# Challenging Cases in Oncology: Managing Opioid-Induced Constipation in Cancer Patients

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**Dr. Gudin:** Hello and welcome. My name is Dr. Jeff Gudin, and I am Director of Pain Management and Palliative Care at the Englewood Hospital and Medical Center in New Jersey. We're happy to bring you today's activity on a very important topic titled *Managing Opioid-Induced Constipation in Cancer Patients*. I'm joined by my colleagues, Jeffrey Fudin and Yvonne D'Arcy. Yvonne, please introduce yourself.

**Yvonne:** Thank you. My name is Yvonne D'Arcy. I'm an adult nurse practitioner and a fellow of the American Academy of Nurse Practitioners. I'm from Ponte Vedra, Florida; and I have over 20 years' experience in pain management and palliative care.

**Dr. Gudin:** That's great. Thanks for joining us. Dr. Fudin.

**Dr. Fudin:** Hi. My name is Jeff Fudin. I'm from the upstate New York area. I have academic affiliations at the Albany College of Pharmacy in Albany, New York; and also Western New England University College of Pharmacy in Springfield, Massachusetts. I am the CMO and CEO of Remitigate, LLC; and my expertise is in pharmacotherapeutics. I do have a clinic in upstate New York where I see chronic pain patients.

**Dr. Gudin:** That's great, and thank you for joining us. You know, there's been much focus in pain management on preventing the dangerous and bothersome complications of opioid therapy including opioid-induced constipation which we're going to call OIC throughout this presentation. The assessment and management of patients with OIC can be complex and challenging. It's extremely important to assess our patients early and monitor them routinely in order to avoid potential complications, as well as reductions in quality of life.

Our presentation will offer the latest information on the diagnosis and treatment including a review of the newer select therapeutic options approved for the management of this opioid adverse event. In addition, we will work together to demonstrate how you may apply this knowledge in your practice by working through a typical patient case scenario you may find in your oncology practice setting. At the conclusion of this activity, do not forget to complete the posttest evaluation in order to claim credit. To view answers from some of the most frequently asked questions your peers have, click on the OIC FAQ button below the video monitor. Let's get started.

## Adult Cancer Pain Guidelines

Principles of management of opioid adverse effects

- Maximize non-opioid and non-pharmacologic interventions to limit opioid dose and treat adverse effects
- Adverse effects to opioids are common, should be anticipated, and should be managed aggressively. If adverse effects persist, consider opioid rotation
- Patient and family/caregiver education is essential for successful anticipation and management of pain and opioid adverse effects
- Opioid adverse effects generally improve over time, ***except with constipation***

NCCN Guidelines Adult Cancer Pain version 1. 2018

The NCCN Guidelines for adult cancer pain have laid out some principles of management for opioid adverse events. One of the first primers they teach is that as clinicians, we should maximize non-opioid and non-pharmacological interventions to try to limit opioid doses, thereby limiting the adverse effects. Now we know adverse effects to opioids are common and should be anticipated and managed aggressively. When adverse effects persist, clinicians should consider either discontinuing opioids or, more commonly, rotating to another type of opioid. We understand that patient or family and caregiver education is essential for successful anticipation and management not only of pain, but also of opioid-related adverse effects. One of the interesting things about adverse effects is that they generally improve over time. For example, somnolence, or nausea, or pruritus with opioids usually gets better over time; but with constipation, it tends to be an enduring side effect. It doesn't appear to get better over time.

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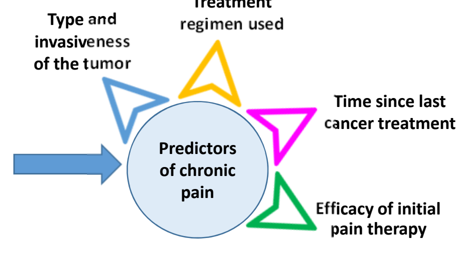
## The Prevalence of Pain in Cancer

- 25% for those newly diagnosed[1]
- 33% for those in active treatment[1]
- >75% for those with advanced illness[1]
- 40% for those who are cancer survivors[2]




[1]Paice J, et al. *CA Cancer J Clin*. 2011;61:157-182. [2]van den Beuken-van Everdingen MH, et al. *J Pain Symptom Manage.* 2016;51:1070-1090.

Now as oncologists, or those of you seeing cancer patients, we understand that this syndrome is associated with pain. The prevalence of pain in cancer patients is estimated at 25% of those newly diagnosed, a third for those in active treatment, more than three quarters of those with advanced illness, and some may find this surprising, but 40% of those who are cancer survivors have chronic pain. You see some of the predictors of chronic pain on your screen and it's important for clinicians to recognize that pain goes along with cancer quite frequently.

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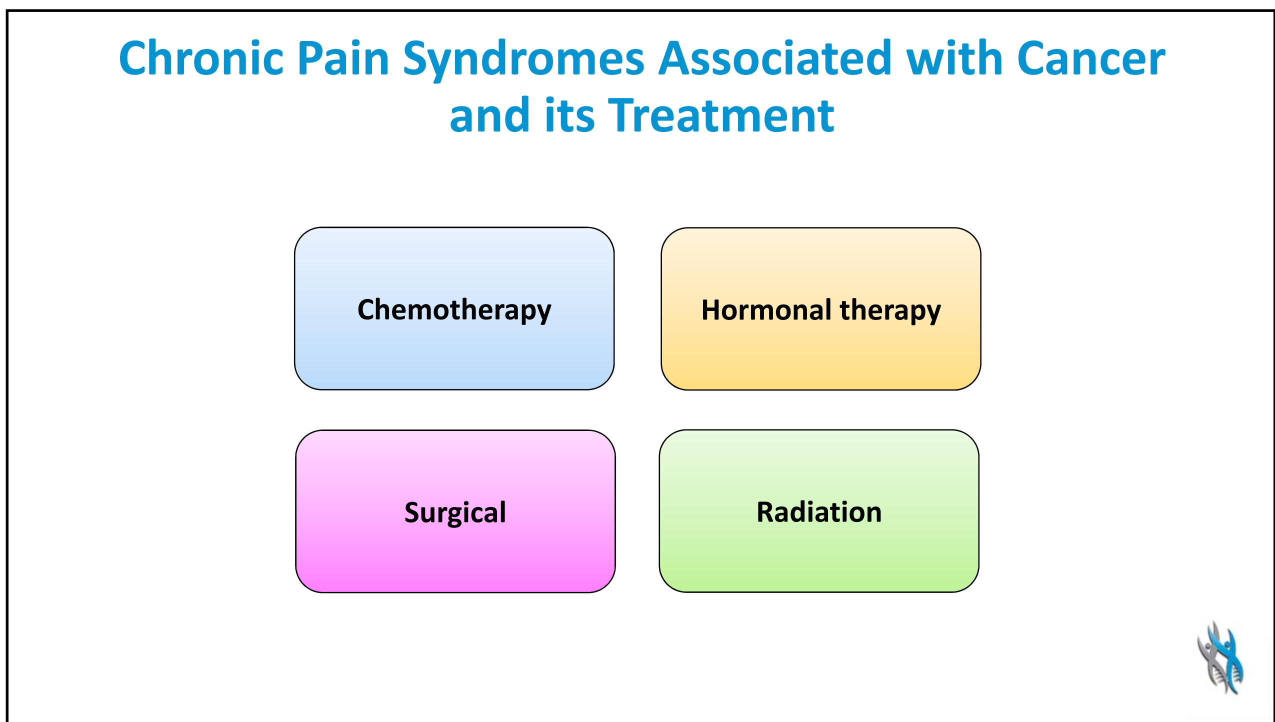


When we think of the causes for pain in cancer patients, much of it is related or as much of it is related to the tumor itself as it is to the treatments. On the screen, you see some examples. Chemotherapy-related pain syndromes. A very common one is peripheral neuropathy due to chemotherapy agents. Hormonal and radiation-related pain syndromes, which we see quite frequently in the chronic pain center. There are complications from stem cell transplantation; graft-versus-host disease; complications from surgeries like debulking surgeries; and as we mentioned, pain that comes from expansion of the tumor itself.

