

# **Clinical Dialogues in Pain: Management of Opioid-Induced Constipation – A Case Presentation**

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**Gudin:** Hello and welcome to part two of *Emerging Solutions in Pain*, Clinical Dialogues in Pain, Managing Opioid-Induced Constipation or OIC. My name is Dr. Jeff Gudin, and I specialize in pain management, addiction medicine, and palliative care at the Englewood Hospital and Medical Center in Englewood, New Jersey, one of the teaching affiliates of Mount Sinai University, School of Medicine. It is my pleasure to introduce to you today, Dr. Christopher Herndon. Chris is an associate professor at Southern Illinois University Edwardsville in Edwardsville, Illinois. Thanks for being here today Chris.

## Meet Caroline

- ◆ 52-year-old female with persistent non-cancer pain due to osteogenesis imperfecta
- ◆ PMHx: Osteogenesis imperfecta, HTN, depression
- ◆ Meds: Fentanyl TTS 75 mcg/hr Q72 hours, hydromorphone IR Q8H as needed, lisinopril 40 mg QD, citalopram 40 mg QD, senna plus docusate 2 tablets Q12, PEG 17 g QD, lubiprostone 24 mcg Q12 hours
- ◆ All: NKDA
- ◆ SHx: Denies tob, EtOH, recreational drug use
- ◆ ROS: Unremarkable other than significant constipation. Last BM 5 days ago
- ◆ Vitals: 130/74 mmHg, HR 90, RR 16, Temp 98.6
- ◆ Labs: All within normal limits, specifically Ca and Mg
- ◆ Tests: Abdominal CT negative for diverticulitis



**Herndon:** Thanks. It is a pleasure to be here discussing opioid-induced constipation with you today. I would like to start by sharing with you a little about a patient that I have had the pleasure of taking care of over the last several years. This is Caroline, a very pleasant 52-year-old lady, who has osteogenesis imperfecta, and due to a number of surgeries in the past, she has refractory pain and it has taken us quite some time to get her on a reasonable analgesic regimen where she can function and return to work. The problem with Caroline is she suffers from quite significant opioid-induced constipation. You can see her medications listed on the slide and you obviously would agree that she is not on low doses of opioids by any means. We also have her on several medications to try to address her opioid-induced constipation including senna plus docusate, polyethylene glycol, as well as lubiprostone at probably what should be considered maximum doses. She does not really have any other issues going on from a medication standpoint, and she will report that other than her constipation that she is dealing with she really does not have any other significant review of systems. When we look at her vitals, they appear to be normal, and her laboratories all seem to be within normal limits specifically looking toward those that may affect constipation that Dr. Gudín had discussed earlier, magnesium, calcium, etc. Her abdominal CT did come back normal.

On April 26, 2013, the FDA announced the approval for lubiprostone 24 mcg twice-daily as an oral medication for the treatment of opioid-induced constipation in adults with chronic noncancer pain.

## **Bowel History**

- ◆ Hard, ball-like stool (Bristol Scale Type 1)
- ◆ Last BM 5 days ago
- ◆ Tried sodium phosphate enema without laxation
- ◆ Normal BM frequency every other day in the morning
- ◆ Describing cramping and abdominal pain

When you look at little bit more detail on Caroline's bowel history, she does have what we would call to be Bristol Scale type I type bowel movements and this is described as hard ball-like stool, and we will cover that in a little bit of more detail here shortly. We also like to ask our patients specifically, when was your last bowel movement and how was it from a consistency standpoint? Her last bowel movement was 5 days ago. She has trialed enemas, including sodium phosphate enemas, and previous to opioid therapy to the best of her recollection, she remembers being able to have a BM about every other day without any problems. She is describing today significant cramping and abdominal pain associated not only with her defecation but also in between periods of laxation as well.

## Opioid-Induced Bowel Dysfunction

- ◆ Xerostomia
- ◆ Gastroesophageal reflux
- ◆ Retroperistalsis
- ◆ Bloating
- ◆ Abdominal pain
- ◆ Incomplete evacuation
- ◆ Opioid-induced constipation

Brock C, et al. *Drugs*. 2012;72(14):1847-1865.

So let us talk a little bit about opioid-induced bowel dysfunction, and really from a term, this incorporates a number of different gastrointestinal symptoms that includes xerostomia, esophageal reflux, we can have some symptoms of retroperistalsis or feelings of esophageal reflux or burping or things along those lines. A lot of patients including Caroline described very uncomfortable feelings of bloating and feeling irregular and just not themselves. They also feel like even when they do manage to have a bowel movement, they described symptoms or descriptions of not feeling like they were able to completely empty their bowels and that there are still some work left to be done, so to speak. Opioid-induced constipation, while part of opioid-induced bowel dysfunction, is probably the most significant of the problems that are patients in pain management experience.

