**Dr J Otte (MD, CCFP)'s conceptual framework for management of chronic and opiate-induced constipation**

**ROME IV criteria for functional (chronic) constipation:**
1. Two or more of the following over past 3 months:
   - Fewer than 3 spontaneous defecations per week
   - Straining
   - Lumpy or hard stools
   - Sensation of anorectal obstruction
   - Sensation of incomplete evacuations
   - Manual maneuvers to defecate

   **At least 25% of the time**

2. Loose stools are rarely present without laxatives
3. Insufficient criteria for IBS

**Rx CAUSING CONSTIPATION:**
- Calcium Channel Blockers, Calcium, Iron, Aluminum-antacids; Multivits w minerals
- NSAIDs
- Opiates
- Diuretics
- Antidiarrheals, resins, bismuth
- Anticholinergics, eg. anti-histamines, antidepressants
- Antiemetics, eg. ondansetron
- Anticonvulsants and antipsychotics
- Antiparkinsons medications

**STOP CONSTIPATING MEDICATIONS**

**Igneous**

**CONSIDER SURGERY**

**IBS-C**

**TREAT COMORBID CONDITION**
- eg. hypothyroidism

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**REX CARUS AGENTS**
- "PAMORAs" eg. methylnaltrexone

**CONSIDER SURGERY**

**Dr J Otte (MD, CCFP)'s conceptual framework for management of chronic and opiate-induced constipation**

**jessica.otte@ti.ubc.ca**
<table>
<thead>
<tr>
<th>Therapy - examples</th>
<th>Mechanism</th>
<th>Usual/Severe Side Effects</th>
<th>Cost</th>
<th>Efficacy (increasing number of patients who have &gt;= 3 complete spontaneous bowel movements/wk; other measures described)</th>
<th>LOE</th>
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<tbody>
<tr>
<td><strong>Water – H₂O</strong></td>
<td>?</td>
<td></td>
<td></td>
<td><strong>LIMITED:</strong> unless dehydration is present (in elders in LTC)</td>
<td>III¹ ²</td>
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<tr>
<td><strong>Biofeedback</strong> (relax anus while pushing intraabd. to extrude balloon w sensors)</td>
<td>Retraining control of anorectum</td>
<td>Invasive, requires diagnostics, not readily available</td>
<td>MSP vs private $$$</td>
<td><strong>MAYBE:</strong> Might improve psych/clinical outcome measures in pelvic floor dysfunction; wide diversity in protocols.</td>
<td>IB³</td>
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<td><strong>Positioning</strong> – feet up (eg. Squatty Potty™)</td>
<td>Allows structurally easier transit of stool</td>
<td></td>
<td>$</td>
<td><strong>MAYBE:</strong> increased bowel emptiness, reduced straining patterns, but ?funding, small N, short time (2wks), cross-over study</td>
<td>IA⁴</td>
</tr>
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<td><strong>Exercise</strong></td>
<td>?Magic; ^ peristalsis by increasing HR/RR</td>
<td></td>
<td></td>
<td><strong>LIMITED:</strong> One small RCT &amp; some case-control studies: decreased constipation (self-report or Rome criteria); other studies: no effect. Review of 9 RCTs in China: may improve “symptoms” but LOW quality</td>
<td>IIA³</td>
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<td><strong>Soluble Dietary Fiber, Bulk-forming Agents</strong> (psyllium [Metamucil], inulin [Benefibre] calcium polycarbophil, methycellulose, prunes, etc.)</td>
<td>Expand with water, increase bulk of the stool, thereby increasing frequency</td>
<td>Require adequate fluid to act. Dose-dependent bloating, gas. Risk of bowel obstruction.</td>
<td>$</td>
<td><strong>PROBABLY, IF LOW FIBRE DIET:</strong> 3RCTs psyllium &gt; placebo; 1 RCT methylcellulose &gt; placebo; 2 RCT prunes ~= psyllium in ‘validated questionnaires’; mixed data on straining, # spont BMs/wk, consistency</td>
<td>IB³</td>
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<td><strong>Stool Softeners</strong> (docusate [Colace], mineral oil)</td>
<td>Detergent effect, lowers surface tension at interface, allows water to soften the stool</td>
<td>Bitter taste, nausea. Aspiration of mineral oil → dehydration. Rare: electrolyte disturbances.</td>
<td>$</td>
<td><strong>PROBABLY NOT:</strong> No study comparing docusate efficacy against placebo. No effect on stool weight, transit time. Inferior to psyllium. 1 Sys review: small effect on stool frequency in chronically ill, but overall quality of evidence was poor.</td>
<td>IA⁹ IB¹⁰</td>
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<td><strong>Osmotic Agents</strong> (PEG [Lax-a-Day, RestoraLax], lactulose, sorbitol, Mg-OH, glycerin PR)</td>
<td>Hyperosmolar, non-absorbable molecule so adsorb, retain water thereby facilitating stool passage</td>
<td>Diarrhea, nausea, flatulence, dehydration. Rare: electrolyte disturbances.</td>
<td>$$$[* PEG not on Plan P]</td>
<td><strong>YES,</strong> of osmotic agents, PEG best combo of effective/tolerated: PEG increased frequency of stools relative to placebo (high-quality studies: additional 2.34 stools/week) Retrospective data suggests enduring efficacy of PEG to at least 24mos PEG better tolerated (no taste). ?Less cramping with milk of magnesia but lower efficacy; PEG more effective than lactulose in terms of need for additional products, stool frequency &amp; form, and relief of abdo pain; mostly peds data but adult subgroup analysis consistent</td>
