methane production](#). *J Dairy Sci*. 2017 Mar;100(3):1923-1934. doi: 10.3168/jds.2016-11928. Epub 2017 Jan 11.
73. Gottlieb K, Wachter V, Sliman J, Pimentel M. [Review article: inhibition of methanogenic archaea by statins as a targeted management strategy for constipation and related disorders](#). *Aliment Pharmacol Ther*. 2016 Jan;43(2):197-212. doi: 10.1111/apt.13469. Epub 2015 Nov 11.
74. Muskal SM, Sliman J, Kokai-Kun, Pimentel M, Wachter V, Gottlieb K. [Lovastatin lactone may improve irritable bowel syndrome with constipation \(IBS-C\) by inhibiting enzymes in the archaeal methanogenesis pathway](#). *Version 3. F1000Res*. 2016 Apr 8 [revised 2016 Jun 22];5:606. doi: 10.12688/f1000research.8406.3. eCollection 2016.
75. Hubert S, Chadwick A, Wachter V, Coughlin O, Kokai-Kun J, Bristol A. [Development of a Modified-Release Formulation of Lovastatin Targeted to Intestinal Methanogens Implicated in Irritable Bowel Syndrome With Constipation](#). *J Pharm Sci*. 2018 Feb;107(2):662-671. doi: 10.1016/j.xphs.2017.09.028. Epub 2017 Oct 6.



References

96. Safe Upper Levels for Vitamins and Minerals: Expert Group on Vitamins and Minerals. Food Standards Agency, May 2003, p338. <https://cot.food.gov.uk/sites/default/files/vitmin2003.pdf>
97. Chan M Wallace J. [Hydrogen sulfide-based therapeutics and gastrointestinal diseases: translating physiology to treatments](#). American Journal of Physiology-Gastrointestinal and Liver Physiology, 2013 vol: 305 (7) pp: G467-G473.
98. Zhong C1, Qu C, Wang B, Liang S, Zeng B. [Probiotics for Preventing and Treating Small Intestinal Bacterial Overgrowth: A Meta-Analysis and Systematic Review of Current Evidence](#). J Clin Gastroenterol. 2017 Apr;51(4):300-311. doi: 10.1097/MCG.0000000000000814.
99. Quigley EMM. Prokinetics in the Management of Functional Gastrointestinal Disorders. Curr Gastroenterol Rep. 2017 Sep 8;19(10):53.
100. Ghayur MN, Khan AH, Gilani AH. [Ginger facilitates cholinergic activity possibly due to blockade of muscarinic autoreceptors in rat stomach fundus](#). Pak J Pharm Sci. 2007 Jul;20(3):231-5.
101. Foxx-Orenstein AE. [Does co-administration of a non-selective opiate antagonist enhance acceleration of transit by a 5-HT4 agonist in constipation-predominant irritable bowel syndrome?](#) A randomized controlled trial. Neurogastroenterol Motil. 2007 Oct;19(10):821-30.
102. Abdel-Aziz H, Windeck T, Ploch M, Verspohl EJ. [Mode of action of gingerols and shogaols on 5-HT3 receptors: binding studies, cation uptake by the receptor channel and contraction of isolated guinea-pig ileum](#). Ginger: Eur J Pharmacol. 2006 Jan 13;530(1-2):136-43. Epub 2005 Dec 20.
103. Scarpignato C. [Commentary: towards a cardiac safe prokinetic](#). Aliment Pharmacol Ther. 2012 May;35(10):1243-4. doi: 10.1111/j.1365-2036.2012.05077.x.
104. Lazzini S1, Polinelli W, Riva A, Morazzoni P, Bombardelli E. [The effect of ginger \(Zingiber officinalis\) and artichoke \(Cynara cardunculus\) extract supplementation on gastric motility: a pilot randomized study in healthy volunteers](#). Eur Rev Med Pharmacol Sci. 2016;20(1):146-9.
105. van Tilburg MA, Palsson OS, Ringel Y, Whitehead WE. [Is ginger effective for the treatment of irritable bowel syndrome? A double blind randomized controlled pilot trial](#). Complement Ther Med. 2014 Feb;22(1):17-20. doi: 10.1016/j.ctim.2013.12.015.
106. Wu KL, Rayner CK, Chuah SK, Changchien CS, Lu SN, Chiu YC, Chiu KW, Lee CM. [Effects of ginger on gastric emptying and motility in healthy humans](#). Eur J Gastroenterol Hepatol. 2008 May;20(5):436-40. doi: 10.1097/MEG.0bo13e3282f4b224.
107. Hu ML, Rayner CK, Wu KL, Chuah SK, Tai WC, Chou YP, Chiu YC, Chiu KW, Hu TH. [Effect of ginger on gastric motility and symptoms of functional dyspepsia](#). World J Gastroenterol. 2011 Jan 7;17(1):105-10. doi: 10.3748/wjg.v17.i1.105.