## Risk Factors for OIC

- ◆ Female gender
- ◆ Age >70 years
- ◆ Concurrent aluminum antacids, antidepressants, and antihistamines
- ◆ Opioid dose
- ◆ Magnesium and calcium status
- ◆ Opioid type and route of administration

Rosti G, et al. *Eur Rev Med Pharmacol Sci.* 2010;14:1045-50.; Talley NJ, et al. *Am J Gastroenterol.* 2003;98:1107-1111.; Herndon CM, et al. *Pharmacotherapy.* 2002;22:240-250.

There are number of risk factors that are associated with opioid-induced constipation. Most of them are fairly intuitive. One is female gender. Advanced age can also serve as a risk factor for this disorder. Different types of medications that may be taken concurrently with opioids can certainly contribute to this problem. The actual opioid dose, so the higher the dose of the opioid most frequently we will see worsening problems of opioid-induced constipation. Different types of antacids can significantly contribute to OIC, and then the actual type of opioid that we give as well as the route of administration has also been shown to contribute to the likelihood of developing opioid-induced constipation.

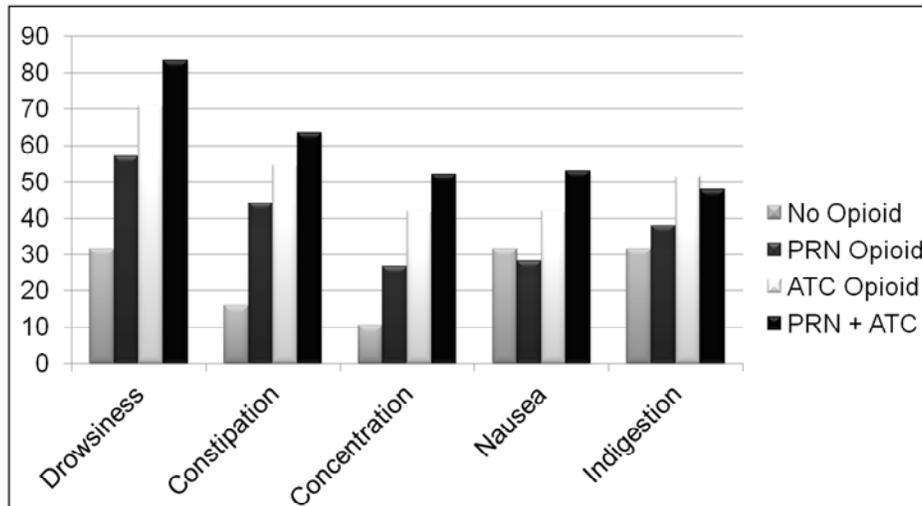
## Incidence vs Bothersomeness of Common Opioid Adverse Effects

Symptom	% patients reporting	Bothersomeness Rank
Constipation	81	1
Straining	58	2
Fatigue	50	3
Small/hard bowel movement	50	4
Insomnia	40	5
Incomplete evacuation	45	6
Passing gas	34	7
Bloating	33	8
Lower abdominal discomfort	31	8
Nausea	26	10

Bell TJ, et al. *Pain Med.* 2009;10:35-42.

The thing that I find most interesting about some of the data that surrounds opioid-associated adverse effects is, what are the most commonly encountered adverse effects associated with opioids? But this study presented by Bell and colleagues actually did a really nice job, not only about discussing the incidents of these opioid-associated adverse effects but also the patient's self-perceived bothersomeness of these adverse effects. The thing that I find most telling about this slide is as you go down the middle column on this particular slide, you will see that a lot of the adverse effects associated with opioids actually involve the gastrointestinal system, and then when we go over to the bothersomeness rank, this is how problematic these patients found these adverse effect to be, I have listed these actually in the order of severity of bothersomeness. The top several are actually distinctly and specifically associated with opioid-induced constipation or with opioid-induced dysfunction as we discussed earlier.

