Managing the Gastrointestinal Effects of Opioids

Learning Objectives
Upon completion of this activity, the participant will be better prepared to:

- Discuss the frequency, impact, and importance of the gastrointestinal side effects of opioids, with a particular focus on opioid-induced constipation, nausea, and vomiting
- Describe the pathophysiology of opioid-induced gastrointestinal adverse effects
- Identify contemporary and future management modalities for opioid-induced constipation, nausea, and vomiting

Credit Designation
Purdue University College of Pharmacy designates this enduring material for a maximum of 1.0 AMA PRA Category 1 Credit(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Physician Accreditation Statement
This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Purdue University College of Pharmacy and the Gi Health Foundation. Purdue University College of Pharmacy, an equal access/equal opportunity institution, is accredited by the ACCME to provide continuing medical education for physicians.

Disclosure of Conflicts of Interest
All faculty and staff involved in the planning or presentation of continuing education activities sponsored/provided by Purdue University College of Pharmacy are required to disclose to the audience any real or apparent commercial financial affiliations related to the content of the presentation or enduring material. Full disclosure of all commercial relationships must be made in writing to the audience prior to the activity. The Gi Health Foundation staff and Purdue University College of Pharmacy staff have no relationships to disclose.

Introduction
Chronic use of opioids to manage pain is common in clinical practice,1-3 with approximately 3% of adults in the United States currently receiving long-term opioid therapy for noncancer pain.4 In the United States, opioid use has increased sharply over the past decade. Currently, over 235 million prescriptions are written for opioids each year; approximately 20% of these prescriptions are for ≥30 days, suggesting that they are written for patients with chronic pain.5 Among patients who require chronic opioids, the balance between the incidence and severity of side effects and analgesia plays an important role in the success or failure of adequate pain management. Side effects can have a dramatic negative impact on quality of life as a result of both the direct impact of side effects and the subsequent need to limit adequate dosage. In fact, concern about potential risks of side effects is an important reason for not prescribing adequate amounts of pain medications for patients with pain.6 Current clinical practice guidelines recognize the critical need for titration of pain medications to achieve analgesia with tolerable side effects.

The gastrointestinal (GI) tract is a particularly important source of opioid-related side effects. The most common GI side effects include constipation, nausea, vomiting, and dyspepsia.7 Opioids interfere with GI motility and secretion through activation of μ-opioid receptors located in the submucosa and through effects on enteric and spinal neurons.8 Nearly all patients develop some degree of constipation after opioid initiation or dose increases, and—while most of the side effects of opioids resolve over time—resolution of the constipating effects of these agents often does not occur with continued exposure.9 The symptoms associated with opioid-induced constipation can have a profound impact on quality of life; so much so that some patients prefer to discontinue analgesic therapy rather than suffer from the discomfort arising from constipation.10 Nausea and vomiting, albeit less frequent than constipation, are ranked among the most highly distressing side effects of opioids by patients.11 Patients taking opioids may also suffer from decreased gastric emptying (often leading to gastroesophageal reflux and heartburn), abdominal cramping, spasms, bloating, delayed GI transit, and hard, dry stools.8,12,14 Understanding the incidence, severity, and mechanisms of the GI side effects of opioids can help the physician develop an optimal management plan for patients who require these agents.15
Effects of Opioids

FREQUENCY AND IMPACT OF OPIOID-INDUCED GI EFFECTS
A recent Cochrane systematic review of adults who had taken opioids for noncancer pain for at least 6 months found the most common GI complications to be constipation, nausea, and dyspepsia, with 22.0% (95% CI, 15.2-32.8) of patients discontinuing therapy due to adverse effects. In a recent survey of patients with noncancer pain taking a median daily dose of morphine-equivalent 127.5 mg (range 7.5-600 mg), the most commonly reported GI side effect was constipation (46.9%; 95% CI, 36.8-57.3), followed by gastroesophageal reflux disease (33%; 95% CI, 23.5-42.9), nausea (27%; 95% CI, 17.2-35.3), and vomiting (9%; 95% CI, 17.2-35.3). A multinational study involving 322 patients taking oral opioids and laxatives found constipation was most often reported as severe, with 45% reporting <3 bowel movements (BMs) per week. Importantly, nearly a third of patients altered the dose of their opioid therapy to alleviate constipation.