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## Opioids in Cancer Pain

- Considered “broad spectrum” analgesics effective for multiple nociceptive and neuropathic pain types
- In 2016, approximately 214 million prescriptions were written annually for opioids in the US
- Many potential side effects
  - Somnolence, nausea, itching, respiratory depression
- Constipation most common and bothersome
  - Affects quality of life and function

Coyne KS, et al. *Clinicoecon Outcomes Res*. 2014;6:269-281. *https://www.cdc.gov/drugoverdose/maps/rxstate2016*

Now opioids have been a mainstay in pain management for cancer pain. We call these broad spectrum. Almost as you might reflect on your antibiotics is that they are analgesics effective for multiple types of pain, like nociceptive and neuropathic pain. We know that there are commonly written medications; in 2016 for example, there were over 200 million prescriptions written for opioids in the United States. Now clearly there's controversy surrounding things like how to prescribe opioids, when to prescribe opioids, total daily doses of opioids. Many of our states, our Veterans Administration, and the CDC have come up with guidelines around how to use opioids appropriately in pain management, but the one thing that we recognize is that opioids are not going away. They are one of, if not the only class of medicine that treats severe pain; and therefore as clinicians, we need to be familiar with how to use these agents appropriately, and how to anticipate and manage the side effects, not just constipation but some others which I mentioned already: somnolence, nausea, itching, even understanding respiratory depression; but of all those side effects, constipation appears to be one of the most common and bothersome side effects, which clearly affects the quality of life of our patients.

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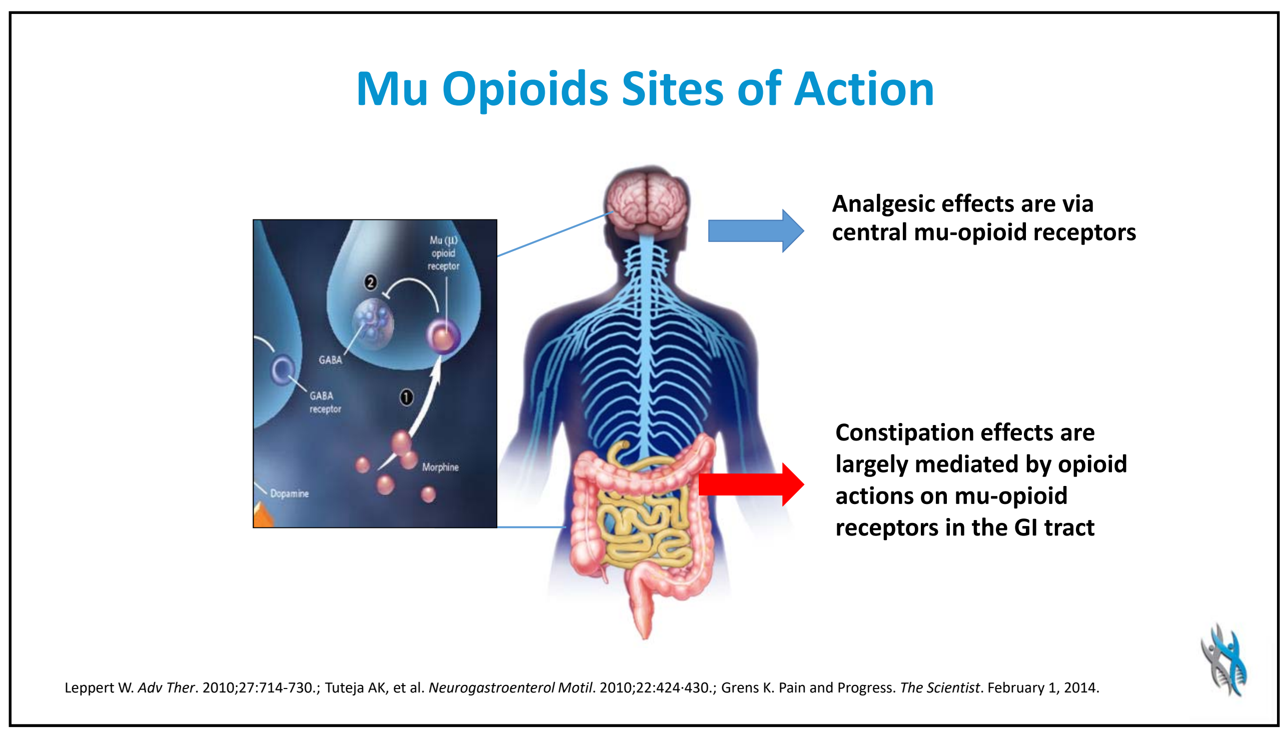


Now we understand that the analgesic, or the pain relieving effect of opioids, occurs because of the binding to the mu opioid receptors in the central nervous system, but something very interesting. We have millions of opioid receptors in our GI tract, in our gut, what we call the enteric nervous system.

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## Physiological Effects of Opioid-Agonists in the GI Tract: More than "Constipation"

- Delay gut transit time
- Results in excessive water resorption
- Stimulate non-propulsive motility
- Reduce GI secretions
- Tightens/constricts pylorus and ileocecal sphincters

GI=gastrointestinal
Camilleri M, et al. *Am J Gastroenterol*. 2011;106(3):497-506.; Panchal SJ, et al. *Int J Clin Pract*. 200761(7):1181-1187.

We're not really sure what they do there; but one thing we know is that when opioids bind to the mu-opioid receptors in the enteric nervous system, it causes some physiological changes which we interpret as constipation. It delays transit time. It stops your propulsive motility. We get less secretions into the bowel and more resorption of water out of the bowel. We tighten our sphincters above and below. Each of these physiological effects contributes to what we call OIC, or opioid-induced constipation.

Yvonne, from your experience, can you share with our audience how opioid-induced constipation impacts patients in the palliative care environment and maybe how prevalent the problem this is.

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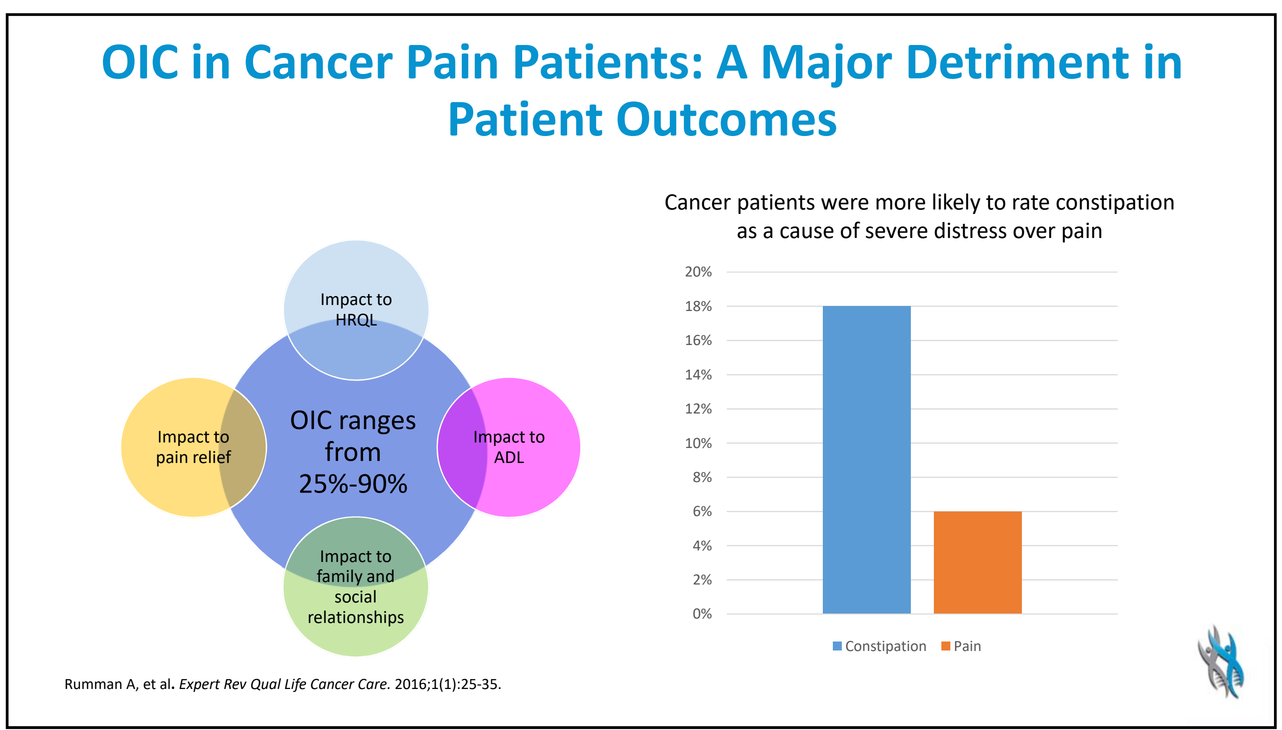
## Opioid-Induced Constipation

- Is one of the most common and troublesome symptoms[1]
- Is expected to occur at initiation and ongoing continuation of opioid therapy[1]
- Is unlikely to improve over time; tolerance rarely develops[1]
- May be severe enough to require opioid discontinuation[2]
- Can contribute to underdosing and inadequate analgesia[2]

OIC=opioid-induced constipation
[1]Vanegas G, et al. *Cancer Nurs*. 1998;21(4):289-297. [2]Thomas JR, et al. *J Palliat Med*. 2008;11(suppl 1):S1-S19.