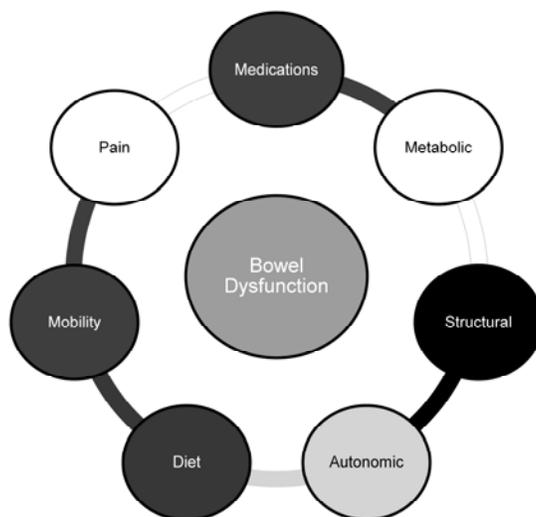
## Prevalence of OIC, Opioid Regimen



Villars P, et al. *J Pain Symptom Manage.* 2007;33:67-77.

The prevalence of opioid-induced constipation has also been looked at by determining what type of opioid the patient is on, and one of the things that comes up quite frequently in my practice is whether or not patients should be on around-the-clock or long-acting opioid therapy, or as-needed only or short-acting opioid therapy, and their effects on adverse symptoms associated with these medications. As you can see here looking specifically at the second set on the X-axis, constipation is listed as being significantly greater when you combine as-needed as well as around-the-clock opioid as compared to around-the-clock opioid or PRN opioid. So based on this data here, PRN or immediate-release opioid only does have a lower prevalence of opioid-induced constipation compared with either long-acting or their therapy combined.

## Etiologies of Constipation



There is a number of different etiologies associated with constipation of which opioids may just be one small piece, but it is important to take the whole patient into consideration, and whether we are talking about a chronic pain patient who may have debilitating low back pain or osteoarthritis of the knee, or a patient with palliative care needs who may have endstage disease or cancer, a number of these different things can significantly play into each other. Pain can reduce mobility. Mobility and pain can reduce the patient's intake or actually increase the patient's intake or change their diet around. There can be significant autonomic changes which can affect the bowel as Dr. Gudin had referenced a little bit earlier, and there can also be unfortunately metabolic and structural changes to the bowel that can come about from either hypercalcemia associated with malignancy or direct tumor infiltration of the bowel itself.

## Assessment

- ◆ Patient medical and medication history
- ◆ Physical exam
- ◆ Laboratory
  - Electrolyte abnormalities
  - Fluid status
- ◆ Testing
  - Abdominal CT
- ◆ Adherence

One of the things that is very important when we talk about this is assessment of the patient. It is important that we do a good patient medical and medication history. It is important that we talk about the physical exam and actually examine the patient's abdomen to make sure that there is no concern for an acute abdomen. It is important to look at laboratory findings and make sure that there are no electrolyte abnormalities that could be contributing to the opioid-induced constipation, as well as paying particular attention to fluid status, especially with our patients during the end of life. It is not unheard of to look at an abdominal CT to see if there is anything that could be contributing to the patient's refractory constipation, and it is also important to look at adherence as well from not only a medication standpoint but also some of the medications that we may be prescribing to try to alleviate the symptoms associated with that.

## **Assessment Tools**

- ◆ Bristol Scale
- ◆ Constipation Assessment Scale
- ◆ Bowel Function Index
- ◆ Patient Assessment of Constipation Symptoms

There are a number of different assessment tools that we can employ when we look at opioid-induced constipation. My favorite is the Bristol Scale, and a lot of times when I show this to students or colleagues, I will get a little bit of chuckle, but it is actually a very nice tool that the patients sometimes can look at, and it makes for breaking the ice when we go into start talking about something that oftentimes patients are not very comfortable speaking about. There is a constipation assessment scale that goes into more of the symptoms associated with opioid bowel dysfunction altogether. There is the bowel function index and the patient assessment of constipation symptoms,

