Meeting the challenges of opioid-induced constipation (OIC)

HOT SPOT

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Background

- Opioid analgesics are the cornerstone of pain management for moderate to severe pain in cancer and end-of-life (EOL) care
- Despite their proven analgesic efficacy, opioids are frequently associated with a number of bothersome side effects including constipation, nausea, vomiting, drowsiness and confusion
- Constipation affects up to 90% of cancer and EOL patients, with opioid-induced constipation (OIC) being the leading cause
- More than 40% of patients report reducing or stopping their opioids due to OIC
- In Ontario (2002–2005), for patients with cancer, constipation was the 11th most common reason for a trip to the emergency room within the last six months of life
- Constipation is under-assessed and under-addressed by physicians and health care providers, and is not a formal component of the ESAS-r

What is constipation

Definitions/scales include:

- Rome III Criteria:
  Must include two or more of the following:
  - Straining, lumpy or hard stools, sensation of incomplete evacuation, sensation of anorectal obstruction or blockage, manual manoeuvres needed to facilitate defecation, fewer than three defecations per week
- DISH:
  - **D**ifficult to pass
  - **I**nfrequent compared to normal
  - **S**mall
  - **H**ard
- Bristol Stool Form Scale
- Victoria Bowel Performance Scale (BPS)
- Bowel Function Index (BFI):
  - Mean (NAS 0–100) of: ease of defecation, feeling of incomplete bowel evacuation, personal judgment of constipation
  - Higher scores indicate worse bowel function
  - A change of BFI > 12 is regarded as clinically significant

- Constipation in cancer and EOL management is multifactorial and causes include: cancer, cancer treatment, co-morbid conditions, and debility
- Many medications are associated with constipation including: opioids, NSAIDs, anticholinergics, antipsychotics, antidepressants, antiemetics, antispasmodics, calcium channel blockers, iron, calcium, antacids, chemotherapy agents…

What is opioid-induced constipation (OIC)

- Opioids bind to peripheral opioid receptors ($\mu > \delta, \kappa$) in the enteric nervous system of the gastrointestinal tract
- Activation of these receptors decreases gastrointestinal (GI) motility by decreasing propulsive peristalsis, increasing segmental contractions and intestinal fluid absorption, decreasing gastric motility/emptying and pancreatic and biliary secretions, and increasing anal sphincter tone
- Opioid bowel dysfunction (OBD) encompasses a wide range of associated symptoms including: abdominal distension, pain and cramps, gastric fullness, gastro-esophageal reflux, nausea, vomiting, anorexia, and constipation
- The most bothersome symptom is opioid-induced constipation (OIC)

Consequences and burden of OIC

- Clinical burden
  - Barrier to optimal pain management (including missing, decreasing or stopping opioids)
  - Medical complications including fecal impaction, bowel obstruction/perforation, rectal tearing/fissure/hemorrhoids, urinary retention, respiratory failure…
- Patient burden
  - Reduced health-related quality of life (QoL) and daily living including: bother, worry, staying in control, reduced time being active/engaged with family and loved ones…
- Economic burden
  - Increased physician, alternative care provider, emergency room visits
  - Increased caregiver/nursing time

Traditional approaches for OIC

- Non-specific management of OIC may include nonpharmacological and pharmacological approaches (Tables 1, 2)
- Often leads to high pill/liquid/rectal burden for patients and caregivers
- Non-specific regimens often do not provide satisfactory relief from OIC
- Droney et al. (2008) observationally studied constipation and laxative use in cancer outpatients (n=274) on oral morphine at a tertiary referral cancer hospital
  - 15% had no constipation and needed no laxatives
  - 13% had no constipation and were adequately treated with laxatives
  - 72% complained of mild to severe constipation
    - 27% were not taking any laxatives
    - 11% had been titrated to maximum recommended doses of combination laxatives

Table 1. Nonspecific management of OIC

Nonpharmacological Approaches
• Scheduled toileting, upright position, privacy • Encourage fluid intake, improve diet and activity, if possible • Avoid bulk agents (bran, psyllium, citrucel…) in palliative patients, as they may precipitate bowel obstruction • Natural laxatives include prune juice, flax seed oil, lactose, hot fluids • Education of patient/caregivers
Pharmacological Approaches
• Reduce/eliminate unnecessary constipating medications • Opioid-sparing regimens for pain management • Opioid rotation/alternative route of administration • Prokinetic agents (domperidone, metoclopramide) • Laxatives (Table 2)

Table 2. Types of laxatives

Type	Examples	Comment
Stool softeners	Docusate sodium/calcium	No laxative effect on their own
Osmotics	Magnesium citrate/hydroxide Lactulose, Sorbitol PEG 3350 others	Avoid Mg salts in renal impairment
Stimulants	Senna Bisacodyl others	Prolonged use may result in "laxative/cathartic" bowel
High-affinity 5-HT4 receptor agonists	prucalopride	Phase III study in cancer OIC planned for 2011
Rectal interventions	Enemas, suppositories, disimpaction	

Newer approaches for OIC—Using opioid receptor antagonists

- Unique concept where opioid antagonists are used to address/target the root cause of OIC—the opioid-receptor-mediated mechanism of bowel dysfunction
- Separating the central and peripheral effects of opioid receptors offers the potential to manage and/or prevent OIC without compromising analgesic efficacy