**Yvonne:** Opioid-induced constipation is really very prevalent in the cancer patients; and in the palliative care setting, it's really quite often overlooked because there are so many other really important aspects of the care at that point. The family is very, very involved and they are looking for some answers as far as cure or palliation, and often constipation gets overlooked. It is one of the most common and troublesome symptoms that patients do experience. You really can expect it to occur anywhere along the spectrum of care so it's important to educate the patient and the caregivers about what to look for and what to consider in constipation. It's very unlikely to improve over time. I know some folks tend to wait out a little bit and see if it can be helped with natural type of substances or increased fluid intake; but by and large in a palliative care patient, they are very anorexic, they are very dehydrated. Their activity is very minimal and so you can expect that constipation would be right in there with them. Sometimes you look at, is it serious enough that you might want to discontinue the pain medication? For some of the patients, that would be a real tragedy. Looking at this, you think what it is we can do to maybe mitigate the dose or try to add an adjuvant to make sure that the patient does not get as constipated as they are?




I always instruct nurses caring for palliative care patients that they really have to inspect the patient and monitor their bowel movements and look to see if they aren't having increasing abdominal girth and really having very troublesome constipation because in the palliative care patient, it actually causes pain in addition to their original syndrome. It's really something that I think is very, very significant. It ranges anywhere from 25% to 90%. It really is something that I think is overlooked. Now people will tend to say, well, of course, they monitor how many bowel movements they have if they are in hospice or the hospital; but in fact, that may not be so, so it's important for the caregivers to understand. I will ask a family member, "When was your mother's or father's last bowel movement?" and they kind of look at each other like, "We really don't know." So it's important to actually understand that it can be more serious than the pain itself.

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## OIC – Often Underdiagnosed

Constipation may vary from one individual to the next

Clinical measures of constipation, ie, the number of bowel movements/week, do not often correlate with patients' perception of what is regular

Patients may deny yet meet clinical criteria for constipation

Patients may neglect or be embarrassed to discuss their constipation issues

**Assessing symptoms by talking to patients is the most efficient and cost-effective way to determine the presence of OIC**

Coffin B, et al. *Expert Rev Gastroenterol Hepatol*. 2011;5(5):601-613.

It's very much underdiagnosed and it can really vary from one individual to the next; and so as I look at it, I talk to the patient about what their regular bowel movements are or ask the family members, "What is it that your mom or dad was usually having for a bowel movement?" Sometimes you have to really get down to their terminology. They might not be using the term that we use so you have to make sure they understand what you're looking for. You ask them the number of bowel movements. They don't know what's regular. Some patients can have a bowel movement once or twice a week and consider that to be regular when in fact, it's really more symptomatic. They really say, "Well, I don't know if that's constipation. I think maybe it's just a little bit of a problem with slow bowels." Very often, patients and even caregivers and family members are really embarrassed to talk about it. They really think it's something that's "bathroomy" and they don't want to talk about it; but they don't really understand what a highly significant problem this is.

**Dr. Gudin:** I'd say we've been involved with coming up with tools or figuring out the best way for clinicians to assess whether patients have opioid-induced constipation, and I think you'll both agree with me that assessing symptoms by talking to the patients is the most efficient and cost-effective way to determine the presence of OIC.

**Yvonne:** You know, I would agree with you. If you talk to the patient and you let them know what you're asking and what you're looking for, they're pretty much very conversant once they get the understanding; but talking to the patients, I think is really important.

**Dr. Gudin:** I think we have a case, Yvonne, if you could take us through.

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- Susan is 45 years old and diagnosed with ovarian cancer this past year
- Following her diagnosis, she underwent three surgical procedures followed by a course of chemotherapy
- Her cancer is now in remission, but she has been suffering with chronic pain related to adhesions and abdominal pain
- Her pain has been controlled with extended-release morphine

- She reports issues today with her bowels and voices that she thinks she is “chronically constipated”
- Reports having two bowel movements per week with need to painfully strain at each movement
- Spending a long time in the bathroom and it is interfering with her ability to work

**Yvonne:** Okay. So let's take a look at Susan. Susan is a person that I would be seeing in my practice, somebody in a hospital setting or a clinic. She is a 45-year-old who had been diagnosed with ovarian cancer this past year. Ovarian cancer really sometimes comes with very broad symptomology according to how they describe their pain. She underwent three surgical procedures and chemotherapy, so she has had a lot of surgical intervention in her abdomen which may lead to adhesions, or she can have a mixed presentation with a neuropathic type of element along her surgical area. Her cancer is now in remission, but she has been suffering with chronic pain related to adhesions and abdominal pain. I don't know about you gentlemen, but when I see patients like this, they tend to have a lot of focus on the abdominal pain and a lot of focus on the cramping and the disability they have with it. Her pain has been well controlled with extended-release morphine. She reports issues today with her bowels and has told me that she thinks she is chronically constipated, so that's the key. She is kind of identifying she has got an issue. She reports having two bowel movements a week with a need to painfully strain at each bowel movement. She spends a long time in the bathroom, and it's really interfering with her ability to work. What would you gentlemen think? Do you think this is OIC?

**Dr. Gudin:** Well, I think when it comes to me evaluating my patients, the first thing I want to decide if it's OIC is the O. Is it opioid-related? Has she had a change in her bowel function related to the opioids; or considering her underlying disease, could this be adhesions or some other type of functional obstruction? Jeff, how about you?

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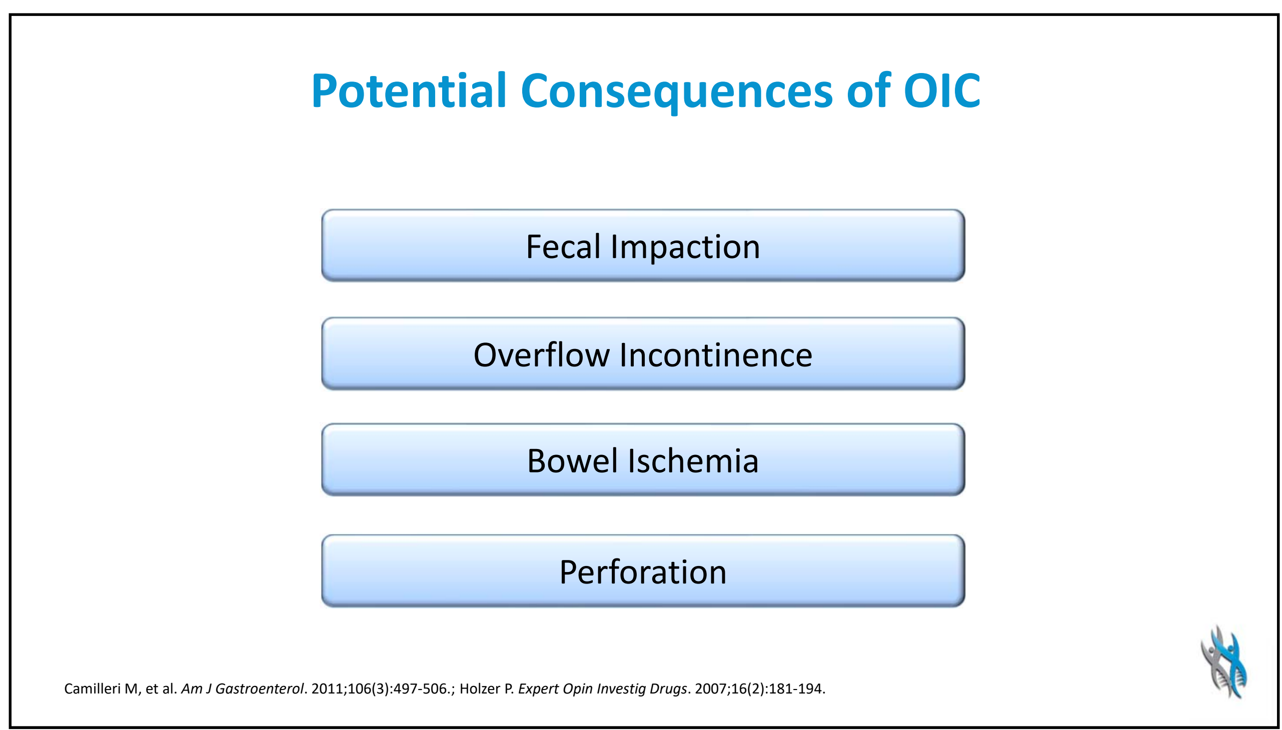
**Dr. Fudin:** Yes. So I mean from my perspective, all those things obviously are very important; but I'm going to look at the drugs as well. If she developed a neuropathy and somebody put her on amitriptyline, she could still have OIC for certain; but the OIC could be even worse now because she is on amitriptyline which is an anticholinergic. I'm going to look at all the other medications. As it turns out from my experience, sometimes even though these other drugs are constipating, it's not really enough to push these patients over the edge where they go three to four days without a bowel movement. But once we add in even a small dose of an opioid on top of that, then you've got an issue. You could have opioid-induced constipation that's mixed with some of these other agents. I'm going to look at the whole therapeutic picture in terms of medications.

