




Prokinetics in SIBO & Motility Disorders

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Prokinetics: Definition

- Increase transit/motility in GI tract
- Improve coordination of GI movement
 - Increase LES tone, relax pylorus
 - ❖ Amplify & coordinate GI muscular contractions
- Can have different sites of action: upper or lower GI
- Vs Laxative = stimulate BM's, loosen stool
 - Pk can be laxative but often aren't, esp at low dose
 - Pk can be used w/diarrhea to (+) upper GI motility, esp at lower dose

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Key Points

Not all prokinetics are unsafe

Side Effects/Reactions are common

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Adapted from Scarpignato '98 and '12, with Ottillinger '13

Table III. Prokinetic compounds: comparison of activity profiles

Compound	Crossing BB barrier	Antiemetic effect	Activity on proximal gut	Activity on distal gut	Untoward effects
Metoclopramide	yes	yes	yes	no	many
Domperidone	no	yes	yes	no	some
Cisapride	no	no	yes	yes	few
Erythromycin	no	no	yes	yes	few
Prucalopride	no	no	yes	yes	few
Iberogast		yes	yes	yes	few

• Prucalopride helps: nausea, bloating, pain, constipation (Emmanuel '12, Diederer '13)

• Iberogast helps: nausea, GERD, bloating, cramping/pain, constipation, diarrhea (Ottillinger '13)

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Prokinetics: Mechanisms of Action

- Muscarinic Acetylcholine Receptor Agonist: M (+)
- Acetylcholinesterase Inhibitor: ACh (-)
- Dopamine₂ Receptor Antagonist: D₂(-)
- Serotonin₃ Receptor Antagonist: 5-HT₃ (-)
- Serotonin₄ Receptor Agonist: 5-HT₄ (+) = (+) ACh
- Motilin Receptor Agonist
- Cholecystokinin_A Receptor Antagonist: CCK-A (-)
- Opioid Receptor Antagonist

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Adapted from Scarpignato '98 with Manabe '10, Simmen '06

Table II. Prokinetic compounds: drug-receptor interaction.

Compound	D ₂ receptor antagonist	5-HT ₃ receptor antagonist	5-HT ₄ receptor agonism	Motilin receptor agonism	CCK-A receptor antagonist	M ₃ receptor agonism	Opioid receptor antagonist
Metoclopramide	yes	yes	no	no	no		
Domperidone	yes	no	no	no	no		
Cisapride	no	yes	yes	no	no		
Erythromycin	no	no	no	yes	no		
Prucalopride	no	no	yes	no	no	no	no
Iberogast	no	yes	yes	no	no	yes	yes
Low Dose Naltrexone	no	no	no	no	no	no	yes

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Prokinetic Usage

1. Symptom Relief in Motility or Functional GI Disorders
 - Dosed: tid before meals. Or after/in between meals and first a.m.
 - for GERD, dyspepsia/gastroparesis (sx after meals), bloating
 - ❖ to move food, acid, gas out of St/SI
 - Dosed: qd may enough for constipation depending on Pk
 - Dose: standard Pk dose
2. Prevention of SIBO Relapse (maintenance of remission)
 - Dosed: before bed
 - ❖ to (+) MMC overnight
 - Dose: low dose
 - to prevent return of sx

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Prokinetics Usage

1. Symptom Relief
 - TID (or QD constipation)
 - Regular dose
2. SIBO Relapse Prevention
 - HS
 - Low Dose

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Prokinetic Dose

Motility, FGI Disorders Sx Relief

- Pharmaceutical
 - **Low Dose Erythromycin (LDE)** 50-100 mg tid-qid
 - **Prucalopride** 1-4mg qd or 1mg bid-tid
 - **Low Dose Naltrexone (LDN)** 2.5- 4.5 mg hs or bid
 - 2.5mg- diarrhea, 4.5mg- constipation
- Herbal
 - **Iberogast** 20 drops tid or PRN
 - **Ginger** 500mg tid, 1000mg bid
 - **MP** 2-3caps bid-tid (5Htp, Acetyl L Carnitine, Ginger, Vit C, B6)

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Prokinetic Dose SIBO Relapse Prevention

- Pharmaceutical
 - **Low Dose Erythromycin (LDE)** 50-62.5 mg at bedtime (hs)
 - **Low Dose Prucalopride (LDP)** 0.5 mg hs (up to 2 mg if needed)
 - **Low Dose Naltrexone (LDN)** 2.5- 4.5 mg hs or bid
 - 2.5mg- diarrhea, 4.5mg- constipation
- Herbal
 - **Iberogast** 30-60 drops hs
 - **Ginger** 1000mg hs
 - **MP** 2-3caps hs or hs & a.m. (5Htp, Acetyl L Carnitine, Ginger, Vit C, B6)

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Erythromycin & Prucalopride

- LDE
 - No/weak Abx activity at low dose. Standard Tx for Gastroparesis
 - Delayed SIBO relapse by 2.5 mo (Pimentel '09)
 - SE vary. Tolerance possible. Prolong QT waves. P450 3A4 interactions
- Prucalopride
 - Safer/stronger alternative to Tegaserod which delayed SIBO relapse by 6mo (Pimentel '09)
 - Dr P thinks may help heal MMC over time. 1st choice of many GE/most effective Pk
 - SE: h/a, urinary urge, temporary diarr, varied. Tolerance possible.
 - Obtained through Canadadrugs.com. Available in US soon.

