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MANAGEMENT OF OPIOID-INDUCED CONSTIPATION

1 AMA PRA CATEGORY 1 CREDIT(S)™
1 HOUR CATEGORY 2B, AOA

CME MONOGRAPH
VALID MAY 25, 2009 – MAY 31, 2010

MANAGEMENT OF

OPIOID-INDUCED CONSTIPATION

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EDUCATIONAL CONTENT COMMITTEE

Bruce Chamberlain, MD, FACP

Director, Palliative Consulting
Medical Director, Sunrise Hospice, Orem, UT

Disclosures: Nothing to disclose **Resolution:** N/A

Gail Austin Cooney, MD, FAAHPM

Director & Medical Director Emeritus
Sari Asher Center for Integrative Cancer Center
West Palm Beach, FL
President Elect - American Academy of Hospice and Palliative Medicine

Disclosures: Non-CME Speaker: Honorarium-Wyeth; JPM Supplement: Editorial Stipend – Wyeth

Resolution: Input was restricted to reviewing content for clinical accuracy. Input was screened for bias by non-conflicted faculty. Bias was not detected.

Ricardo Alberto Cruciani, MD, PhD

Associate Professor of Clinical Neurology,
The Saul R. Korey Department of Neurology
Assistant Professor, Department of Anesthesiology
Albert Einstein School of Medicine Yeshiva University, New York, NY

Disclosures: Non-CME Speaker: Honoraria – ENDO, Pfizer, Merck; Clinical Trial: Research Support – Cephalon, FRALEX, GW Pharmaceuticals, Abbott; Pain Course Organizer/Speaker – Grupo Ferret (Spain), Laboratories Nolver (Venezuela)

Resolution: Input related to pain management and consequences of not treating OIC considered. Other Input screened for bias by non-conflicted faculty. Bias was not detected.

Janice A. Knebl, DO, MBA, FACOI, FACP, CMD

Dallas Southwest Osteopathic Physicians' Endowed Chair
in Clinical Geriatrics, Professor of Medicine and Chief, Division of Geriatrics, General Internal Medicine and Endocrinology, Department of Medicine
University of North Texas Health Science Center at Fort Worth, Texas

Disclosures: Research support – Elan and Novartis **Resolution:** No conflict identified, N/A

Judy Lundgren, RN, MSN, AOCN®

Past President, Oncology Nursing Society
Radiation Oncology Nurse, Fort Worth, Texas

Disclosures: Nothing to disclose **Resolution:** N/A

LeeAnne Vandergriff, RN, BSN, OCN

Oncology Nurse, Fort Worth, Texas

Disclosures: Nothing to disclose **Resolution:** N/A

Chun-Su Yuan, MD, PhD

Cyrus Tang Professor of Anesthesia & Critical Care Department of Anesthesia & Critical Care Director of the Tang Center of Chinese Herbal Medicine , University of Chicago, Chicago, IL

Disclosures: Consulting Fee-Wyeth

Resolution: Treatment recommendations restricted to complementary and alternative therapies. Other input screened for bias by non-conflicted faculty. Bias was not detected.

OBJECTIVES

After completing this program, participants will be able to:

1. Recognize opioid-induced constipation (OIC) as one of the most common side effects of opioid therapy
2. Identify and implement steps to remove barriers to effectively communicate with patients about OIC and treatment options
3. Determine appropriate prophylactic and prevention measures for individual patients
4. Employ an evidence-based OIC treatment protocol which maintains patient dignity, quality of life and pain control

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Release Date: May 25, 2009

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The University of North Texas Health Science Center is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor continuing medical education for physicians.

PHYSICIAN CREDIT DESIGNATION

The University of North Texas Health Science Center has requested that the AOA Council on Continuing Medical Education approve this program for 1 hour of AOA Category 2B CME credits. Approval is currently pending.

The University of North Texas Health Science Center at Fort Worth designates this educational activity for a maximum of 1 *AMA PRA Category 1 Credit(s)*™.

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The American Academy of Physician Assistants (AAPA), the National Commission on Certification of Physician Assistants (NCCPA), the American Academy of Nurse Practitioners (AANP), the American Council on Nurse Credentialing (ANCC) and most state boards of nursing recognize and accept *AMA PRA Category 1 Credit(s)™* from organizations accredited by ACCME.

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OTHER HEALTH PROFESSIONALS

Other health professionals will receive a certificate of participation for individual reporting.

OPIOID-INDUCED CONSTIPATION: BANISHING A BARRIER TO SUCCESSFUL PAIN MANAGEMENT

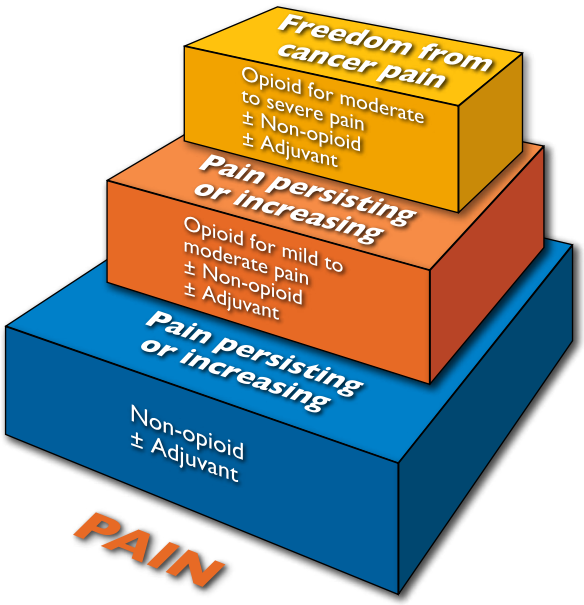
An estimated 10% to 40% of community-living adults experience pain severe enough to affect their quality of life and/or interfere with activities of daily living.[1-5] World Health Organization (WHO) guidelines for the treatment of cancer-related pain (Figure 1) call for immediate oral administration of drugs beginning with nonopioids then move onto mild opioids such as codeine then "strong opioids such as morphine, until the patient is free of pain . . .To maintain freedom from pain, drugs should be given 'by the clock,' that is, every 3-6 hours, rather than 'on demand.' "