While less common than constipation, nausea and vomiting are ranked by patients as highly distressing side effects of opioids. Importantly, in contrast to opioid-induced constipation, which is chronic, nausea and vomiting, as side effects of opioids, are usually transient.

PATHOPHYSIOLOGY OF OPIOID-INDUCED GI EFFECTS
The physiology of opioid receptors has been reviewed extensively elsewhere. Endogenous opioids, such as metenkephalin, leu-enkephalin, β-endorphin, and dynorphin, inhibit both propulsive motor and secretory activities. The activity of opioids in the gut is mediated by µ-, δ-, and κ-opioid receptors, the distribution of which varies within the layer of the GI tract. In particular, µ-opioid receptors—through which most opioid analgesics function—are present on the myenteric and submucosal neurons and on immune cells in the lamina propria and are present in the highest concentrations in the stomach and proximal colon. Through their effects on enteric neurons, opioids delay intestinal transit by stimulating nonpropulsive motility, increasing intestinal tone, and stimulating the pyloric and ileocecal sphincters. Opioid agonists also stimulate fluid absorption in the gut by increasing the contact time for absorption and stimulating mucosal sensory receptors; these agents also appear to inhibit chloride secretion by depressing the excitation of cholinergic secretomotor neurons in the enteric nervous system.

MANAGEMENT OPTIONS FOR OPIOID-INDUCED CONSTIPATION
Since the dose that produces constipation is generally only 25% of that required to provide adequate analgesia, simple opioid dose reduction is generally not an effective option for the management of opioid-induced constipation. Thus, alternative options for managing constipation must be explored.

Opioid Rotation
Opioids have slightly different propensities to cause constipation in individual patients; thus switching opioids—or “opioid rotation”—may be used as a strategy to relieve constipation or other adverse effects. A prospective trial enrolled 118 cancer patients at a single institution who underwent opioid switching due to an unacceptable balance between analgesia and adverse effects, despite symptomatic treatment of side effects. Eighty-one percent of substitutions were successful in finding a more acceptable balance between analgesia and adverse effects after the first switch in opioids, and an additional 6% responded after a second switch in therapy. The mean time required to identify an appropriate dose after switching was 3.2 days and time to hospital discharge was directly related to the time needed to achieve dose stabilization. While this small trial suggests that algorithm-guided opioid rotation can be effective, prospective randomized trials regarding the efficacy and cost of this strategy are lacking, and caution is necessary as equianalgesic doses can vary from person to person. At present, no equianalgesic tables are available that apply directly to opioid rotation, although efforts are underway to generate appropriate algorithms to guide switching in light of current relative potency data in the setting of the opioid-tolerant patient. In the absence of such a table, an ad hoc panel of experts developed a guideline for opioid rotation based on the best evidence available and expert opinion. This guideline (Box 1) uses existing equianalgesic tables as a starting point, but uses a 2-step process to address the risks inherent in opioid rotation: First, an “automatic” safety factor should be calculated.

Accredited by: Purdue University

This material is supported by an educational grant from Salix Pharmaceuticals, Inc.

Sponsored by: Gastrointestinal Health Foundation

Box 1. Guidelines for Opioid Rotation Based on the Recommendations of an expert Ad Hoc Panel Convened to Develop Recommendations for Opioid Rotation