## Rome IV Criteria Defines Opioid-Induced Constipation

1. New or worsening symptoms of constipation when initiating, changing, or increasing opioid therapy, that must include two or more of the following (25% of the time):
   - Straining during defecations
   - Sensation of incomplete evacuation
   - Lumpy or hard stools (BSFS 1-2)
   - Sensation of anorectal blockage or obstruction
   - Manual maneuvers to facilitate defecation
   - Fewer than three spontaneous bowel movements per week
2. Loose stools are rarely present without the use of laxatives

BSFS=Bristol Stool Form Scale
Simren M, et al. *Curr Gastroenterol Rep*. 2017;19(4):15.

**Dr. Gudin:** That's great and I agree. We kind of need to define it because one of you mentioned before, constipation is not the same to everyone. It turns out that the gastroenterologists have put together criteria. They're called the Rome criteria and they've updated these over the years. We're up to Rome IV, and you could find the Rome criteria that discuss opioid or just bowel dysfunction in general; but they do define opioid-induced constipation as new or worsening symptoms of constipation when initiating, changing or increasing opioid therapy. So that might sound like a surprise, but to be labeled as or defined as opioid-induced constipation, it has to occur after starting, changing or increasing your opioid therapy; but just number of bowel movements is not enough. You need to have two or more of the following, at least a quarter of the time you have a bowel movement: straining, a sense of incomplete evacuation, lumpy or hard stools, and we're going to introduce the Bristol Stool Form Scale in just a moment, and a sensation of blockage or obstruction at the anus or the rectum. Many patients will use manual maneuvers to facilitate defecation, and I'm always surprised to hear how often they do that. Fewer than three spontaneous bowel movements per week, that's the number of bowel movements we have, and that's what many patients associate with constipation. The other thing about opioid-induced constipation is patients rarely have loose stools unless they're using laxatives.




It's important we understand that there are some consequences to opioid-induced constipation, fecal impaction; and when you talk to your emergency room colleagues, they'll tell you that constipation comes into the ER all the time. Overflow continence, where patients will have only liquid come out around the mass of stool and they think it's diarrhea, but it really is a blockage due to a mass of stool. You can have ischemic bowel, depending upon how big the mass gets, and even we've seen bowel obstruction and perforation due to opioid-induced constipation, so it can be quite significant.

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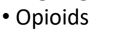
## Development of Constipation
## *Risk Factors*

**It is important to note, not all constipation while on opioids is OIC**

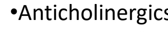
Patient Characteristics
- Female gender
- Advanced age

Dietary Considerations
- Dehydration
- Nutritional deficits

Drug Regimen
- Opioids



- Anticholinergics



- Calcium

- Antidepressants
- Antihistamines

Medical Issues
- Relative immobility
- Nausea/vomiting
- Mechanical obstruction
- Recent hospitalizations

Kalso E, et al. *Pain*. 2004;112(3):372-380.; Ahmedzai SH, et al. *Clin Evid* (Online). 2010;pii:2407.; Clemens KE, et al. *Ther Clin Risk Manag*. 2010;6:77-82.; Wan Y CS, et al. Las Vegas, Nevada; 2013; Abstract 132.

Now we know there are certain risk factors for developing constipation in general, as well as risk factors for opioid-induced constipation. You can see some of those on the screen. Elderly age, female gender, certain dietary issues. Dr. Fudin mentioned and we'll talk more about drug regimens, tricyclic antidepressants, antihypertensives, medications that basically have a drying effect we anticipate to cause or contribute to constipation. We think of immobility as a risk factor for developing constipation.

So Jeff, maybe now's a good time. Can you maybe comment, give our audience some insight on what are some of the other common drugs used in this population that might lead to worsening constipation?

**Dr. Fudin:** Great question. So we already talked about things like amitriptyline. If these patients are on antihypertensives, which you mentioned, most often we're worried about diuretics, because with diuretics they're going to reduce the amount of fluid. A lot of times, there are anticholinergics that we don't really think about, but they have anticholinergic properties; and even the antidepressants that are not tricyclics, things like mirtazapine. We also can get decreased motility by giving skeletal muscle relaxants because they certainly have an effect on the bowel and musculature in general. Things like methocarbamol; carisoprodol which is not often thought of as a TCA. It's not really an antidepressant but it is a tricyclic, so it's almost identical in chemistry to amitriptyline. Some of the anticonvulsants can cause a drying effect as well. I think that, you know, you need to look at the whole picture. Yvonne mentioned about hospice patients. When you think about it, there are hospice patients who are looking for a dry death because it's more comfortable, so what do we do? We give atropine, right? So all of these things could potentially have an effect on constipation.

**Dr. Gudin:** That's some great insight. So Yvonne, from a nurse practitioner perspective, what is the nurse's role in identifying the risk factors or the red flags for opioid-induced constipation?

**Yvonne:** I think the most important thing is to do an assessment. At each visit or at each time you view the patient, I know when I worked as a floor nurse in the hospital, one of the things I would do when I came on shift was to look and see if the patient had had a bowel movement, when it was and how recently because it tends to get overlooked. So I think you should have to look at the clinical assessment and seeing whether the patient's had a bowel movement, ask them how many they've had weekly, the type of stool. You, I think, are going to talk about the Bristol Scale so that's a little bit more descriptive of that, and if the evacuation feels complete because sometimes they'll have small little pebbles of stool that they'll pass and consider that to be a bowel movement; but that's really only a partial bowel movement so their defecation is really incomplete. You have to talk to the patients again as you indicated about the importance of fiber, exercise and hydration if they are able to tolerate that. As I said, for some of the palliative and end-of-life patients, that's not possible; but most folks really have to be taught to drink more water and include fiber, and they should be instructed on which foods contain that helpful fiber that they could take. Frequent liquid stools or increased abdominal cramping means that they may have a bowel blockage as you indicated in your information, and they really should contact somebody because they may need immediate intervention on that. Again, it's really very important, I believe that patients really need to have a comfort goal in palliative care and hospice; and making sure that they're not impacted would be very, very important.

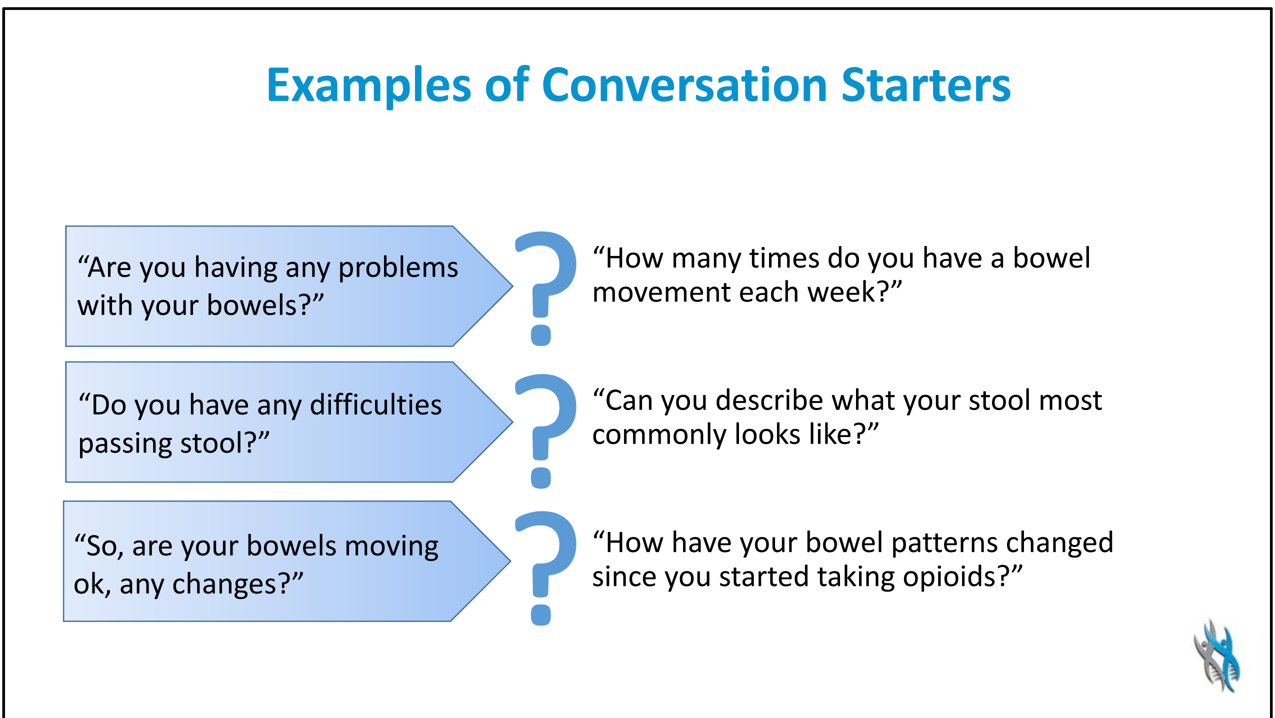
**Dr. Gudin:** That's right. So you know, a question that we often post to clinicians is how often do you currently use a specific assessment tool to evaluate the bowel habits of patients on chronic opioid therapy? If you would've asked me this a couple of years ago, I would have said, well, I didn't know there are any assessment tools available for constipation in pain patients; but it turns out that there are and we will discuss those with you. Then the other question is, when, how often, and how do you initiate a conversation with your patients regarding his or her bowel function? So those are some of the things that we will talk about. But let's go back to our patient Susan. She has no record of a prior bowel regimen when her opioid was first prescribed. She admits to us that she hasn't brought it up on previous visits as she didn't see the relevance or importance, and it was kind of embarrassing to talk about. She's a cancer patient. She has other important issues to talk about. She didn't want to use the time to talk about her bowel functions. She says that she tried increasing her fluid intake and adding fiber to her diet and making some other modifications, but it didn't help with her constipation. So Yvonne, give us a little bit of background on patient perceptions of opioid-induced constipation.