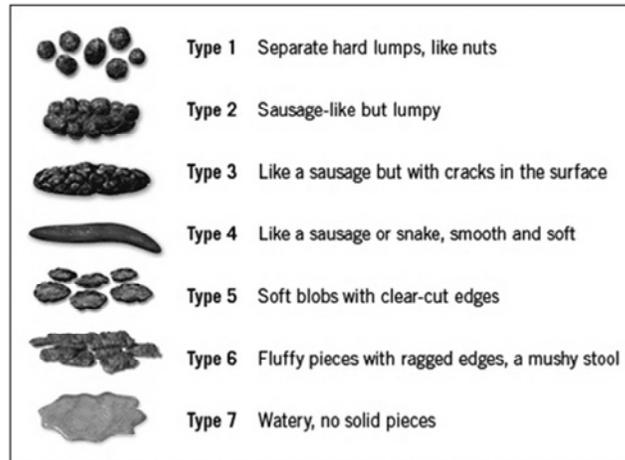
# Constipation Assessment Scale

Symptom	Patient Rating
Abdominal distension or bloating	None/Some/Severe
Change in amount of gas passed rectally	None/Some/Severe
Less frequent bowel movements	None/Some/Severe
Oozing liquid stool	None/Some/Severe
Rectal fullness or pressure	None/Some/Severe
Rectal pain with bowel movement	None/Some/Severe
Small volume of stool	None/Some/Severe
Unable to pass stool	None/Some/Severe

McMillan SC, et al. *Cancer Nurs.* 1989;12:183-188.

and we will cover off real briefly on the constipation assessment scale. As you noticed, they do not just talk about bowel frequency or the description of the bowel movement, but some of these other symptoms associated with opioid bowel dysfunction that I have mentioned earlier, and some of these can be quite bothersome to patients as you saw from that bothersome index that we talked about. Caroline, our case that we had talked about at the very beginning, does mention numerous of these symptoms as being significantly problematic for her and thus her wanting to look at changing her opioid regimen.

# Bristol Scale



Bristol Stool Form Scale. [www.bowelcontrol.nih.gov/Bristol Stool Form Scale 508.pdf](http://www.bowelcontrol.nih.gov/Bristol_Stool_Form_Scale_508.pdf). Accessed March 29, 2013.

When you look at the Bristol Scale, it is very easy to look at and have the patient compare, and most of the time, like I said the patients who will look at this and get a little bit embarrassed or flushed a little bit and then they will jump right into describing exactly what they are dealing with. Once we break that barrier down, we tend to be able to have a pretty frank conversation about what is going on and their specific problems, and I oftentimes will find that patients are not actually taking their opioid medications as prescribed because of problems with constipation.

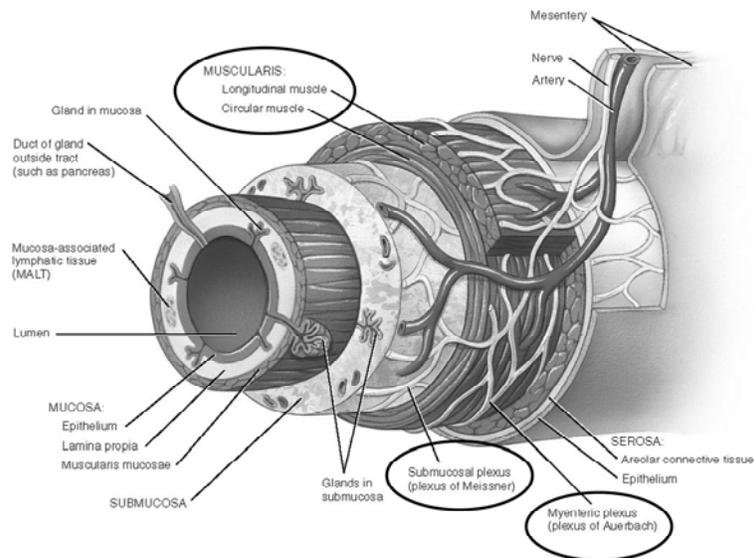
## Opioid Receptors and the Intestine

- ◆ Inhibition of distension-dependent peristaltic contractions
- ◆ Gastric emptying inhibition
- ◆ Gastrointestinal ion and fluid transport inhibition
- ◆ Increased pyloric resting muscle tone
- ◆ Elevation in resting anal sphincter pressure
- ◆ Decreased defecation response

Holzer P. *Regul Pept.* 2009;155:11-17.; Rosti G, et al. *Eur Rev Med Pharmacol Sci.* 2010;14:1045-1050.