The WHO notes that this approach, which focuses on administering the right drug at the right dose at the right time, is inexpensive and 80%-90% effective.[6] Although initially developed to relieve cancer pain, the WHO "ladder of pain" has since been validated for other types of chronic pain.[7-12]

The majority of patients with chronic pain (an estimated 90% in some studies), however, receive some form of opioid therapy.[13]

Figure 1

World Health Organization Pain Relief Ladder



Source: World Health Organization. WHO's pain ladder. http://www.who.int/cancer/palliative/painladder/en/, April 7, 2009.

Since 1997, due in part to efforts by the American Academy of Pain Medicine and the American Pain Society, the use of opioid therapy for pain management has greatly increased.[13, 14] Retail sales of prescribed opioid medications increased 127% between 1997 and 2006, from 50.7 million grams to 115.3 million grams.[14] Opioids are prescribed not just for cancer pain, but are also considered an "effective therapy for carefully selected and monitored patients with chronic noncancer pain." [15]

The number of opioid prescriptions will likely continue to increase in the next 20 years as the population ages. Studies find that between 25% and 50% of community-dwelling older people, and up to 80% of nursing home patients, experience chronic pain necessitating treatment. While older people are more sensitive to the analgesic properties of pain relievers, particularly opioids, they are also more likely to experience side effects.[16]

Whether in a geriatric or younger population, in patients with cancer or non-cancer chronic pain, the most common side effect of opioid therapy is constipation, known as opioid-induced constipation (OIC) or opioid-induced bowel dysfunction (OBD). While functional constipation affects approximately 20% of individuals,[17] OIC affects between 40% and 95% percent of those taking opioids for pain.[13, 18-21] Even a single dose of an opioid can induce constipation.[13] In addition, unlike other opioid-related side effects that improve over time, OIC does not improve and remains chronic as long as the patient receives the medication.[13]

PATHOPHYSIOLOGY OF OPIOID-INDUCED BOWEL DYSFUNCTION

The pathophysiology of OIC is fairly well understood. Normal gastrointestinal (GI) function is regulated by various neurocrine, endocrine, paracrine and autocrine mechanisms. Several endogenous opioids (endorphins, enkephalins, and dynorphins) are present within the digestive tract, where they act upon μ, δ, and κ receptors to inhibit enteric nerve, propulsive motor, and secretory activities.[22]

Exogenous opioids have a high affinity for μ receptors, which play a critical role in the mechanisms that govern GI motility, secretion, fluid absorption, and blood flow.

When occupied by exogenous opioids, motility and mucosal secretion is reduced, fluid absorption increases, and colonic transit is delayed, resulting in constipation.[22]

FUNCTIONAL CONSTIPATION VERSUS OPIOID-INDUCED CONSTIPATION

Constipation is typically either primary, related to lifestyle issues; secondary, related to physiologic or metabolic causes; or iatrogenic, related to pharmacologic agents or medical procedures. The Rome III criteria defines idiopathic constipation in patients who experienced two or more of the following at least 3 days a month in the past 3 months, with symptoms beginning at least 6 months prior to diagnosis: straining, lumpy or hard stools, sensation of incomplete evacuation and/or anorectal obstruction/blockage, and/or manual maneuvers, all at least 25% of the time; and/or fewer than 3 defecations per week.[23]

TABLE 1
FUNCTIONAL CONSTIPATION VERSUS OIC

	Functional	OIC
Hard, Dry Stools	✓	✓
Straining	✓	✓
Incomplete Emptying	✓	✓
Bloating	✓	✓
Abdominal Distension	✓	✓
Gastric Reflux		✓
Cramping		✓
Nausea		✓
Vomiting		✓
Improves Over Time	✓	

Sources: De Luca A, Coupar IM. Insights into opioid action in the intestinal tract. *Pharmacology & Therapeutics*. 1996;69(2):103-115; Fallon MT, Hanks GW. Morphine, constipation and performance status in advanced cancer patients. *Palliat Med*. 1999;13(2):159-160; Goodheart CR LS. Managing opioid-induced constipation in ambulatory-care patients. . *Pain Treat Topics*. 2008. Available at http://www.webcitation.org/5fRvJ7Tv9. Accessed March 21, 2009.