**Yvonne:** Well interestingly enough, 1 out of every 3 patients really fails to initiate a conversation about their bowel function with their healthcare provider. It's not something that they're going to be forthcoming with, so it's incumbent on the healthcare provider to actually try to open a discussion about the topic. There was a patient survey and they found that 58% of the 513 respondents indicated that straining affected their quality of life.

You can say, oh, what do you really mean about quality of life? Their ability to work as the patient's scenario indicated. She felt it was really impinging on her work. Respondents in the survey stated that straining cause pain, rectal bleeding, leakage, and made the area sore. A lot of patients said that they really didn't feel that they could sit properly and comfortably after they've had straining at their bowel movement. Some of the feelings that the patients shared indicated that difficult bowel movements created anxiety and depression.

**Dr. Gudin:** Jeff, considering that opioid-induced constipation is painful or can be painful and have such an effect on patient's quality of life, how do you initiate conversation, let's say when you're starting a patient on an opioid?

**Dr. Fudin:** So obviously when we're starting on an opioid, we'd have all sorts of conversations, but we like to assess their overall risk and make sure that there are no family members at home that are prone to abusing these substances or that the patients themselves are not going to abuse or misuse the drug. When we get past that assessment and a decision has been made to move on to chronic opioid therapy, then we need to list the side effects, the risks, the potential harms and the benefits. We are going to go through a whole battery of discussions; one is going to be a discussion on opioid dependence and the fact that you may need a higher dose, and if you abruptly stop you can have withdrawal; the difference between addiction and dependence and all those sorts of things. That's important; but I think that as part of that discussion, we need to have a discussion about constipation and make the patient aware right up front that this is a side effect that probably they are not going to get tolerant to. They may get tolerant to the drug, to the somnolence of the drug or other side effects as you mentioned earlier: pruritus, GI upset; but they're not going to get tolerant likely to the constipation. They need to know this and they need to know that it's okay for us to have this discussion. In the subsequent visits, we're always going to ask them questions about this. We're going to ask them, "How are your bowel movements? How often is the bowel movement? What is the consistency of the stool?" We're going to ask them, "Have you started any over-the-counter vitamins or natural food products?" I find a lot of times that when a patient has survived cancer, they all of a sudden become health freaks. They start taking all of these natural food products over-the-counter and nobody knows what they are. We need to make an assessment and look at those and think, "Oh, wait a minute. Yes, you have opioid-induced constipation, but did you know that you're taking XYZ and this could potentially make the problem worse?" If someone is taking a high-dose aluminum supplement or zinc or something like that, and it's making them much worse. Another patient is take magnesium and they're pooping their guts out, and don't know what's going on. So, it's really very important to have this conversation with them, not only at the first visit. Tell them what to expect. Maybe set them up with a prophylactic regimen upfront when they go home, make sure they know it's okay to call us and that they shouldn't be embarrassed if something happens, and bring this conversation up every single time that the patient comes in for a follow-up visit.




**Dr. Gudin:** That's great. So as a parent, I recognize as many of you will, sometimes the answers to questions depend upon how we pose those questions. When it comes to side effects like opioid-induced constipation, we have some examples of rather than saying to your patients "Are you constipated?" or "Are you having any problems with your bowels?" You need to ask more focused questions like "How many times do you have a bowel movement each week?" Instead of saying "Do you have any difficulties passing stool?" "Describe what your stool looks like" or "Describe your difficulties passing your stools." Maybe ask them "How has your bowel pattern changed since you started taking your opioids?" So as clinicians doing the assessment we need to figure out the right way to ask our patients questions.

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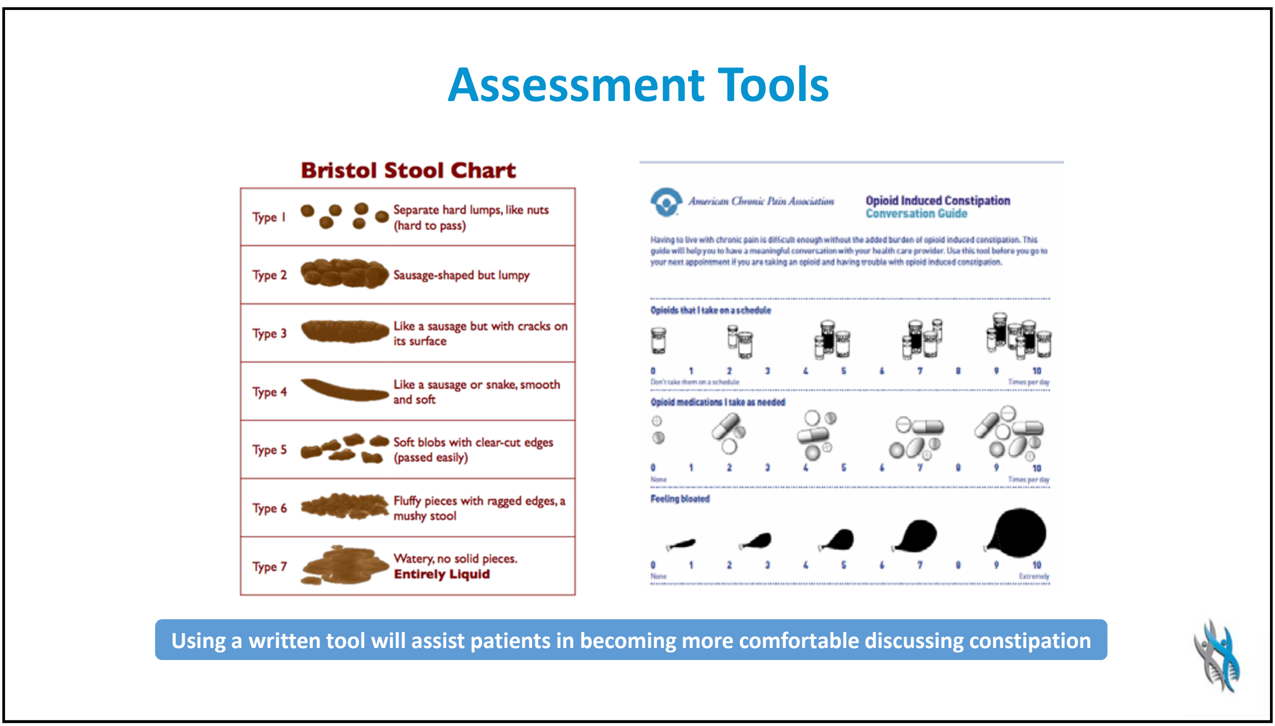
# Managing Opioid-Induced Constipation in Cancer Patients




There are some tools that clinicians could use to measure and monitor opioid-induced constipation. Many of you will recognize the Bristol Stool Form Chart that you see on the left here. I have these hanging in my exam rooms; and the first time I introduce patients or family members to it, they all chuckle because they can't believe we actually have a poop poster, but this is very helpful for determining what is the patient's stool like. Most often the opioid patients are either a type 1 or a type 2. Type 1 are the little pellets. They'll call them mouse droppings or rabbit pellets. Type 2, they are usually described by size or mass more than by anything else. This is helpful for us to document the severity of their opioid-induced constipation; and then as we use treatment, we still use this tool to see if their stool number goes up over time. Clearly, we don't want a type 6 or type 7. Our goal is to get them to have a normal, in the middle type bowel movement. There are some other tools available, the American Chronic Pain Association has some quality-of-life tools surrounding constipation that we could use as well.