References

108. Dugasani S, Pichika MR, Nadarajah VD, Balijepalli MK, Tandra S, Korlakunta JN. [Comparative antioxidant and anti-inflammatory effects of \[6\]-gingerol, \[8\]-gingerol, \[10\]-gingerol and \[6\]-shogaol](#). J Ethnopharmacol. 2010 Feb 3;127(2):515-20. doi: 10.1016/j.jep.2009.10.004.
109. Mullin, G. [The Johns Hopkins Approach to SIBO: Herbal Antibiotics, Diet & More](#). 2015 SIBO Symposium, NUNM June 7 2017.
110. Sun J. [D-Limonene: Safety and Clinical Applications](#). Alternative Medicine Review Volume 12, Number 3 2007.
111. A V Emmanuel, M A Kamm, A J Roy, R Kerstens, and L Vandeplasseche. Randomised clinical trial: the efficacy of prucalopride in patients with chronic intestinal pseudo-obstruction - a double-blind, placebo-controlled, cross-over, multiple n = 1 study. Aliment Pharmacol Ther. 2012 Jan; 35(1): 48-55.
112. Camilleri M, Kerstens R, Rykx A, Vandeplasseche L. A placebo-controlled trial of prucalopride for severe chronic constipation. N Engl J Med 2008;358:2344-54.
113. Tack J, van Outryve M, Beyens G, Kerstens R, Vandeplasseche L. Prucalopride (Resolor) in the treatment of severe chronic constipation in patients dissatisfied with laxatives. Gut 2009;58:357-65.
114. Quigley EM, Vandeplasseche L, Kerstens R, Ausma J. Clinical trial: the efficacy, impact on quality of life, and safety and tolerability of prucalopride in severe chronic constipation - a 12-week, randomized, double-blind, placebo-controlled study. Aliment Pharmacol Ther 2009;29:315-28.
115. Sheptulin AA, Belousova IB. Modern Prokinetics And Their Role In The Treatment Of Gastroenterological Pathology. Klin Med (Mosk). 2016;94(3):178-82. Review. Russian. PubMed PMID: 27522721.
116. Camilleri M, Parkman HP, Shafi MA, et al, "Clinical Guideline: Management of Gastroparesis," *Am J Gastroenterol*, 2013, 108(1):18-37
117. Kariv R, Tiomny E, Grenshpon R, Dekel R, Waisman G, Ringel Y, Halpern Z. [Low-dose naltrexone for the treatment of irritable bowel syndrome: a pilot study](#). Dig Dis Sci. 2006 Dec;51(12):2128-33.
118. Patten DK, Schultz BG, Berlau DJ. [The Safety and Efficacy of Low-Dose Naltrexone in the Management of Chronic Pain and Inflammation in Multiple Sclerosis, Fibromyalgia, Crohn's Disease, and Other Chronic Pain Disorders](#). *Pharmacotherapy*. 2018 Mar;38(3):382-389. doi: 10.1002/phar.2086.
119. Younger J, Parkitny L, McLain D. [The use of low-dose naltrexone \(LDN\) as a novel anti-inflammatory treatment for chronic pain](#). Clin Rheumatol. 2014 Apr;33(4):451-9. doi: 10.1007/s10067-014-2517-2.