Table 1 depicts the differences between functional constipation (primary or secondary) and OIC. Unlike functional constipation, frequency of bowel movements should not be the primary criteria in assessing OIC severity. Instead, the patient's perception of the impact of the OIC, including related symptoms such as incomplete emptying, nausea, vomiting and gastric reflux, should also be considered.[24-26]

In one survey, 76 patients with non-cancer chronic pain who were treated with opioids had a mean of 5.3 bowel movements compared with 8.7 in a control group. While 8.9% of the control group experienced straining, 40% of the opioid group did. In addition, 45% of the opioid group had hard, lumpy stools compared with 16% of the control group.[19]

The opioid group also had nearly 4 times as many incomplete bowel movements per week as the control group (8.8 vs 36.1). They were also more likely to use a laxative to treat their constipation, but were nearly half as likely to experience a significant benefit from the treatment (84% vs 46%).[19]

IMPACT ON QUALITY OF LIFE

Opioid-induced constipation significantly affects patients' quality of life. Quite often, the effect is so debilitating that patients stop taking or refuse to take their medication. In effect, this means they choose pain over constipation.[18]

When Bell et al surveyed 611 patients with non-cancer chronic pain who took opioids 2 or more days a week as well as laxatives, 81% reported constipation as a side effect of opioids and nearly all said it affected their quality of life. More than half said the effect on their quality of life was "moderate-to-great or great." The condition also affected their activities of daily living. [18]

To relieve their constipation, one-third reduced the dosage, skipped dosages, or stopped using their medication altogether. Of those who reduced their opioid dose or stopped taking their medication, 92% reported increased pain as a result, pain so severe it impacted their quality of life.[18]

In addition to its effects on quality of life, OIC may also contribute to morbidity and mortality through hemorrhoids, rectal pain and burning, fecal impaction, bowel obstruction or rupture, and death.[13]

Opioid-induced bowel dysfunction is also quite time consuming for the medical professional, with physicians spending an average of 20 to 70 minutes a week and nurses 55 to 120 minutes a week discussing or treating it in their patients.[27]

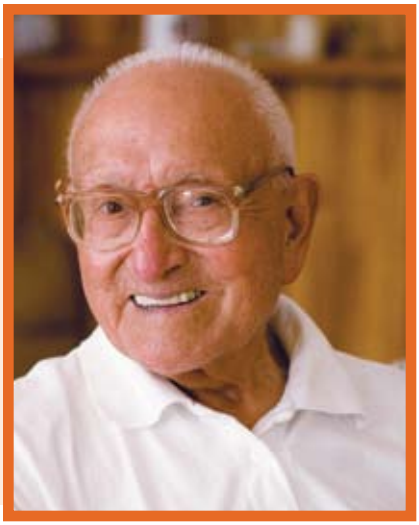
PREVENTING OR MINIMIZING OIC

When prescribing opioids, it is important to reach and maintain a balance between pain relief and side effect-related morbidity. In addition to constipation, other opioid-related side effects include sedation, nausea and vomiting, sleep disturbances, respiratory depression, and cognitive impairment. Long-term effects may include tolerance and physical dependency, immunologic suppression, hormonal changes, and hyperalgia.[13] Thus, it is important that the clinician clearly communicate these potential side effects to the patient before prescribing opioids.

THE PATIENT SPEAKS...

"The (constipation) is terrible. I tell you, at first I guess they didn't tell me about it. And I must have taken (a mild opioid with acetaminophen) for some ungodly reason. I don't know why. But I took it. And I took it for 24 hours or something like that. Anyway, I had such terrible constipation. I mean, it was just absolutely horrendous. Nobody told me anything. . . I tell you, I was pretty upset. I gave up on the pain medicine."[28]

---Patient with lung cancer



To ascertain the effect of the medication on the patient's bowel and abdominal function, the clinician should obtain a baseline bowel history. Ask patients how often they have a bowel movement and have them describe the bowel movement. Many patients, particularly the elderly, consider themselves constipated if they don't have a bowel movement at least once a day.[29] Reassure them that studies find that normal frequency varies from 3 bowel movements a day to 3 a week, so there is no single variable to define constipation strictly on frequency.[23, 30] A bowel movement log, however, can help both patient and clinician objectively evaluate what is "normal' in the patient at baseline and as therapy commences.[16]

A medication history, including vitamins and herbal remedies, should also be obtained. Antihypertensives and antidepressants, for instance, may contribute to constipation. Also consider the patient's reaction to previous opioids when choosing a pain reliever.[31]

In addition, clinicians should counsel patients regarding lifestyle approaches that may minimize constipation. While the evidence is mixed, sparse, or nonexistent for the following, they remain an important part of clinical care. Warn patients, however, that these actions alone are unlikely to improve OIC once it occurs.

Specific lifestyle interventions include:

Hydration	Two to 3 liters a day should be sufficient. This additional hydration is particularly important for those who increase their fiber intake.[31]
Physical Movement	Encourage movement, whether through actual exercise, regular walks, housework, gardening, etc. Inactivity has been linked to reduced colonic motility and regular exercise has been shown to prevent functional constipation. [31-33]
Toileting Routine and Privacy	Counsel patients on the importance of following a regular toileting routine, i.e., sitting on the toilet at the same time every day regardless of the urge to defecate. Privacy is also important.[31]

The discussion prior to commencing opioid therapy should include a plan for follow-up communication, whether in the office or over the telephone, to assess the response to the medication. Ideally, this should occur 1 to 2 weeks after opiate initiation, then every 3 months thereafter to assess pain control, side effects, patient function and behavior.[29]

While opioid titration does not appear to affect constipation, it can help minimize other side effects. In addition, it provides an opportunity to identify constipation as a problem early in the course of treatment before it becomes severe and more

difficult to treat. [29] It is important, however, that the patient understand why titration is necessary since it may delay complete pain relief.[29]

Figure 2 lists questions that the physician or nurse can ask to elicit information about constipation, a discussion patients may be embarrassed to initiate. Some patients may be concerned that "complaining" about constipation could interfere with pain relief; older patients may view constipation as a normal part of aging. If patients are unable to communicate directly, the clinician should discuss the issue with the caregiver. [29]

FIGURE 2
QUESTIONS TO ASSESS FOR OPIOID-INDUCED CONSTIPATION

- Do you feel more constipated than normal?
- When was your last bowel movement?
- Can you describe the consistency?
- Do you see any blood or mucus in the stool?
- Has there been a change in the frequency or type of bowel movement you have?
- How does it feel during a bowel movement? Pain? Straining?
- How do you feel after defecation? Completely empty?
- When did the change occur?
- What are you doing about it?