Opioid receptor antagonists with limited systemic bioavailability

Naloxone

- A pure competitive antagonist of opioid receptors in both the central and peripheral nervous system
- When given *orally*, naloxone acts locally in the GI tract; oral naloxone undergoes extensive elimination by hepatic first-pass metabolism, resulting in negligible (<3%) systemic bioavailability
- Oral immediate-release naloxone reported more than 20 years ago for use in OIC
  - Some improvement in OIC, but narrow therapeutic window with reversal of analgesia in some patients

Oral controlled-release (CR) oxycodone/ controlled-release naloxone (Targin®)

- Fixed ratio combination oral tablets (2:1) with dual therapeutic effect
  - CR oxycodone component indicated for the treatment of moderate to severe chronic pain
  - CR naloxone component indicated for the relief of OIC
- Available in three strengths: 10/5 mg, 20/10 mg, 40/20 mg
  - Maximum daily dose is 40/20 mg po q12h
  - For patients requiring higher doses for pain control, administration of additional CR oxycodone at the same intervals should be considered
- Contraindicated in patients with moderate to severe hepatic impairment, suspected mechanical GI obstruction, any disease/ condition that affects bowel transit, or suspected surgical abdomen
- Not recommended for patients with peritoneal carcinomatosis or sub-occlusive syndrome related to advanced GI or pelvic cancers

Studies include:

- Vondrackova et al.
  - Analgesic efficacy comparable to OxyContin®
- Simpson et al.
  - Improvement of bowel function with: significant reduction of BFI, fewer patients taking laxatives, and more patients with >3 complete spontaneous bowel movements per week compared with OxyContin®
- Nolte et al.
  - Four-week observational study (n=1178) in patients with cancer; demonstrated effective analgesia, improved bowel function, and improved QoL (Figures 1–3)

Opioid receptor antagonists that are peripherally restricted

(do not cross the blood-brain barrier)

Methylnaltrexone bromide (Relistor®)

- Charged quaternary N-methyl derivative of naltrexone (MNTX)
- Subcutaneous (sc) injection approved for the treatment of OIC in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient
- Dosage by patient weight: 12 mg sc (62–114 kg), 8 mg sc (38–62 kg), 0.15 mg/kg for weight that falls outside of the ranges; in patients with Cr Cl < 30 mL/min reduce the dose in half; no dose adjustment in mild to moderate hepatic impairment
- Contraindicated in patients with known or suspected mechanical GI obstruction or acute surgical abdomen
- Should be used with caution in patients with known or suspected GI lesions; patients with advanced illness may be at increased risk of GI perforation if they have conditions associated with localized or diffuse reduction of structural integrity in the GI wall

Studies in palliative care include:

- Thomas et al.
  - 48% of patients had laxation within four hours of single dose, 52% had laxation within four hours after two or more of the first four doses with no change in analgesic efficacy (Figure 4); three-month open label extension showed sustained efficacy

Figure 1. Targin® Mean pain intensity

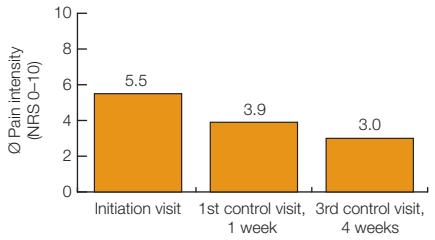


Figure 2. Targin® Bowel Function Index (BFI)

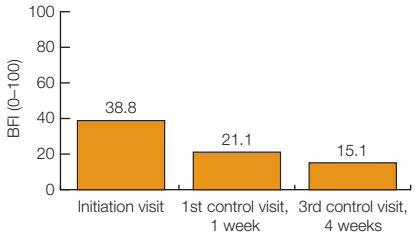
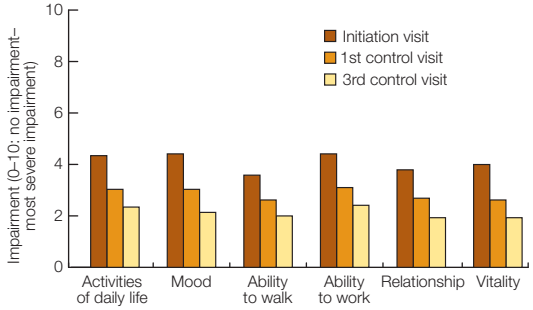


Figure 3. Targin® Impairment of quality of life parameters



Other ongoing/completed MNTX pain studies include:

- Open-label phase 3 study of sc MNTX in 1,034 patients with chronic non-malignant pain
- Oral MNTX for the treatment of OIC in chronic non-malignant pain

Oral alvimopan (Entereg®)

- Not approved in Canada
- FDA approval *only* for inpatient use for postoperative ileus in patients who have undergone partial large or small bowel resection surgery
- Contraindicated in patients who have been receiving therapeutic doses of opioids for more than seven consecutive days
- Not recommended for patients with severe hepatic impairment or end stage renal disease, or for patients undergoing surgery to correct complete bowel obstruction

Oral pegylated naloxol (NKTR 118, 119)

- NKTR 118 reduced OIC without compromising analgesia in phase 2 study
- NKTR 119 is a co-formulation of oral NKTR 118 and an opioid analgesic

Oral TD-1211

- Positive phase 2 results for OIC in patients with chronic non-cancer pain

*** references available upon request**

Figure 4. sc MNTX versus placebo