<table>
<thead>
<tr>
<th>STEP 1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Calculate the equianalgesic dose of the new opioid based on the equianalgesic table</strong></td>
</tr>
<tr>
<td><strong>If switching to an opioid other than methadone or fentanyl, identify an “automatic dose reduction window” of 25% to 50% lower than the calculated equianalgesic dose</strong></td>
</tr>
<tr>
<td>- If switching to methadone, the window is 75% to 90% lower than the calculated equianalgesic dose. For individuals on very high opioid doses (eg, &gt;1000 mg morphine equivalents/d), caution should be exercised in converting to methadone at doses of 100 mg or greater per day; consider inpatient monitoring, including serial electrocardiogram monitoring</td>
</tr>
<tr>
<td>- If switching to a transdermal fentanyl, calculate dose conversions based on the equianalgesic dose ratios included in the package insert for these formulations</td>
</tr>
<tr>
<td>- Select a dose closer to the lower bound (25% reduction) or the upper bound (50% reduction) of this automatic dose-reduction window on the basis of a clinical judgment that the equianalgesic dose table is relatively more or less applicable, respectively, to the specific characteristics of the opioid regimen or patient</td>
</tr>
<tr>
<td>- Select a dose closer to the upper bound (25% reduction) of the reduction if the patient is receiving a relatively high dose of the current opioid regimen, is not Caucasian, or is elderly or medically frail</td>
</tr>
<tr>
<td>- Select a dose closer to the lower bound (25% reduction) of the reduction if the patient does not have these characteristics or is undergoing a switch to a different route of systemic drug administration using the same drug</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>STEP 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Perform a second assessment of pain severity and other medical or psychosocial characteristics to determine whether to apply an additional increase or decrease of 15% to 30% to enhance the likelihood that the initial dose will be effective for pain, or conversely, unlikely to cause withdrawal or opioid-related side effects</strong></td>
</tr>
<tr>
<td>- Have a strategy to frequently assess initial response and titrate the dose of the new opioid regimen to optimize outcomes</td>
</tr>
<tr>
<td>- If a supplemental “rescue dose” is used for titration, calculate at 5% to 15% of the total daily opioid dose and administer at an appropriate interval; if an oral transmucosal fentanyl formulation is used as a rescue dose, begin dosing at one of the lower doses irrespective of the baseline opioid dose</td>
</tr>
</tbody>
</table>
Effects of Opioids

Managing the Gastrointestinal

This safety factor—generally a 25% to 50% reduction in the calculated analgesic dose (with a few exceptions, as outlined in Box 1)—is used because the calculated equianalgesic dose may underestimate the potency of the new opioid due to interindividual variation and incomplete cross-tolerance. Second, an additional dose adjustment of 15% to 30% should be determined after a second assessment of pain severity, other medical or psychosocial characteristics, and adverse effects.

Novel opioids with less constipation

Few studies have directly compared the prevalence of GI side effects among opioids; however, 4 controlled studies found that transdermal fentanyl was associated with less frequent laxative use compared with morphine. A novel, relatively nonconstipating μ-opioid agonist, tapentadol, also inhibits norepinephrine, which is believed to augment its analgesic activity. In a trial conducted in patients with lower back pain, tapentadol extended-release 100 to 250 mg twice daily and oxycodone HCl controlled-release 20 to 50 mg twice daily were both effective in controlling pain; however, the GI side effect profile of tapentadol was substantially better than that seen with oxycodone. Similar results were seen in a trial conducted in patients with moderate-to-severe chronic osteoarthritis-related knee pain.

Adjunctive pharmacologic treatment

Conventionally, opioid-induced constipation is first approached through the use of laxatives. However, only about 50% of patients experience satisfactory relief using this strategy. For this reason, treatment with laxatives often requires frequent dose adjustments, combination therapy, and laxative switching before achieving satisfactory results. Preliminary results from a phase 3 clinical trial with lubiprostone, a type-2 chloride channel activator, approved for use in chronic constipation and IBS with constipation, found that 24 mcg twice daily of oral lubiprostone improved the symptoms associated with opioid-induced constipation during a 12-week trial. The primary end point was overall spontaneous BM (SBM) response rate, defined as having 3 or more SBMs per week for at least 9 weeks and at least 1 additional SBM over the mean baseline. At the end of the 12-week treatment, significantly more patients taking lubiprostone were overall SBM responders compared with those receiving placebo (26.9% vs 18.6%, P =.035). The median time to first SBM was also significantly reduced for patients who received lubiprostone compared with those who received placebo (24.3 vs 38.5 hours, P =.019). Straining, stool consistency, and constipation severity also improved. The adverse events occurring more commonly in the lubiprostone group compared with the placebo group were diarrhea (9.6% vs 1.4%), nausea (8.2% vs 2.7%), and abdominal pain (5.5% vs 0%). There were no serious adverse events.