During the discussion, listen for clues that may be more representative of OIC than frequency, including cramping, hard, small stools, and significant straining. Also evaluate any reports of diarrhea, which could result from stool leaking around a fecal impaction, rule out impaction and obstruction, and treat any secondary contributors to the constipation.[29, 34, 35]

Also consider prophylactic bowel management. While the appropriate use of prophylaxis will vary by patient, it is generally recommended. A typical prophylaxis regiment is one dose of senna at bedtime and docusate 100 mg bid, adding dosage or therapies as needed.[29, 36]

EVIDENCE-BASED PRACTICE

RECOMMENDATION 1

Opioid-induced constipation or bowel dysfunction should be defined by both quantitative and qualitative criteria, including its impact on the patient's quality of life. Patient/physician communication regarding the likelihood of OIC, prevention, treatment options, and treatment efficacy should be incorporated into the overall plan for pain management.

Sources: Larkin PJ, Sykes NP, Centeno C, et al. The management of constipation in palliative care: clinical practice recommendations. *Palliat Med*. 2008;22(7):796-807; Woolery M, Bisanz A, Lyons HF, et al. Putting evidence into practice: evidence-based interventions for the prevention and management of constipation in patients with cancer. *Clin J Oncol Nurs*. 2008;12(2):317-337. Learning Experience Architectural Planning (LEAP) Group. Opioid Induced Constipation Dallas, Texas. February 17, 2009.

TREATING OPIOID-INDUCED CONSTIPATION

The goals of treatment for OIC are to increase motility and create a softer stool while maintaining or improving the patient's quality of life.[29]

While there is little clinical evidence regarding the efficacy of laxatives in the treatment of OIC, they still provide the mainstay of treatment. Laxatives are either stool softeners, stimulant, osmotic, or bulking. Table 2 depicts the various types.

TABLE 2
LAXATIVES FOR OIC

MEDICATION	MECHANISM OF ACTION	COMMENTS
STOOL SOFTENERS		
Docusate	Softens stool by attracting liquid and fat	Use only in combination with stimulant; will not improve OIC on its own
Lactulose, magnesium sulfate, magnesium hydroxide, sodium sulfate, sorbitol, polyethylene glycol	Attract water into the colon for easier transit	Varied onset of action; magnesium and sodium salts generally work quicker May cause flatulence Long-term or overuse could lead to dehydration and/or electrolyte imbalance
Mineral oil	Lubricates stool for easier transit	**Do not use**; risk of aspiration pneumonia, particularly in the elderly
STIMULANTS		
Bisacodyl, cascara sagrada, senna	Stimulates peristalsis, increases secretions, reduces intestinal water and electrolyte absorption	Use with stool softener Cramping and hypokalemia may occur Do not use if fecal impaction or obstruction suspected
BULK-FORMING		
Methylcellulose, psyllium, malt soup extract, calcium polycarbophil	Stimulate water absorption, increasing mass and water content of stool Reduces transit time	Not recommended for OIC because this population may have difficulty in obtaining the necessary of fluid and in engaging in the appropriate level of physical activity. This could lead to impaction and/or obstruction.
RECTAL OPTIONS		
Bisacodyl suppositories Phospho-Soda enemas	Reflex evacuation	Contraindicated in neutropenic and thrombocytopenic patients Reserve for use in patients with fecal impaction or those who cannot swallow oral preparations Consider patient's dignity and quality of life

Sources: Goodheart CR, Leavitt SB. Managing opioid-induced constipation in ambulatory-care patients. *Pain Treat Top*. August 2008. Available at: http://www.webcitation.org/5fRvJ7Tv9. Accessed March 21, 2009. Thomas J. Opioid-induced bowel dysfunction. *J Pain Symptom Manage*. 2008;35(1):103-113. Larkin PJ, Sykes NP, Centeno C, et al. The management of constipation in palliative care: clinical practice recommendations. *Palliat Med*. 2008;22(7):796-807; Miles CL, Fellowes D, Goodman ML, et al. *Cochrane Database Syst Rev*. Laxatives for the management of constipation in palliative care patients. 2006;(4):CD003448; Fine P, Portenoy RK: Opioid analgesia. New York: McGraw Hill, 2004. Xing JH, Soffer EE. Adverse effects of laxatives. *Dis Colon Rectum*. 2001;44(8):1201-9;

Stimulant laxatives are typically the first line pharmacologic option for OIC. Ideally, begin with senna, generally the least expensive option. Possible side effects of stimulant laxatives include cramping, which may be minimized with a divided dose. Other side effects include low potassium levels (hypokalemia) and, possibly, enteric nervous system damage or melanosis coli, a usually benign black pigmentation of the colon wall.[37]

Although stimulant laxatives are often given in conjunction with stool softeners, a recently published study comparing a senna laxative alone with senna plus docusate in 60 hospitalized cancer patients found the senna-only protocol resulted in more bowel movements than the combined bowel protocol ($P<0.05$). However, more patients in the senna-only group experienced diarrhea than in the combination group.[38]