So, let us dive into how opioids are actually causing problems in these patients. I have heard a number of neurologists say in the past that the GI system is like the second brain and that there are just as many neurotransmitters and nerve connections in the GI system as there are in the CNS, and it is not surprising that we typically have some very significant neuroendocrine changes when we give opioids in the GI system of the patient. And as Dr. Gudín had mentioned in the first part of this series, what you will find is that they do a number of different things that may actually sound familiar or more familiar after having gone through this seminar. The first thing that they can do is that they can inhibit the actual distention to peristalsis. So when you take in a load or you take in a meal and that moves through the stomach and into the small intestine, that distention of the small intestine will actually trigger the myenteric nerve system to try to push or to create contractions. We can also see changes with the actual gastric emptying time. We can also see one of the more predominant causes of opioid-induced constipation and that the opioids can inhibit both the myenteric as well as the smooth muscle plexus systems that actually create or are responsible for ion flux and hence water movement in or out of the gastrointestinal movement. We can see increases in pyloric resting muscle tone, which obviously can decrease the stomach's ability to move food stuffs into the small intestine. We can see an elevation in resting anal sphincter pressure, which can make it even more difficult to pass stool out of the large bowel and from the rectum, and we also can see a decreased neural response when we actually do have pressure up on the rectal vault and being able to actually expel feces out of the anus. So there are a number of different things that opioids can do to contribute to opioid-induced constipation.

# Pathophysiology of OIC



[http://dc127.4shared.com/doc/RwDmxbNv/preview\\_html\\_m6db2454a.jpg](http://dc127.4shared.com/doc/RwDmxbNv/preview_html_m6db2454a.jpg). Accessed March 29, 2013.

This nice figure that you are looking at here is just another way of looking at the gastrointestinal lumen. You will notice that down at the bottom one of the red circled areas is the myenteric plexus and that is the major plexus that enters the gastrointestinal lumen and innervates a number of the different smooth muscle systems. Further branches of the myenteric plexus are broken down into the submucosal plexus, and so an easy way to remember this, or at least the way I remembered this is the myenteric plexus is responsible more so for the peristalsis, the movement of foodstuff through the intestine. The submucosal plexus is more responsible for innervation of the smaller circular muscle that is responsible for mixing stool with fluid with the ions that Dr. Gudin was talking about earlier, and opioids inhibit both of these nerve plexuses.

## Patient Education

- ◆ Adequate fluid intake
- ◆ Maintain activity
- ◆ Dietary fiber intake
- ◆ Avoidance of bulk forming laxatives
- ◆ Avoidance of straining

From a patient education standpoint, we covered this a little bit in better detail earlier. It is very important to talk to these patients about some of the lifestyle changes that they may be able to make in addition to the pharmacotherapy that we can recommend. Adequate fluid intake is absolutely paramount, and I would be a rich man if I had a nickel every time a patient told me that they just did not drink very much water anymore, that they did not taste right, that they just did not have enough desire to get up and go and get the drink. They also sometimes will tell you that water makes them nauseous, especially if they have fairly severe constipation. It is really important, especially for our chronic pain patients, that they get up and they maintain activity. Sitting on the couch just will not get the bowels moving. Dietary fiber intake is important. A lot of times, our patients may not have the best dietary intake that we could ask of them in having high-fiber and low high-fat meals really will help out, and one of the things that we have to make sure we tell our patients, especially on higher dosage of opioids, is avoid bulk-forming laxatives because again, opioids will decrease that distension-dependent peristalsis and we can wind up actually predisposing patients to an obstruction. And it is important that we counsel them to avoid straining, like Dr. Gudin so eloquently put earlier. It is very important that we tell them about maintaining good healthy bowel habits and trying to pick a time of day when they can set some time aside and make sure that that is their sole focus and to avoid straining and rushing through it.

## Constipation in Advanced Disease

- ◆ Opioid analgesics used in ~50% of palliative care of patients with cancer in the United States<sup>1</sup>
- ◆ Estimates of constipation frequency vary
  - 23% to 63% of patients with cancer pain receiving opioids<sup>2</sup>
  - 15% to 90% of patients receiving opioids for noncancer pain<sup>2</sup>
- ◆ OIC may cause distress, increase cost of care, lead to discontinuation of analgesics, negatively affect HRQOL<sup>3</sup>

HRQOL=health-related quality of life

<sup>1</sup>Coi YS, et al. *J Pain Symptom Manage.* 2002;24(1):71-90.; <sup>2</sup>McMillian SC. *Cancer Control.* 2004;11(suppl):3-9.; <sup>3</sup>Meuser T, et al. *Pain.* 2001;93(3):247-257.

Some of the issues with constipation in advanced disease can actually make things a little bit more muddy when it comes to assessment. Opioid analgesics are used very predominantly in our advanced or terminal disease patients. Estimates of constipation do vary somewhat, but when we look at those who have cancer that are receiving opioids, up to two-thirds may actually experience significant constipation. Those who are receiving opioids for non-cancer pain can actually jump even more significantly to approximately 90%, but as you notice here, the actual response rates can vary quite significantly, and I do see this in practice that patients do report in high variance. Opioid-induced constipation, like we said earlier, can cause a significant amount of distress. I get a lot of follow-up phone calls when we do not aggressively predict opioid-induced constipation, and we can actually see some patients that are sent home that are supposed to come back for hospital follow-up to our clinic that do not make it that far, they wind up going back into the hospital because of problems or concerns with adverse effects associated with the opioids that we are giving them.