Naloxone, a competitive antagonist at opioid receptors with much higher affinity for μ receptors relative to both κ- and δ-receptors, has been used to reverse opioid-induced constipation. Naloxone has a low oral systemic bioavailability due to extensive first-pass metabolism; nevertheless, it is still widely distributed throughout the body and central nervous system (CNS), and thus, even when used at low dosage (2 to 4 mg, 3 times daily), analgesia reversal and induction of opioid withdrawal symptoms can occur. For this reason, naloxone should be started at a low dose to minimize the risk of inducing withdrawal symptoms. Recently, combination oxycodone and naloxone prolonged-release tablets have shown improvement in symptoms of constipation without significant reduction in analgesia for up to 52 weeks.

Methylnaltrexone, a quaternary ammonium derivative of naltrexone, is largely restricted to the periphery due to poor lipid solubility; thus, this agent is less likely than naloxone to reverse analgesia and induce opioid withdrawal symptoms. When administered intravenously, infusion of methylnaltrexone has been shown to reverse the constipation induced by methadone, both increasing stool frequency and decreasing orocecal transit time. Methylnaltrexone 0.15 mg/kg, administered subcutaneously every other day for 2 weeks, was examined in 133 patients with advanced illness and opioid-induced constipation who had not responded to ≥3 days of laxatives. The coprimary outcomes of the study were defecation within 4 hours after the first dose of the study drug and defecation within 4 hours after ≥2 of the first 4 doses. In the methylnaltrexone group, 48% of patients had a BM within 4 hours after the first study dose compared with 15% in the placebo group, and 52% had a BM within 4 hours after ≥2 of the first 4 doses compared with 8% in the placebo group (P=.001 for both comparisons) (Figure 1). The response rate remained consistent throughout the 3-month extension trial. Evidence of withdrawal mediated by CNS opioid receptors or changes in pain scores were not observed. Abdominal pain and flatulence were the most common adverse events.

A Primary Outcomes

Figure 1. Primary Outcomes of a Clinical Trial Comparing Methylnaltrexone and Placebo in Patients With Opioid-induced Constipation.

Subcutaneous methylnaltrexone is approved by the FDA for opioid-induced constipation in patients with advanced illness who are receiving palliative care when response to laxative therapy has not been sufficient. This drug is usually dosed once every other day but no more frequently than 1 dose in a 24-hour period. The recommended dose of methylnaltrexone is 8 mg for patients weighing between 38 kg and 62 kg, 12 mg for patients weighing 62 kg to 114 kg, and 0.15 mg/kg for patients outside these ranges. Further studies are needed to identify the optimal dosage of methylnaltrexone for acute opioid use in opioid-naive patients. Results from a 12-week, phase 3 trial in 804 patients with...
chronic noncancer pain and opioid-induced constipation with oral
methylnaltrexone (150 mg, 300 mg, or 450 mg; 4 weeks daily dosing,
followed by 8 weeks PRN dosing) were recently presented. The
primary end point was average percentage of doses per patient
resulting in a rescue-free BM (RFBM) within 4 hours during the once-
daily dosing period. A greater percentage of patients receiving oral
methylnaltrexone (300 mg and 450 mg) compared with placebo met
the primary end point (P < 0.01). Throughout the study, there were
minimal changes from baseline in pain intensity scores regardless of
the treatment group.

Alvimopan is an oral μ-opioid receptor antagonist that does not cross
the blood-brain barrier. Alvimopan is approved by the FDA for
postoperative ileus and is not approved for the management of opioid-
induced constipation; the agent is available only in hospitals that have
registered with and met all the requirements for the Entereg Access
Support and Education Program. Nevertheless, this agent has been
extensively studied for the management of opioid-induced constipation.
In one of the pivotal trials, 522 patients taking ≥30 mg oral morphine
with constipation (ie, <3 SBMs per week) were randomized to 6 weeks
of alvimopan 0.5 mg twice daily, 1 mg once daily, 1 mg twice daily, or
placebo. Alvimopan at all doses tested was associated with a
significant increase in the mean number of SBMs per week over the
first 3 weeks of treatment. Alvimopan was also associated with
improvements in straining, stool consistency, incomplete evacuation,
decreased appetite, and abdominal bloating/discomfort. In this study,
the side effect profile of the 0.5 mg twice-daily dose was similar to
placebo.