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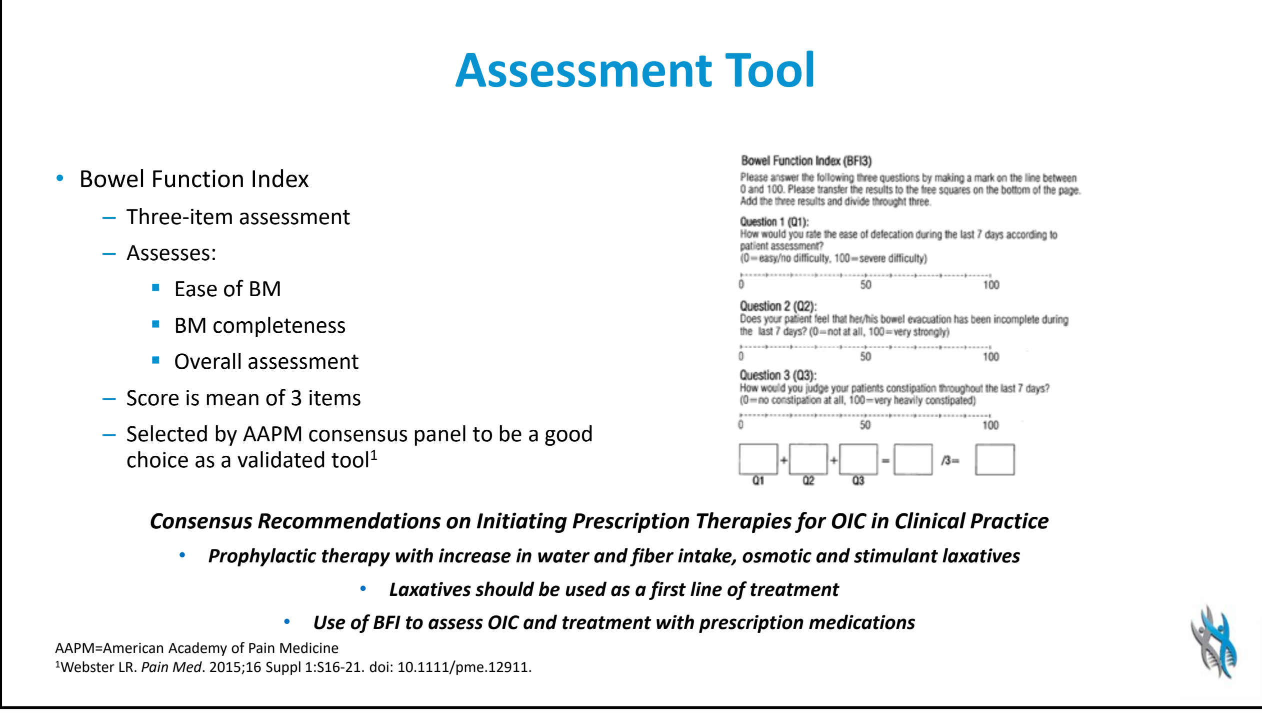
As Dr. Fudin knows, we were involved with these consensus recommendations. They are published in *Pain Medicine*, and it was sponsored by the American Academy of Pain Medicine to put together a group of experts in pain and opioid therapy to decide what's the threshold for using a prescription agent to treat opioid-induced constipation? Now 20 years ago, as a fellow at the Yale Pain Clinic, I learned to give patients docusate sodium which we know of as Colace, and Senna products. Yesterday, seeing pain patients, I gave them docusate and Senna. Nothing has changed in 20 years; and from evaluating the clinical trials that are done for OIC or opioid-induced constipation laxatives, we noticed that the majority of patients coming into those trials are on docusate sodium or Senna products, or some other type of laxative. So clearly, for many patients, those over-the-counter laxative products are not sufficient to treat their opioid-induced constipation.




The tool that we decided as a consensus panel to use is called the BFI or Bowel Function Index. It's a three-question assessment over the last seven days, so patients don't need to remember two weeks or four weeks' worth of bowel movements. They just have to think back over the last week, and they rate their ease of bowel movements, their completeness of bowel movements, and then their overall assessment of their constipation. Each one gets a score of 0 to 100. You add them up and divide by three, and the report says anything greater than 30 is considered constipation where we should consider some prescriptive therapy. So here's a simple three-item assessment tool if you're in the habit of using quantitative assessment tools in your clinical practice.

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## Does Susan Have OIC?

- Bowel function assessment
  - No record of prior bowel regimen when opioid first prescribed four months ago
  - Admits she has not brought this up on previous visits as she didn't see the relevance or importance and it was embarrassing to talk about
  - Tried increasing her fluid intake and adding bulky foods to her diet
  - BFI score: 70
  - Bristol Stool Form Scale: Type 2

**Susan's presentation is positive for OIC**

Let's get back to Susan. We do our bowel function assessment. There's no record of prior bowel regimen when she was first given her opioid. She says that she hasn't brought it up on previous visits. She has tried increasing her fluid and her fiber; we've talked about that. Her Bowel Function Index score was a 70. Remember I told you 30 was our threshold for using a prescriptive agent. Her Bristol Stool Form Scale was the type 2, the big mass, hard mass of stool; and she has had no other changes in her prescriptions, her diet, or her lifestyle. Susan's presentation is clearly positive for opioid-induced constipation.

Dr. Fudin, maybe we could start to talk now a little bit about medications. What are some of the options, and I've mentioned one or two already. What are some of the over-the-counter treatment options that patients have at their hands?

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## OTC Options: Current Therapy Falls Short

*OIC treatment is currently dominated by the use of laxatives, which are only partially effective and cause complications of their own[1]*

- Laxatives do not prevent or treat the cause of OIC
  - Activation of mu-opioid receptors in the gastrointestinal tract[1,3-5]
- Laxatives are only partially effective for OIC, providing relief for fewer than 50% of patients 50% of the time[2]
- Laxatives pose serious risks with prolonged, frequent or excessive use

[1]Thomas J. *N Engl J Med*. 2008;358:322. [2]Pappagallo M. *Am J Surg*. 2001;182:Suppl. S11-S18. [3]Miralax Product Label, Schering-Plough Healthcare Products. [4]Metamucil Product Label, Proctor and Gamble.

**Dr. Fudin:** Sure. So you know, I haven't worked actually at a community pharmacy in some years; but I think it's important for all of us to know that many times when these patients don't want to discuss their constipation, the first place they end up is in a supermarket or some kind of store trying to treat themselves. Their second stop is the community pharmacist. Generally speaking, my rule of thumb is one 8.6-mg Senna tablet for each 30 mg of oral morphine or its equivalent, but also docusate because we know there's a motility issue. It's not okay to give docusate alone because you end up with a soft stool but it's not going to go any place. So that's important. I think that also we need to think about some of the other over-the-counter drugs. Things like psyllium can actually make the problem worse because if you create a bulk and you've got decreased fluid in there, Yvonne mentioned encouraging fluids. It's extremely important. So laxatives really don't prevent or treat the actual cause of OIC. Laxatives are really only partially effective and you may end up getting a lot of cramping. If you're pushing out the stool with a stimulant laxative and there's an obstruction, then there's a higher risk obviously of perforation, so that's very important.

## Appropriate Use of Laxatives Requires an Understanding of How Different Agents Work, Their Effectiveness, and Associated Risk

| Type | Mechanism of Action | Examples | Side effects/complications |
|---|---|---|---|
| Bulk laxatives | Dietary fiber; causes water retention in the colon and increases stool bulk | Psyllium, husk, methylcellulose | Increased gas; risk for bowel obstruction in patients with strictures |
| Osmotic laxatives | Salt content retains fluid retention and increases intestinal secretions | Sorbitol, lactulose, polyethylene glycol, magnesium citrate | Electrolyte imbalances; increased gas, nausea, and dehydration |
| Stool softeners | Decrease surface tension to lubricate and soften fecal matter | Docusate sodium | Require adequate fluid intake, useless in patients with compromised bowel motility |
| Stimulants | Increase colonic motility and electrolyte transport; stimulate fluid secretion | Senna, cascara, bisacodyl | Electrolyte imbalances; abdominal pain, nausea, and colonic dysmotility |

Brenner D, et al. *Pain Medicine News*. September 2013.; Schafer DC, et al. *Am Fam Physician.* 1998;58(4):907-914.; Benyamin R, et al. *Pain Physician*. 2008;11(2 suppl):S105-120.