NON-LAXATIVE APPROACHES

Opioid Rotation: For patients in whom laxatives are ineffective, consider opioid rotation. Several studies find less constipation in patients receiving transdermal fentanyl than in those receiving oral morphine or oxycodone, likely related to the ability of transdermal opioids to bypass intestinal opioid receptors.[39] Staats et al evaluated claims data from 1,836 adult Medicaid patients with cancer and non-cancer chronic pain to determine the incidence of constipation in patients receiving 1 of 3 long-acting opioids: transdermal fentanyl, oxycodone HCl controlled-release (CR), or morphine CR. When adjusted for race, supplemental opioid use, and days of opioid exposure, the risk of constipation was 78% higher in the oxycodone CR group and 44% higher in the morphine CR group ($P = 0.2242$) compared with the transdermal fentanyl group.[40]

Radbruch et al also found lower rates of constipation with transdermal fentanyl compared with oral morphine CR. They conducted an open-label trial in 46 patients who received oral morphine for 30 days, followed by transdermal fentanyl for 30 days. Thirty-nine patients were switched to fentanyl; 23 completed the study. After the switch, 22%-48% of the patients required laxatives compared with 78-87% while taking morphine. However, total bowel movements did not change and patients required higher levels of rescue medication with fentanyl than with morphine.[41]

2 EVIDENCE-BASED PRACTICE

RECOMMENDATION 2

When opioids are prescribed, educate patients regarding lifestyle approaches that may prevent OIC or reduce its severity. Clinicians should also begin laxatives (bowel routine) prophylactically.

Sources: Chou R, Fanciullo GJ, Fine PG, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain.* Feb 2009;10(2):113-130; Larkin PJ, Sykes NP, Centeno C, et al. The management of constipation in palliative care: clinical practice recommendations. *Palliat Med.* Oct 2008;22(7):796-807; American Geriatrics Society. The management of chronic pain in older persons. *Geriatrics.* 1998;53 Suppl 3:S8-24.

Level/type of evidence: Strong recommendation; moderate quality evidence; expert clinical opinion

A meta-analysis of opioids and constipation noted a "significant advantage" in terms of constipation between transdermal opiates (fentanyl and buprenorphine) and slow-release oral morphine. It also found that patients preferred transdermal fentanyl, most likely because of its impact on their quality of life.[42]

Lubiprostone: Lubiprostone is a selective chloride channel-2 activator currently indicated for chronic idiopathic constipation in adults and for irritable bowel syndrome in women that is sometimes used off-label for OIC. It increases secretion of chloride-rich enteric fluid with no concurrent impact on serum chloride, sodium, or potassium. The increased secretion leads to improved gut motility and stool passage, reducing straining, bloating and constipation.[43] Clinical trials in patients with constipation-predominant irritable bowel syndrome show significant improvements in abdominal bloating and discomfort, bowel movements and the use of rescue medication compared with placebo.[44]

The most common adverse effect is nausea, occurring in about one-third of patients. The nausea appears to be dose related and may be mitigated by taking lubiprostone with food. Other adverse effects include diarrhea and headache and, less commonly, abdominal distention and pain, dyspnea and chest tightness.[44-46] A phase III trial evaluating lubiprostone for use in OIC is ongoing.[47]

OPIOID ANTAGONISTS

Another option for laxative-refractory OIC is opioid antagonists, designed to block peripheral "μ" opioid receptors. Naloxone was the first such compound developed. While it did provide some relief from OIC, it has systemic properties and crosses the blood/brain barrier, leading to opioid withdrawal.[48] Nalmefene, another opioid antagonist, has a longer elimination half life and, thus, a more prolonged effect, but it, too, led to opioid withdrawal and reversed analgesia, as did nalmefene glucuronide, an inactive metabolite of nalmefene.[48]

More recently, novel peripherally acting opioid antagonists have been developed. Methylnaltrexone, a naltrexone derivative, received marketing approval in 2008 for the treatment of OIC in laxative-refractory patients in palliative care. It was developed by adding a methyl group to nitrogen to reduce naltrexone's lipid solubility. Thus, methylnaltrexone does not cross the blood/brain barrier, maintaining strong antagonistic effects at the μ receptor level, with some affinity for the κ receptor but no affinity for "δ" receptors.[49]

Efficacy and safety was demonstrated in 2 randomized, double-blind clinical trials in patients with a median age of 68 and a life expectancy less than 6 months. Most had cancer and all were receiving palliative opioid therapy. All had OIC, defined as less than 3 bowel movements in the preceding week, or no bowel movements for 3 or more days. In the first dose-defining study, patients who received a single dose of methylnaltrexone (0.15 mg/kg or 0.3 mg/kg) showed similar rates of rescue-free laxation within 4 hours of administration (62% and 58% respectively) compared with a 14% rate for the placebo group ($P < 0.0001$).[50]

3 EVIDENCE-BASED PRACTICE

RECOMMENDATION 3

Patients with opioid-induced constipation should be initially treated with a stool softener and stimulant laxative (senna preferred). Increase the dose as needed and, if necessary, add an osmotic laxative. Avoid bulking agents in those unable to consume large amounts of fluid. Consider switching opioids or adding lubiprostone or methylnaltrexone in laxative-resistant OIC.