Subsequently 2 large, phase 3 clinical trials have been published
comparing alvimopan 0.5 mg once daily, twice daily, or placebo for 12
weeks in noncancer opioid-induced constipation. Only 1 of the 2
met their primary end point (ie, the proportion of patients experiencing
≥3 SBMs per week over the treatment period and an average increase
from baseline of ≥1 SBM), and both studies showed improvement in
straining, stool consistency, incomplete evacuation, and abdominal
bloating/discomfort. Alvimopan did not significantly reverse opioid
analgesia.

Agents under investigation
Naloxegol (formerly known as NKTR-118) is an oral, pegylated naloxol
conjugate for once daily administration that is currently under
investigation for the management of opioid-induced constipation. The
results of 2 phase 3 trials (KODIAC-04 and -05) and a safety extension
trial for naloxegol were recently announced, although they have not yet
appeared in a peer-reviewed publication. Both studies evaluated the
efficacy of 12 weeks of treatment with naloxegol 12.5 mg and 25 mg
compared with placebo; the primary end point was response at 12
weeks (defined as ≥3 SBMs per week, with a ≥1 SBM increase over
baseline for ≥9 of 12 weeks). In KODIAC-04, both the 12.5- and 25-mg
doses of naloxegol demonstrated statistically significant results for the
primary end point (P = .015 and .001, respectively). In KODIAC-05, only
the 25-mg dose was statistically significant (P = .021). Arthralgia was
the only adverse event that occurred at a greater frequency in the
naloxegol 25-mg arm.

MANAGEMENT GUIDELINES
The National Comprehensive Cancer
Network (NCCN) Guidelines
As the mainstay of treatment for cancer pain, the NCCN provides
comprehensive guidance for the management of opioid-induced
constipation and nausea/vomiting. According to these guidelines, a
stimulant laxative, with or without a stool softener (eg, senna, with or
without dioctesate), or polyethylene glycol are appropriate prophylactic
options. Patients should maintain adequate fluid intake and adequate
dietary fiber intake; however, supplemental medicinal fiber, such as
psyllium, is unlikely to control constipation and is not recommended. The
patient should be encouraged to exercise, if possible.

If constipation develops, the patient should be assessed for the cause
and severity of constipation, obstruction should be ruled out, and—if
necessary—other causes of constipation beyond opioid administration
should be addressed. Stool softeners should be titrated as needed with
the goal of 1 nonforced BM every 1 to 2 days. An adjuvant
analgesic should be considered to permit reduction of the opioid dose.
If constipation persists, the patient should be checked for impaction
and the cause of constipation reassessed. Consideration should be given
to adding another agent, such as magnesium hydroxide, bisacodyl,
lactulose, sorbitol, magnesium citrate, or polyethylene glycol, and/or the
use of Fleet, saline, or tap water enemas. In severe cases, a prokinetic
agent such as metoclopramide may be used, although the use of the
agent is limited by the potential for developing neurologic complications,
such as tardive dyskinesia. If response remains insufficient, methylnaltrexone should be considered. Finally, opioid rotation to
potentially less constipating agents, such as fentanyl or methadone,
should be considered.

Patients with nausea should first be assessed for other potential causes,
such as CNS pathology, chemotherapy, radiation therapy, or
hypercalcemia. According to the guidelines, nausea in patients taking
opioids may be prevented by ensuring the patient is having consistent
BM; in patients with a prior history of opioid-induced nausea,
prophylactic treatment with antiemetic agents is highly recommended in
those in whom nausea is determined to be opioid-related. Agents that
can be considered for the management of nausea include (in
alphabetical order) haloperidol, metoclopramide, or prochlorperazine,
although it is important to note that metoclopramide can be associated
with neurologic adverse effects, and both metoclopramide and
prochlorperazine can be associated with hyperprolactinemia. If
response remains insufficient, antiemetics should be administered around the clock for 1 week. Addition of a serotonin antagonist, such as ondansetron or
granisetron, should be considered (although these should be used with
cautions because constipation can be a side effect); dexamethasone can
be considered. Among patients whose nausea persists for ≥1 week, opioid rotation should be considered along with other interventions to
potentially reduce opioid dose.
The American Academy of Pain Medicine (AAPM) 
Chronic Noncancer Pain Guidelines

The AAPM provides general guidelines for the management of the GI effects of opioids in patients with chronic noncancer pain. In older patients or those with preexisting risk factors for constipation, consideration should be given to the routine administration of a prophylactic bowel regimen. Such a regimen should include increased fluid and fiber intake, stool softeners, and laxatives. These guidelines suggest that there is insufficient evidence to recommend oral opioid antagonists to prevent or treat opioid-induced bowel dysfunction; however, they note that randomized trials suggest benefits for these agents over placebo. Nausea and vomiting should be managed with antiemetic therapies, although specific recommendations are not provided.