## Return to Caroline

- ◆ Patient is requesting rotation to different analgesics *despite* favorable pain control
- ◆ She has trialed numerous commercially available treatment modalities
- ◆ Discussed with patient the pros and cons of either orally administered naloxone or misoprostol

So let us return to our patient Caroline that we met at the beginning of this presentation. I did see Caroline back in my office approximately 4 weeks ago. She was requesting a change to some different analgesics despite having fantastic results with her current regimen that I had showed you earlier because the constipation was just getting too unbearable. In fact, we wound up having to admit her probably about 3 months ago to the hospital for obstruction and we have really had a difficult time getting her managed. She has failed numerous commercially available medications for constipation, and right now what we are at is I am allowing her to look into her to do some homework on two options that we have not trialed yet. And so by seeing these, obviously we realized that there have been some significant trials done with all of the other laxatives that are out there. So right now, she is looking at the option of either orally administered compounded naloxone, which Dr. Gudín had told you is a non-selective opioid antagonist, or off-label use of misoprostol before actually going to a different type of opioid. I would really be interested in hearing from my colleague, Dr. Gudín about how he might approach Caroline.

**Gudín:** Chris, I appreciate that and a great presentation. I was thinking while you were talking about Caroline, I have had plenty of patients in the past that say the same thing as Caroline does. "You know doc, the medicine is working great for my pain, I just cannot stand the side effects." And whether those side effects are constipation, sedation, nausea, sweating, we hear that all the time. So, the fact that we are developing some algorithms for the treatment of constipation, it sounds like it is critical for patients.

**Herndon:** It really is, it is significantly problematic, and I think that once a lot of times the physicians and pharmacists and nurses and other health care professionals run through the gamut of the first or second tier of the medications we can use, oftentimes I feel like a lot of this will throw our hands up and it is nice to know that there is a number of different things that are out there available to us.

**Gudín:** I was going to say I see in my community that clinicians make use of the compounding pharmacies because like you say, we throw our hands up, we really start to look for some of these novel things which I am glad to see industry is really turning the corner and recognizing, first of all, there is a need to treat opioid-induced constipation, and then the next step is putting into clinical trials novel agents that will really help

## Take Home

- ◆ OIC is a significant barrier to effective pain control
- ◆ Aggressive anticipation, monitoring, and treatment greatly improves patient-related outcomes
- ◆ Discussing the bowel habits of a patient in pain is NOT taboo

**Herndon:** Great. Thank you so much for your input. So to sum up my presentation, opioid-induced constipation really is problematic, as you saw from Caroline and I am sure that we all have patients that have had similar experiences, this really can be a huge barrier to our effective analgesia and the treatment of these patients who need this medicine. If we aggressively anticipate these side effects, if we assume the patient will have constipation, if we assume that we are going to need to start something and educate the patients up front about lifestyle changes that they can make, it will really make our jobs easier in the long run and will help us prevent problem such as Caroline is experiencing. And the other thing that I really find to be the most important is that discussing bowel habits with the patient who experiences pain and is on chronic opioid therapy is not taboo, and it is so important that we have frank conversations about this. Sometimes it is up to you as the clinician to actually approach the patient and to bring those things to the surface. So I would like to turn it over to Dr. Gudín.

**Gudín:** Chris, that was great. I would just like to echo some of your comments. I mean you told us just how high on the list of bothersomeness constipation is as an adverse effect from opioid. It was way up there. It is critically important for clinicians to understand, and we have in our office, and you are right sometimes you get a couple of chuckles and it might be a little embarrassing to talk about. We have the Bristol Stool Scale in each of our exam rooms, and I will show it to patients and I will say, "Hey, point to the number. What are your bowel movements like?" So we can then talk about just how urgent is the need for treatment. That was fantastic Chris. Thanks for joining us today, excellent presentation.

As a reminder, once you have completed this activity on opioid-induced constipation, please do not forget to complete the evaluation form and the posttest, print your continuing education certificate, and most importantly, please provide us with your feedback to further improve our educational offerings to you. Thank you for your attention and we hope you stay tuned to *EmergingSolutionsinPain.com* for your educational needs in pain management. I am Dr. Jeff Gudín.