Moving on then, this slide talks about the various laxatives that are available. So again, bulk laxatives, I think we have to be very careful of that. I won't give a bulk laxative to a patient unless I know that they're going to drink a lot of fluids during the day; and those fluids, of course, are not going to include things like caffeine, tea or caffeinated sodas, because caffeine can cause dehydration as well. The osmotics can certainly offer some benefit. We've talked about stool softeners and some of the stimulants. I try to stay away from bisacodyl because that is an extremely potent stimulant and even patients who don't have opioid-induced constipation become reliant on them. So even if you can treat the underlying cause of the opioid-induced constipation, which we're going to talk about here, if you start taking a lot of bisacodyl, you could become reliant on that. So we can only go so far with these nonprescription medications. These nonprescription medications are laxatives; but the new class of medications known as PAMORAs which we're going to talk about. They're not really laxatives. They actually prevent the problem from happening.

**Dr. Gudin:** That's great. So we've talked about using over-the-counter laxatives as a first-line therapy, and it sounds like we all agree that there are certain non-pharmacologic and pharmacologic measures that we can use. I think I heard from both of you that we need to use caution when talking about psyllium or fiber for these patients with opioid-induced constipation as they have a motility issue. As Dr. Fudin mentioned, if they don't hydrate well enough, you could basically cause a big bulky mass of fiber that doesn't go anywhere, so I usually tend not to recommend fiber supplements to my patients with opioid-induced constipation; and as Dr. Fudin mentioned, laxatives have many side effects that we've all seen.

# Challenging Cases in Oncology:
# Managing Opioid-Induced Constipation in Cancer Patients

Initial treatment:

- Polyethylene glycol 17 gm in 8 oz of water in the morning and in the evening
- Within two weeks she added bisacodyl 5 mg 2 tablets once daily to current regimen

On this visit:

- Susan is still not able to get relief of her constipation, complaining of abdominal discomfort and bloating
- Reports that she has needed to call in sick at work on three occasions over the past month due to issues with abdominal discomfort and constipation

So for our patient Susan, here's what we decided to do on follow-up. We used one of the osmotic laxatives, polyethylene glycol. We had her take 17 g in 8 oz. of water in the morning, and I have some of my colleagues that will even increase that to twice-daily as needed. Within a few weeks, she added bisacodyl 5 mg two tablets once a day to her current regimen, but yet she comes back to the office and she still can't get relief of her constipation, her abdominal discomfort, or her bloating. She tells you that she has needed to call in sick for work on three occasions in the past month because constipation is such a big issue.

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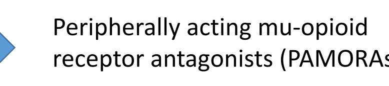
## FDA-Approved Agents for The Treatment of OIC

Indicated for the treatment of OIC in adult patients with chronic non-cancer pain, *including patients with chronic pain related to prior cancer or its treatment who do not require frequent (eg, weekly) opioid dosage escalation*

- Methylnaltrexone Subcutaneous*
- Methylnaltrexone Oral
- Naloxegol Oral
- Naldemedine Oral



→ Peripherally acting mu-opioid receptor antagonists (PAMORAs)

- Lubiprostone Oral → Chloride Channel-2 (ClC-2) activator

*Methylnaltrexone injection is indicated for OIC treatment with advanced illness or pain caused by active cancer who require opioid dosage escalation for palliative care

**Dr. Fudin:** Well, I mean at this point, I would move on to one of these drugs. These drugs are basically a new class of drugs, abbreviated PAMORA which stands for peripherally acting mu-opioid receptor antagonists. I mean to me, it makes a lot of sense. You have a drug that's activating mu receptors, and those mu receptors are causing more fluid to come out of bowel and less fluid to come into the bowel, paralyzing the anal sphincter and decreasing paralysis. So in my mind, it's kind of common sense from a pharmacological perspective to give a drug that blocks receptors in the gut without the risk of passage into the CNS to block the actual analgesic activity of the opioids. On the bottom, we have lubiprostone which does have an indication for opioid-induced constipation. In my mind, I would prefer to block the opioid receptors; but any of these things are potentially useful and, in my experience, work really quite well.

**Dr. Gudin:** So let's just elaborate for those of you watching today. There are FDA-approved agents for the treatment of opioid-induced constipation, and that is one of the things we're here to talk about today. Their indications are for the treatment of opioid-induced constipation in adult patients with chronic non-cancer pain, including patients with chronic pain related to prior cancer or its treatment who do not require frequent opioid dose escalation. So the PAMORAs that Dr. Fudin mentioned, peripherally acting mu opioid receptor antagonists, you see them on the screen. Two of them are methylnaltrexone formulations. One is a subcutaneous injection. The other is an oral formulation. There's naloxegol which is oral, and naldemedine which is oral. Those are the ones that bind and block the opioid receptor in the periphery but do not cross through the blood-brain barrier.

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As Dr. Fudin mentioned, we have another one, lubiprostone which many of you may be familiar with, which opens up ion channels in the colon. Ions flow in and water follows. It lubricates the intestine. It bulks up the mass of stool there, all contributing to a laxation affect.

## PAMORAs Target the Underlying Cause of OIC

- In the GI tract, opioids delay gastric emptying and slow GI transit
- Opioid antagonists that bind to mu opioid receptors in the gut, displacing or preventing opioids from binding
- PAMORAs are designed to block the opioid receptor activation outside of the CNS (ie, GI tract)

So as Dr. Fudin mentioned, PAMORAs target the underlying cause of opioid-induced constipation. That is opioids binding to the receptors in the GI tract and causing the effects that we've already discussed. So having these peripherally acting opioid antagonists that bind or block the receptors in the gut, it prevents your opioid analgesics from binding, and therefore diminishes the constipating effects of those opioids. They are designed to not cross through the blood-brain barrier so we don't cause withdrawal. We don't diminish the analgesic effect. It just reverses the opioid receptors in the periphery.

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# Challenging Cases in Oncology:
# Managing Opioid-Induced Constipation in Cancer Patients

| PAMORAs | Methylnaltrexone | | Naloxegol | Naldemedine |
|---|---|---|---|---|
| Mode of Action | SC | Oral | Oral | Oral |
| Dose and Frequency | 12 mg SC/ once daily | 450 mg once daily on empty stomach with water 30 min. prior to first meal. | 25 mg /12.5 mg once daily.<br>Reduce dosage to 12.5 mg for those who cannot tolerate the 25 mg dose.<br>Take on an empty stomach at least 1 hour prior to the first meal of the day or 2 hours after the meal. | 0.2 mg/once daily.<br>May take with or without food. |
| Clinical Recommendations | • Discontinue laxative therapy prior to use<br>• Close proximity to toilet once administered<br>• **May be used concomitantly for length of opioid treatment**<br>• Monitor for signs of opioid withdrawal | | • Discontinue all maintenance laxative therapy prior to initiation<br>• Laxative(s) can be used as needed if there is a suboptimal response after three days<br>• Patients receiving opioids for less than 4 weeks may be less responsive<br>• Avoid consumption of grapefruit or grapefruit juice during treatment<br>• **Discontinue if treatment with the opioid pain medication is also discontinued** | • Alteration of analgesic dosing regimen before initiating is not required<br>• Patients receiving opioids for <4 weeks may be less responsive<br>• **Discontinue if treatment with opioids is also discontinued**<br>• **Avoid using in patients with known or suspected GI obstruction or those at risk of obstruction** |

Jamal MM, et al. *Am J Gastroenterol.* 2015;110 (5):725-732.

Now I'm going to highlight each one of these without going into too much detail. From the PAMORAs, we have methylnaltrexone. I mentioned there's a subcutaneous form. That's the original formulation. We've been using that in the hospital and palliative care setting for years. There's a newer oral formulation. We have naloxegol which is an oral formulation available in two dosages, FDA-approved at 25 mg, with a 12.5 mg for those patients with renal dysfunction or those patients who have a hyper response to the higher dose.

One of the newer orally administered agents is known as naldemedine, and I would recommend that clinicians read the labels for each one of these because there are some nuances regarding dosing and drug-drug interactions, and be familiar with at least one or two of them for use in your own practice.

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## Chloride Channel Activator

| | Lubiprostone |
|---|---|
| Mode of action | Oral |
| Dose and Frequency | 24 mcg twice daily |
| Clinical Recommendations | • Swallow capsules whole and do not break apart or chew<br>• Take capsules with food and water<br>• Concomitant use of methadone may interfere with the efficacy<br>• Syncope and hypotension: may occur after taking the first dose or with subsequent doses. Generally resolves prior to the next dose, but may recur with repeat dosing. Instruct patients to discontinue and contact their healthcare provider if symptoms occur.<br>• Dyspnea: may occur within an hour of first dose. Generally resolves within 3 hours, but may recur with repeat dosing. Instruct patients to contact their healthcare provider if symptoms occur |

Jamal MM, et al. *Am J Gastroenterol.* 2015;110 (5):725-732.