CONCLUSIONS

Opioids are the foundation of the management of moderate-to-severe pain. Given the aging population and an increasing focus on improved management of pain, it is likely that chronic use of opioids will continue to increase. Constipation is the most common GI side effect of opioid treatment and is one of the few side effects of these agents that does not attenuate over time. For these reasons, it is critical for physicians to recognize the GI side effects of these agents and manage them appropriately. There is a broad range of management strategies for opioid-induced constipation, with stimulant laxatives, with or without stool softeners, as the first-line pharmacologic treatment used in most patients. Unfortunately, these inexpensive and readily available agents rarely provide complete relief from constipation; in these patients, methylnaltrexone or opioid rotation should be considered. With appropriate attention, the impact of constipation and other GI symptoms can be minimized while maintaining adequate pain relief.
Managing the Gastrointestinal Effects of Opioids

References


Managing the Gastrointestinal Effects of Opioids

If you wish to receive acknowledgement of participation for this activity, please fill in your contact information and fax back pages 7-11 to (973) 867-3684.

Please select the one best answer by circling the appropriate letter.

1. Among patients taking opioids for noncancer pain, the reported prevalence of constipation is ____%.
   a. 21.5%
   b. 37.1%
   c. 46.9%
   d. 67.2%

2. Which receptor is the primary receptor through which opioids exert their analgesic and constipating effects?
   a. µ
   b. δ
   c. κ
   d. α

3. Why does cross-tolerance vary among opioids?
   a. Receptor density in the CNS influences relative tolerance to opioids
   b. Splice variants of the opioid receptor bind different opioids with varying affinity
   c. The ratio of µ to κ receptor binding affinity varies among opioids
   d. The ratio of κ to δ receptor binding affinity varies among opioids

4. A safety factor of ____ to ____ reduction in calculated analgesic dose should be used when switching opioids.
   a. 10% to 20%
   b. 25% to 50%
   c. 30% to 60%
   d. 30% to 70%

5. Adjunctive laxative therapy provides adequate relief of opioid-induced constipation in about ____ of patients.
   a. One-quarter
   b. One-third
   c. One-half
   d. Three-quarters

6. Which of the following is a potential adverse effect of metoclopramide?
   a. Tardive dyskinesia
   b. Hypomagnesemia
   c. Severe constipation
   d. Increased risk for infection
7. Which of the following agents may be constipating in patients taking opioids?
   a. Ondansetron
   b. Metoclopramide
   c. Haloperidol
   d. Prochlorperazine

8. The recommended dose of methylnaltrexone for patients who weigh >114 kg is:
   a. 0.05 mg/kg
   b. 0.10 mg/kg
   c. 0.15 mg/kg
   d. 0.20 mg/kg

9. In the pivotal trial of subcutaneous methylnaltrexone, laxation was observed in ____ of methylnaltrexone patients within 4 hours of administration, compared with ____% of placebo patients.
   a. 12.3%, 6.5%
   b. 24.3%, 9.5%
   c. 48.0%, 15.0%
   d. 67.2%, 21.3%

10. Methylnaltrexone is less likely to reverse opioid analgesia because:
    a. The molecule is too large to pass through the blood-brain barrier
    b. The molecule has poor lipid solubility
    c. The molecule does not act directly at opioid receptors
    d. The molecule is nonabsorbable and thus remains restricted to the GI tract
# Managing the Gastrointestinal Effects of Opioids

Purdue University College of Pharmacy respects and appreciates your opinions. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form.