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LDN & Iberogast



- LDN
 - 68% success for SIBO Prevention, 38% failure (Ploesser '10)
 - ❖ Doesn't work as Pk (not strong enough) in many (Combine w/other Pk)
 - SE: varied, sleep disturbance- titrate up to help avoid
 - Also used for inflammation, depression, Auto Immune dz (=PI-IBS)
- Iberogast
 - 75-85% success= IBS, Significant Sx improvement= Dyspepsia (Ottillinger)
 - ❖ Miracle for nausea
 - More effective vs metoclopramide, similar vs cisapride = Dyspepsia
 - SE: 0.04%. Safe for long term use, pregnancy, children

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Ginger & MP

- **Ginger**
 - MoA: + gastric emptying/MMC, M Rec (+), 5-HT₃ (-)
(Micklefield '99, Hu '11, Haniadka '13, Wu '08 Thompson '14)
 - SE: 28% GERD/Ginger Burn (Thompson '14)
 - helped by drinking water
- **MP** (no studies)
 - Ginger, 5HTP, acetyl L-carnitine, Vit C, B6
 - MoA: saa + extra ACh/Cholinergic
 - SE: GERD, diarrhea (+ LI motility too)

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Other Natural Prokinetics

- **Japanese Daikenchuto**
 - Motilin agonist + lots more (Tominaga '13, Nagano '99, Mochiki '10)
 - Thought to effect distal SI & LI best (Nakaji '11)
 - 190mg/kg/day (Endo '14) or 5g tid before meals
 - Processed Ginger 3-5g + Ginseng 3g + Sichuan Pepper (Zanthoxylum piperitum) 2g
- **Bitter Orange** (immature/fructus auranti /Zhi Shi)(poncirus fructus)
 - 5-HT₄ (+) (Qiu '11, Jiang '14, Kim '13, Shim '10)
 - ingredient in Chaihu Shugan San
- **Triphala**
 - mild prokinetic, laxative (Mukherjee '97, Jirankalgikar '12, Tamhane '97)

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How To Choose Pk

- ❖ When you need to be sure: choose Pruc or LDE
- Pruc: need effectiveness, chronic cases, constipation, PI-IBS
- LDE: chronic/recurrent cases w/o constipation, gastroparesis
- LDN: inflammation, auto-immunity, depression
- Iberogast: want natural, broad sx relief, nausea
- Ginger: nausea/gastroparesis, not w/GERD
- MP: constipation, depression, not w/GERD
- ❖ PARQ patient & ask their input

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Pk PARQ: Pro's & Con's

- **Prucalopride:** Pro: strongest, safe (no QT/p450), low se, may heal MMC over time. Con: tolerance/se possible, expensive, 3wks to get in mail/not FDA approved
- **Eryth:** Pro: studied for SIBO, inexpensive/easily available, low se. Con: tolerance/se possible, long-term low-dose Abx, p450 interactions. Cx: preexist Ht cond (can prolong QT), w/Berb (p450)
- **LDN:** Pro: anti-inflam, used for AI dz & depression, natural MoA. Con: not strong enough for some (1/3+)(tech not Pk), se: sleep disturbance
- **Iberogast:** Pro: natural, well studied as a Pk, broad GI sx relief, safe: kids, preg, lactation, no s.e.'s in studies. Con: not strong enough for many, indiv se poss
- **Ginger:** Pro: natural, anti-nausea/inflam. Con: se: GERD/ginger burn, tolerance, not strong enough for many
- **MP:** Pro: (+)BM's/LI motility, anti-depressant/sleep aid. Con: (+)BM's/LI motility, se: GERD/ginger burn, emotional, sleep, not strong enough for many

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Start/Duration/Stop

- **Start:** Sx Relief- any time
 - Dr Scarp suggests LI purging 1st to avoid anti-peristalsis (not w/diarrhea pt)
- **Start:** SIBO prevention- 1-5 days after tx
 - Important to be on Pk between tx courses to hold gains/prevent relapse
 - Plan ahead: Give the Rx/Pk Plan when Tx is given
- **Duration:** Sx- ongoing PRN. SIBO- min 3mo, ongoing for many
 - May be stopped at any time- only risk is relapse of Sx or SIBO
- **Stop:** Titrate down slowly, esp w/SIBO to catch a relapse

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Other Motility Considerations

- Stress
 - Decrease stress/sympathetic: Rushing, worrying
 - Increase parasympathetic: Conscious breaths, Gratitude, Rest
- Meal Spacing/ Overnight Fast
 - 4-5 hrs between meals, 12 hr overnight fast to optimize MMC
- Physical Tx/Body work
 - Wurn technique, visceral manipulation, cranial osteopathy ...

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Pk: Pregnancy, Lactation & Pediatrics

- Preg & Lact:
 - There are no category listing for the low Rx Pk doses used
 - LDE (Cat B at regular Abx dose)
 - Prucalopride is analogous to US Cat B (at regular 2-4mg dose)
 - Safe: LDN, Iberogast, Ginger (max 2g/d)
- Peds Doses: LDE 25mg, LDN & Prucalopride 0.01mg/kg, Iberogast 10-30 gtts, Ginger 250mg

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