Types/levels of evidence: Likely to be effective; clinical experience, randomized clinical trials

Sources: Donner B, Zenz M, Tryba M, et al. Direct conversion from oral morphine to transdermal fentanyl: a multicenter study in patients with cancer pain. *Pain.* 1996;64(3):527-534; Learning Experience Architectural Planning (LEAP) Group. Opioid Induced Constipation Dallas, Texas. February 17, 2009; Radbruch L, Sabatowski R, Loick G, et al. Constipation and the use of laxatives: a comparison between transdermal fentanyl and oral morphine. *Palliat Med.* 2000;14(2):111-119; Staats PS, Markowitz J, Schein J. Incidence of constipation associated with long-acting opioid therapy: a comparative study. *South Med J.* 2004;97(2):129-134.Thomas J, Karver S, Cooney GA, et al. Methylnaltrexone for Opioid-Induced Constipation in Advanced Illness. *N Engl J Med.* 2008;358(22):2332-2343.

The second trial compared methylnaltrexone 0.15 mg/kg and 0.30 mg/kg and placebo given every other day for 2 weeks. Patients receiving methylnaltrexone had a significantly higher rate of laxation within 4 hours of the first dose compared with those receiving placebo (48% vs 16%, $P<0.0001$). They also had higher rates of laxation within 4 hours after at least 2 of the first 4 doses (52% vs 9%, $P<0.0001$). Approximately one-third of patients overall reported a bowel movement within 30 minutes of the initial dose. There was no change in the need for pain medication or in pain scores. [51]

The most commonly reported adverse effects in the studies were orthostatic hypotension (dose-limiting), abdominal cramps, flatulence, abdominal pain, and nausea. Methylnaltrexone has not been studied in trials lasting more than 4 months.[50, 51] it is given by daily subcutaneous injection.[50]

Alvimopan. Similar to methylnaltrexone, alvimopan is a peripherally acting opioid antagonist that does not cross the blood/brain barrier and has little-to-no effect on analgesia. Alvimopan is indicated for postoperative ileus in hospitalized patients only and is administered orally twice daily. It has a very high binding affinity for μ receptors. In studies on healthy volunteers, alvimopan completely reversed the increased gastrointestinal transit time resulting from morphine or codeine.[52]

Webster "et al" evaluated alvimopan in 522 patients with non-cancer chronic pain receiving 30mg/day or more oral morphine [53] Patients were randomized to either 0.5 mg bid, 1 mg qd, 1 mg bid, or placebo for 6 weeks. Patients receiving the study drug significantly increased the frequency of bowel movements with all 3 dosages, with alvimopan 1 mg bid resulting in a more than twofold increase ($P<0.001$). All other OBD symptoms, including incomplete evacuation, straining, abdominal bloating, stool consistency, and appetite suppression also improved, with benefits sustained throughout the study. Dosage-related adverse effects include abdominal pain, nausea, and diarrhea, but there was no evidence of analgesia reversal. Overall, the authors concluded that the alvimopan 0.5mg bid dosage "demonstrated the best benefit-to-risk profile for managing OBD."

A long-term study evaluated alvimopan in 805 patients with non-cancer chronic pain over 12 months. Two thirds were randomized to .05 mg bid, one-third to placebo. While both groups experienced similar adverse effects, 2.8% of the alvimopan group exhibited neoplasms versus 0.7% of the placebo group, and 7 myocardial infarctions (MI) compared with none in the placebo group. These occurred within the first 12 weeks of treatment. Thus, they did not appear to be related to the length of treatment. [54]

COMPLEMENTARY AND ALTERNATIVE THERAPIES

There is little published clinical evidence of the efficacy of complementary and alternative therapies in OIC or, in fact, any type of constipation.[55] The greatest body of evidence attests to the benefits of hypnotherapy and relaxation techniques in patients with IBS.[56] However, since IBS is strongly related to stress, it is doubtful that these approaches would have much effect on OIC, which, as noted earlier, primarily results from the specific mechanism of action of opioids.

Wenk et al evaluated the effects of baker's yeast in an open-label study involving 17 cancer patients upon opioid initiation, 13 of whom were already constipated. Patients received an initial dose of 6g, doubled daily until laxation occurred. Eleven patients had bowel movements with no additional laxative required. The authors hypothesize that brewer's yeast triggers a fermentation process in the intestine leading to water absorption in the lumen.[57]

CONCLUSION

Opioid-induced constipation and bowel dysfunction affects up to 90% of patients who receive opioid therapy for chronic pain. Unlike other opioid-related side effects, it is not dose-dependent nor does it resolve over time. Instead, it remains a significant burden on patients with chronic pain, leading some to stop taking opioids even when the pain returns.

Clinicians who work with chronic pain patients should be aware of the prevalence of OIC and should communicate the risk when prescribing opioids. Prophylactic bowel management combined with lifestyle approaches such as hydration, exercise, and regular toileting efforts may prevent OIC or reduce its severity. If OIC occurs, stimulant laxatives combined with stool softener should be the first-line treatment. In patients who do not respond, an osmotic laxative may be added. Laxative-refractory patients may require a different opioid and/or the addition of lubiprostone or a peripherally acting opioid antagonist.

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POST TEST

Please record your answers in the "POST-TEST RESPONSES" box located at the bottom right of the credit request form.