## How well did this activity meet the following learning objectives?

<table>
<thead>
<tr>
<th>Learning Objective</th>
<th>High Impact</th>
<th>Moderate Impact</th>
<th>No Impact</th>
<th>Not Applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discuss the frequency, impact, and importance of the gastrointestinal side effects of opioids, with a particular focus on opioid-induced constipation, nausea, and vomiting</td>
<td>Knowledge</td>
<td>Competence</td>
<td>Performance</td>
<td>Patient Outcomes</td>
</tr>
<tr>
<td>Describe the pathophysiology of opioid-induced gastrointestinal adverse effects</td>
<td>Knowledge</td>
<td>Competence</td>
<td>Performance</td>
<td>Patient Outcomes</td>
</tr>
<tr>
<td>Identify contemporary and future management modalities for opioid-induced constipation, nausea, and vomiting</td>
<td>Knowledge</td>
<td>Competence</td>
<td>Performance</td>
<td>Patient Outcomes</td>
</tr>
</tbody>
</table>

## Impact of the Activity

- Please indicate which of the following American Board of Medical Specialties/Institute of Medicine core competencies were addressed by this educational activity (select all that apply):
  - Patient care or patient-centered care
  - Practice-based learning and improvement
  - Interpersonal and communication skills
  - Employ evidence-based practice
  - Interdisciplinary teams
  - Professionalism
  - Quality improvement
  - Medical knowledge
  - System-based practice
  - Utilize informatics
  - None of the above

- The content of this activity matched my current (or potential) scope of practice.
  - No
  - Yes, please explain

- Was this activity scientifically sound and free of commercial bias* or influence?
  - Yes
  - No, please explain

* Commercial bias is defined as a personal judgment in favor of a specific product or service of a commercial interest.
Managing the Gastrointestinal Effects of Opioids

• The educational activity has enhanced my professional effectiveness in treating patients ........................................... [ ]    [ ]    [ ]    [ ]    [ ]

• The educational activity will result in a change in my practice behavior ................................................................. [ ]    [ ]    [ ]    [ ]    [ ]

• How will you change your practice as a result of participating in this activity (select all that apply)?
  ☐ Create/revise protocols, policies, and/or procedures
  ☐ Change the management and/or treatment of my patients
  ☐ This activity validated my current practice
  ☐ I will not make any changes to my practice
  ☐ Other, please specify: ______________________________

• What new information did you learn during this activity?
  ______________________________________________________________________________________________________

• Please indicate any barriers you perceive in implementing these changes.
  ☐ Lack of experience
  ☐ Lack of resources (equipment)
  ☐ Lack of time to assess/counsel patients
  ☐ Lack of consensus of professional guidelines
  ☐ Lack of opportunity (patients)
  ☐ Lack of administrative support
  ☐ Reimbursement/insurance issues
  ☐ Patient compliance issues
  ☐ No barriers
  ☐ Cost
  ☐ Other ______________________________

• If you indicated any barriers, how will you address these barriers in order to implement changes in your knowledge, competency, performance, and/or patients’ outcomes?
  ______________________________________________________________________________________________________

• Comments to help improve this activity?
  ______________________________________________________________________________________________________

• Recommendations for future CME/CPE topics.
  ______________________________________________________________________________________________________

  To assist with future planning, please attest to time spent on activity:

  I spent ______ hours on this program.
If you wish to receive acknowledgement of participation for this activity, please fill in your contact information and fax back pages 7-11 to (973) 867-3684.

We need current and complete information to assure delivery of participation acknowledgement.

Degree (please mark appropriate box and circle appropriate degree):

☐ MD/DO  ☐ PharmD/RPh  ☐ NP  ☐ PA  ☐ RN  ☐ Other

Full Name (please print clearly)

Last Name:  First Name:  Middle Initial:

Street Address:

City:  State or Province:  Postal Code:

Phone:  Ext:  Fax:

Specialty:

E-mail Address:

Signature is required to receive statement of credit.

Signature:  Date:

Attestation to time spent on activity is required.

Purdue University College of Pharmacy designates this enduring material for a maximum of 1.0 AMA PRA Category 1 Credit(s)™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

☐ I participated in the entire activity and claim 1.0 AMA PRA Category 1 Credit(s)™.

☐ I participated in only part of the activity and claim _______ credits.