<td>IA¹¹ IB¹² IA¹³ IA¹⁴</td>
</tr>
<tr>
<td>Category</td>
<td>Product</td>
<td>Effect</td>
<td>Grade</td>
<td>Notes</td>
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<tr>
<td><strong>Stimulants</strong> (senna [Sennakot], Bisacodyl [Dulcolax, Ex-Lax, sodium picosulphate, cascara])</td>
<td>Sennakot, Bisacodyl, Ex-Lax, sodium picosulphate, cascara</td>
<td>Stimulate myenteric plexus → increases peristalsis; decreased transit time means decreased water absorption</td>
<td>$</td>
<td>YES, senna effective as adjuvant; Bisacodyl works but poorly tolerated. In network meta-analysis, bisacodyl and sodium picosulfate ranked best at 4 wks BUT Bisacodyl most likely to cause adverse events. No known high-quality study comparing senna vs placebo; 3+ RCTs compared senna with another laxative: groups receiving senna fared better than comparison. 1 large RCT of Bisacodyl vs placebo : increase of 4.3 BMs/wk, better QoL.</td>
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<td><strong>Chloride Channel Activator</strong> (lubiprostone [Amitiza])</td>
<td>Lubiprostone</td>
<td>GI fluid by stim Type 2 Cl- channels in GI epithelium apical membrane</td>
<td>$$$</td>
<td>YES: 3 RCTs: increased spontaneous bowel movements and improved self-reported symptoms of chronic constipation. In opiate-induced constipation, NNT = 15 (95% CI, 9–51).</td>
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<td><strong>Guanylate Cyclase-c Receptor Agonist</strong> (linacotide [Constella])</td>
<td>Linacotide</td>
<td>GI fluid via cystic fibrosis transmbr conductance channel &amp; desensitizes pain fibers via guanylate cyclase C</td>
<td>$$$$</td>
<td>YES: Compared with placebo (n = 1582) showed a smaller risk for therapy failure. Insufficient evidence to support use in OIC.</td>
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<td><strong>5-Hydroxy-Tryptamine Receptor 4 Agonists</strong> (tegaserod [Zelnorm], prucalopride [Resotran] more selective for gut)</td>
<td>Tegaserod, prucalopride</td>
<td>Binds to 5-HT4 receptors, stimulating GI peristalsis and increasing motility</td>
<td>$$$$</td>
<td>YES: Stool frequency was increased with prucalopride vs placebo 6 short RCTs +ve, 1 RCT at 24wks -ve. In IBS, modest improvements in stool frequency with tegaserod; clinical significance unclear. Tegaserod may alter visceral sensitivity (part of pathophysiology of IBS) - Prucalopride ranked 1st in network meta-analysis for 3 SBMs/wk • at 24 weeks prucalopride = placebo... Insufficient evidence to support use in OIC.</td>
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<td><strong>Peripherally Acting μ-Opioid Receptor Antagonists</strong> (“PAMORAs”) - Naloxogel [Movantik] PO - Methylnaltrexone (SQ) [Relistor]</td>
<td>Naloxogel, Methylnaltrexone</td>
<td>Release bound opioids from μ-Opioid receptors in GI tract</td>
<td>$$$$</td>
<td>YES: In opiate-induced constipation (OIC) Network Metanalysis, significant heterogeneity: Naloxegol NNT=7, methylnaltrexone, NNT=3.4, naloxone NNT=4 to achieve &gt;= 3SBMs/wk or increase of &gt;=1BM/wk vs baseline; *Naloxone most effective &amp; safest BUT not only peripheral acting (so reverses analgesia). All laxatives [even non-PAMORAs] have similar effectiveness; limited due to insufficient data from few, small RCTs. No studies on PEG in OIC, no RCTs comparing traditional laxatives vs PAMORAs. *Best reserved for patients for whom other laxatives haven’t worked → naldemedine: N/A yet but 52wk efficacy data (not for other PAMORAs).</td>
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</tbody>
</table>
**Enemas** eg. micro-lax, sodium phosphate [Fleet], etcetera

Mechanically expand colon. Some contain electrolytes/onotic agents to prevent absorption of water; Hyperosmotic variants draw water.

| Mechanism            | Invasive, diarrhea, anal leakage. Risk of bowel perforation. | $$ (+ system costs)$$ | MAYBE: Patients who received osmotic laxative + rectal stimulant + weekly enema vs osmotic laxative: more complete rectal emptying. Enemas: One RCT, 1 three non-randomized studies, all paed popl**: Enema vs PEG: significantly improved symptoms relative to PEG in days 1-3, but no diff day 5. Children who received an enema were significantly more likely to revisit the ED than those who did not. **NICE: option for cases in which all oral medications have failed.

| Evidence            | IIB²⁵ | IV²⁶ |

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9 Canadian Agency for Drugs and Technologies in Health (CADTH). Rapid Response Report: Dioctyl Sulfosuccinate or Docusate (Calcium or Sodium) for the Prevention or Management of Constipation: A Review of the Clinical Effectiveness. June 2014.
26 CADTH Rapid Response: Enemas for the Treatment of Constipation in the Emergency Department: Clinical Effectiveness and Guidelines