We mentioned before lubiprostone, which also has FDA-approval for opioid-induced constipation. This is an orally administered agent which does not bind to the mu opiate receptor but is a chloride channel activator, as we've already mentioned.

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## Treatment Outcomes of FDA Approved Agents for Patients With OIC (Not Head-to-Head Studies)

| | Study Primary Endpoints | Results active comparator (%) | Results placebo (%) |
|---|---|---|---|
| Methylnaltrexone 12 mg SQ daily | Primary endpoint: % patients with >3 in SBMs per week, during 4-week period | 59 | 38 |
| Methylnaltrexone 450 mg PO daily[1] | ≥3 SBM/week + increase ≥1 SBM/week for 3/4 weeks | 51 | 38 |
| Naldemedine 0.2 mg PO daily[2] | | | |
| COMPOSE I trial<br>COMPOSE II trial | ≥3 SBM/week + increase ≥1 SBM from baseline for 9/12 weeks +3 of last 4 weeks | 47.6<br>52.5 | 34.6<br>33.6 |
| Naloxegol 25 mg PO daily[3] | | | |
| KODIAC 04/KODIAC 05 | ≥3 SBM/week + increase 1 SBM from baseline for 9/12 weeks + 3 of last 4 weeks | 44/40 | 29/29 |
| Naloxegol 12.5 mg PO daily<br>KODIAC 04/KODIAC 05 | | 41/35 | 29/29 |
| Lubiprostone 24 mcg twice daily[4] | Overall SBM response rate<br>≥1 SBM/week improvement over baseline for all 12 weeks and ≥3 SBM/week for ≥9/12 treatment weeks | 27 | 18 |

[1]Rauck R, et al. *Pain Pract.* 2017;17(6):820-828.. [2]Hale M, et al. *Lancet Gastroenterol Hepatol.* 2017;2(8):555-5643. [3]Chey WD, et al. *N Engl J Med.* 2014;370(25):2387-2396. [4]Jamal MM, et al. *Am J Gastroenterol*. 2015;110 (5):725-732.

We will provide you with the data of the efficacy of each of these agents in the clinical trials for opioid-induced constipation. I'll remind you of a comment I said before, that many patients that enroll in these clinical trials fail over-the-counter stool softener and laxatives, requiring prescriptive therapies. You could find this data in each of the package inserts of these particular drugs.

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## Side-Effect Profile

| Agents | Abdominal Pain (placebo, %) | Diarrhea (placebo) | Vomiting (placebo, %) |
|---|---|---|---|
| Methylnaltrexone 12 mg SC daily | 28 (10) | 5 (2) | 11 (4) (nausea) |
| Methylnaltrexone 450 mg PO daily[1] | 14 (10) | 5 (2) | 3 (2) |
| Naldemedine 0.2 mg PO daily[2] | 11 (5) | 7 (3) | 3 (2) |
| Naloxegol 25 mg PO daily[3] | 21(7) | 9 (5) | 8 (5) |
| Naloxegol 12.5 mg PO daily[3] | 12 (7) | 8 (5) | 7 (5) |
| Lubiprostone 0.2 mcg PO daily[4] | 7 (0) | 11(4) | 4 (5) |

[1]Rauck R, et al. *Pain Pract.* 2017;17(6):820-828. [2]Naldemedine [package insert]. Florham Park, NJ: Shionogi Inc; 2017. [3]Naloxegol [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2014. [4]Jamal MM, et al. *Am J Gastroenterol.*2015;110 (5):725-732.

And again, I will take a minute and just mention that if these laxative agents promote forward flow in the bowel, you clearly want to use them with caution in anybody that's predisposed to perforation or obstruction. The most common side effects with these class of medicines are abdominal pain, diarrhea as you can imagine, nausea and vomiting, other GI symptoms; and we find those side effects associated with each of these prescriptive laxatives for OIC. I'll open it up to my panel members. Maybe we could talk about challenges faced by patients getting access to these medications. Has that been an issue for either of you?

**Dr. Fudin:** I haven't seen too much of a problem with access. I mean some insurance companies will prefer one product over another product, but access is not usually an issue as long as the patients have failed other therapies. The one thing I think that from a pharmacist's perspective we do need to be careful of, which you've mentioned, is that all of these drugs, the PAMORAs anyway, go through the cytochrome p450 system. The methylnaltrexone is a 2D6, but it's really minor so really no issues with drug interactions. Naloxegol, a strong 3A4 inhibitor, actually has a contraindication. I think it's like clarithromycin, grapefruit juice diets things like that; but with moderate 3A4 inhibitors, just kind of keep an eye on the patient, and the same thing really with naldemedine. Again, lubiprostone is not really an issue because it has really no drug interactions that we know of.

**Dr. Gudin:** You know, to kind of bring us back home. I think Yvonne talked about before just how important patient-centered care is. We need to have conversations with the patients and their caregivers. We need to take into account their symptoms when we think about prescriptive therapies; and I think from our conversation today, we've recognize that opioid-induced constipation does affect patients' quality of lives, and as clinicians, we need to know when to initiate prescriptive therapy. I've seen patients suffer for years with advanced opioid-induced constipation just on over-the-counter stool softeners and laxatives.

## Key Points to Remember

- Opioid analgesics are a mainstay treatment in pain management
- Constipation is one of the most common and troubling symptoms related to opioids; does not usually improve over time
- Assessment is important as patients may not convey the severity
- Stool softeners, laxatives, and dietary modifications are often not effective at controlling opioid-induced constipation
- Newer prescriptive agents are available that promote motility and lubrication of stool to improve the symptoms associated with opioid-induced constipation

So we recognize that opioids are a mainstay treatment in pain management. They're probably not going away. Constipation or OIC, opioid-induced constipation, is one of the most common and troubling symptoms related to opioids; and as we've all talked about, it doesn't improve overtime. Most patients don't really communicate with their clinicians. They may not convey the severity of their symptoms; and as we've mentioned, dietary modifications, exercise, hydration, over-the-counter agents may not be beneficial enough for these patients who would require a prescriptive therapy. We've reviewed with you today some of the agents that are available, specifically the opioid receptor antagonists that don't cross through the blood brain barrier that we could use to block the opioid receptors out in the periphery. So I'd like to open up the floor to Dr. Fudin. Any closing comments about opioid-induced constipation?

**Dr. Fudin:** I think that we just need to make sure that our patients are comfortable discussing this and know that they have a healthcare team that's there for them; and we need to encourage them to discuss it each time they are seen, either at the prescriber's office or when they're getting their prescriptions filled. The question should always be asked then because sometimes they won't volunteer it. I think a very important issue is that some patients finally get their pain under control and they are scared to death to have this discussion because they are afraid you are going to adjust the medications, and that's the last thing that we want. We need to have open dialogue with our patients.

**Dr. Gudin:** Yvonne?

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**Yvonne:** I think it's important to remember that if you're going to prescribe an opioid that you have to prescribe a laxative so that you can get a good start. The key is prevention rather than treatment. Once you have it, it's really, really much harder to treat, so encouraging folks to make sure that their patients have the laxatives is really important.

## Remember to Ask About Bowel Function in Every Patient Prescribed Opioids

There is no tool that replaces communication with the patient!

**Dr. Gudin:** And you know, we introduced to clinicians today some assessment tools that they could use in their office; but in my opinion, there's nothing that replaces communication with the patient. We have to ask every patient about their bowel function when we prescribe them opioids.

So before we close, you're probably wondering what happened to our patient Susan. Well, after failing over-the-counter stool softener and laxative therapy, she was started on a PAMORA and it was remarkable the improvement that she had. Her main question to us is why we hadn't done anything like that sooner? So there are newer agents available for patients suffering with enduring opioid-induced constipation. As mentioned, many of them don't get relief with over-the-counter stool softeners and laxatives. To my team, Dr. Fudin, give me some patient experience example.

**Dr. Fudin:** I've had patients, I'm thinking of this one guy in particular, but I've seen this happen many times. This fellow had opioid-induced constipation for years and he struggled with it. He was miserable. He was depressed. He came into the clinic and I'm like, you know what, why isn't this guy on a PAMORA? So we ended up putting him on naloxegol and he did unbelievable. I had another patient who was on a different PAMORA. These people will tell you it's life-changing. They say, "You know, I feel like I got my life back, now I'm able to function. I'm not afraid to leave the house. I don't have to worry about explosive stool if I took six Senna tablets because I haven't gone in five days." I mean just to listen to them,

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they are probably more appreciative than when I initiated their analgesic therapy. I mean their pain got much better, but after you get rid of that constipation, it’s like, "Oh my god, I feel like I have a new life."

**Dr. Gudin:** Well, that's really great and I think we've all experienced similar success stories. Giving patients some quality of life back is very important and it's why we do what we do.

So I'd like to thank you for joining us today.