1. When you prescribe opiates, how often do you warn patients about constipation as a likely side effect?

1. Almost Always
2. Most of the time
3. Infrequently
4. Almost Never

2. Under the ROME criteria, chronic constipation is defined when a patient defecates...

1. Fewer than 2 times a week
2. Fewer than 3 times a week
3. Fewer than 4 times a week
4. Fewer than 5 times a week

3. Titrating dosages of opioids can prevent constipation

1. True 2. False

4. Lubricant laxatives, such as mineral oil, are safe and efficacious and should be considered a first-line therapy in the treatment of OIC.

1. True 2. False

5. Rotating opioids might be an effective strategy for reducing constipation in patients for whom laxatives are ineffective.

1. True 2. False

6. Many complementary and alternative therapies have shown benefit in OIC in recent studies.

1. True 2. False

7. Case Study – PAUL

On disability as a result of a work-related injury 3 years ago

- Diagnosed with a "failed back" after a 10 foot fall from a roof on a construction job
- Underwent lumbar laminectomy 2 year ago with limited initial response but symptoms have all returned.
- He is in chronic pain which he rates as averaging 8-9 out of 10
- He is overweight due to inactivity, and poor eating habits. 300 lbs, BMI 32
- He is depressed due to his chronic pain and poor self image
- He is beginning to experience some marital problems related to his inability to support the family and the changes in his personality since the injury.
- He is currently prescribed acetaminophen with hydrocodiene 500/5 one or two tabs every four hours as needed. He takes six to eight a day and frequently runs out before he is able to refill his prescription.
- He has frequent ED visits for pain and has been labeled a "drug seeker" by the hospital and several physicians.

- He sees a new doctor who starts him on extended release morphine which is titrated up to 60mg twice a day with significant improvement in his symptoms
- He now presents to the clinic with complaint of severe constipation that has developed over the past few weeks, associated with bloating, abdominal discomfort, few hard stools.

Based on current evidence and guidelines, what therapeutic path is most appropriate?

1. Complementary and Alternative Therapies
2. Lifestyle changes with Physical Therapy
3. Opiate rotation with a laxative
4. Continue to increase dosage of current opiate

UNIVERSITY of NORTH TEXAS HEALTH SCIENCE CENTER
Professional and Continuing Education

CME/CE Credit Request Form

complete online at www.RegisterWithUNT.com

Activity Title:	Management of Opioid-Induced Constipation
Dates Valid:	May 25, 2009 - May 31, 2010
Max Credits Available	1 Category 1 *PRA AMA Credit*™, 1 Hour Category 2B, AOA

INSTRUCTIONS: Please complete this form and return it to the address or fax number below.

PLEASE PRINT CLEARLY

FULL NAME		**DEGREE(s)**	
LAST 4 DIGITS OF SSN (for tracking)		**or AOA Number (if applicable)**	**AAFP Number**
MAILING ADDRESS			
PHONE		**FAX**	
E-MAIL			

CREDIT REQUEST (please check one):

☐ I request a certificate of completion for this activity

SIGNATURE **DATE**

PROGRAM EVALUATION

Please rate to what extent this activity achieved its objectives:

Scale: P=Poor F=Fair G=Good VG=Very Good E=Excellent

	OBJECTIVES	**P**	**F**	**G**	**VG**	**E**
1	Recognize opioid-induced constipation (OIC) as one of the most common side effects of opioid therapy	1	2	3	4	5
2	Identify and implement steps to remove barriers to effectively communicate with patients about OIC and treatment options	1	2	3	4	5
3	Determine appropriate prophylactic and prevention measures for individual patients	1	2	3	4	5
4	Employ an evidence-based OIC treatment protocol which maintains patient dignity, quality of life and pain control	1	2	3	4	5
	CONTENT					
5	Please rate to what extent this activity is fair and balanced	1	2	3	4	5
6	What is the likelihood that you will implement a change in your practice based on information presented at this activity?	1	2	3	4	5
7	What is your OVERALL rating of this activity?	1	2	3	4	5
	PRACTICE Please tell us how the information presented in this monograph will help you in your daily clinical practice.					
8	I am better equipped to educate my patients regarding the prevalence of opioid-induced constipation during opioid therapy.	1	2	3	4	5
9	I am better equipped to help my patients set realistic expectations during treatment.	1	2	3	4	5
10	I am better equipped to recognize and diagnose opioid-induced constipation.	1	2	3	4	5
11	I am better equipped to educate my patients on pharmacologic and non-pharmacologic therapies for opioid-induced constipation	1	2	3	4	5

POST-TEST RESPONSES

Q#	**A / True**	**B / False**	**C**	**D**
1	1	2	3	4
2	1	2	3	4
3	1	2		
4	1	2		
5	1	2		
6	1	2		
7	1	2	3	4

Please provide us with comments and suggestions on the reverse side.

Mail To:
PACE Office/UNTHSC
3500 Camp Bowie Blvd
Fort Worth TX 76107
(see reverse for self-mailer instructions)

Or Fax To: 817-735-2598

2. fold this flap second on dotted lines, covering the comments, seal with tape and add postage to mail

Place postage here

PACE Office/UNTHSC
3500 Camp Bowie Blvd
Fort Worth TX 76107

1. fold this flap first on dotted line, then fold the next flap over it...

COMMENTS/SUGGESTIONS

PAIN & CONSTIPATION ASSESSMENT

Does Not Interfere → Completely Interferes

0	1	2	3	4	5	6	7	8	9	10

Please rate your pain by assigning a number that best describes your pain at its WORST in the past 24 hours.

0	1	2	3	4	5	6	7	8	9	10

Please rate your pain by assigning a number that best describes your pain ON THE AVERAGE.

0	1	2	3	4	5	6	7	8	9	10

How much during the last 24 hours has pain interfered with your daily activities?

0	1	2	3	4	5	6	7	8	9	10

How much during the last 24 hours has pain interfered with your mood?

0	1	2	3	4	5	6	7	8	9	10

How much during the last 24 hours has constipation interfered with your daily activities?

0	1	2	3	4	5	6	7	8	9	10

How much during the last 24 hours has constipation interfered with your mood?

0	1	2	3	4	5	6	7	8	9	10

How much during the last 24 hours has constipation interfered with over all quality of life?

0	1	2	3	4	5	6	7	8	9	10

MANAGEMENT OF OPIOID INDUCED CONSTIPATION

BOWEL HISTORY

- What is normal for you?
- Do you feel more constipated?
- When did it start?
- When was your last bowel movement?
- Can you describe the consistency?
- Has there been a change in the frequency or type of BM?
- How does it feel during a BM?
- How do you feel after defecation?
- When did the change occur?
- What are you doing about it?
- Have you skipped doses of any medication to get relief?
- Are you taking a vitamin or supplement to help?

WORDS TO USE

bloating, stomach "sticking out", gas, crampy, nausea, vomiting, heartburn, straining, not empty, hurts, dry, crampy, stuck

Opioid Induced Constipation Learning Experience Architectural Planning (LEAP) Group February 17, 2009. Dallas, Tx;

Larkin PJ, Sykes NP, Centeno C, et al. The management of constipation in palliative care: clinical practice recommendations. Palliat Med. 2008;22(7):796-807;

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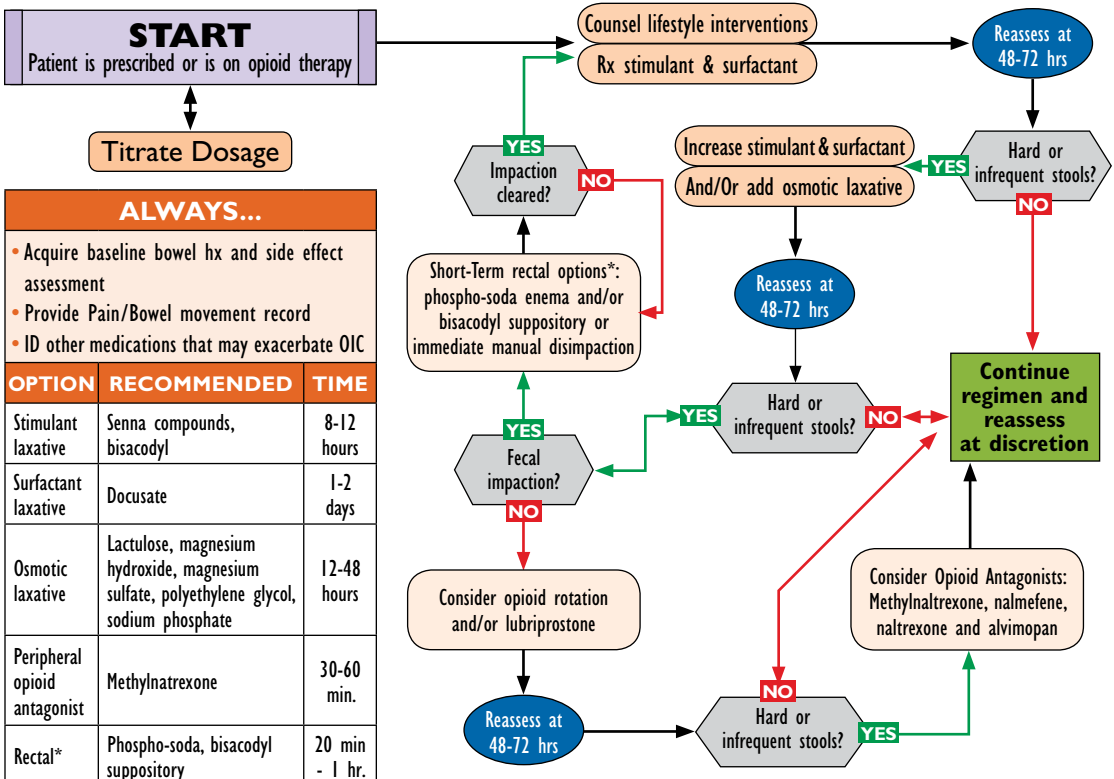
OPIOID INDUCED **CONSTIPATION** MANAGEMENT • QUICK REFERENCE CARD



ALWAYS...

- Acquire baseline bowel hx and side effect assessment
- Provide Pain/Bowel movement record
- ID other medications that may exacerbate OIC

OPTION	RECOMMENDED	TIME
Stimulant laxative	Senna compounds, bisacodyl	8-12 hours
Surfactant laxative	Docusate	1-2 days
Osmotic laxative	Lactulose, magnesium hydroxide, magnesium sulfate, polyethylene glycol, sodium phosphate	12-48 hours
Peripheral opioid antagonist	Methylnatrexone	30-60 min.
Rectal*	Phospho-soda, bisacodyl suppository	20 min - 1 hr.
Bulk	Not recommended	

*Contraindicated in patients w/neutropenia & thrombocytopenia

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Woolery, M. et al. Prevention and management of constipation. Clinical Journal of Oncology Nursing 2008; 12, (2):317-337.
Larkin PJ, Sykes NP, Centeno C, et al. The management of constipation in palliative care: clinical practice recommendations. Palliat Med. 2008;22(7):796-807