Opioid-Induced Constipation: Improving Outcomes with Individualized Evidence-Based Treatment
Program Description
This activity will review the safety and efficacy of available therapies to prevent and treat opioid-induced constipation. It will also examine strategies for optimizing treatment selection and adjusting therapy when necessary to help patients achieve their treatment goals and improve their overall quality of life.

Learning Objectives
After completion of this activity, participants will be able to:

• Develop evidence-based individualized treatment plans for patients with OIC
• Adjust treatment plans for OIC as needed to achieve treatment goals

Target Audience
The target audience for this activity includes primary care physicians and other clinicians involved in the management of patients with constipation, including NPs and PAs.

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The following faculty has reported real or apparent conflicts of interest that have been resolved:
• Dr. Schiller discloses that he has served on speakers’ bureaus for AstraZeneca, Takeda/Sucampo, Valeant/Salix, and Actavis/Ironwood. He has served as a consultant for AstraZeneca, Actavis/Ironwood, Romark, and Janssen.

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• Penn State staff involved in the development and review of this activity have nothing to disclose.
• Lilian McVey, MCM Education Medical Writer, has nothing to disclose.

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Dr. Allen:
This is ReachMD, and I am Dr. Renee Allen, and today we’re talking with Dr. Schiller, who is a Professor of Medicine at Texas A & M College of Medicine at the Baylor University Medical Center campus.

Dr. Schiller, welcome to the program.

Dr. Schiller:
Thank you for having me.

Dr. Allen:
Dr. Schiller, I understand that you actually have a case history to help set the stage for our discussion today.

Dr. Schiller:
Yes, I do. It’s a case history of a patient who developed constipation while taking opiates, an all too common scenario. Charles is a 45-year-old roofer who was referred in for problems with constipation that developed after he fell from a ladder a year ago. He hurt his back and required three months of physical therapy and pain medication. While he noticed some improvement in pain with time, he still required daily doses of hydrocodone to maintain adequate pain control, and he was unable to return to work. Imaging of his back showed evidence of arthritis but no structural problem that would be amenable to surgery.

He first noticed constipation soon after the accident. He previously had bowel movements daily but now would go for a few days between bowel movements. Stools were firmer and now required him to strain to evacuate them. He brought this to the attention of his doctor, who advised him to use a polyethylene glycol laxative. This improved stool consistency, but he continued to be irregular. He would use bisacodyl tablets to release sensations of abdominal fullness that would occur after a few days without bowel movement. After 6 months he was not better and consulted with a gastroenterologist. A colonoscopy was normal, and he was given a prescription for lubiprostone 24 mcg twice daily. He had only a modest response to this medication and stopped taking it after one week because of nausea. Trials of other over-the-counter laxatives, increased fiber and enemas proved to be unsatisfactory due to lack of effect or bothersome-ness.

Dr. Allen:
Dr. Schiller, what are the specific challenges associated with treating patients like the one that you just discussed in this previous case?

Dr. Schiller:
I think there are several problems that come up for these patients. One is the chronicity of symptoms. It's bad enough that they have their chronic pain problem from whatever problem, in Charles’s case falling off a roof, but it's worse when you consider the side effect of constipation that they get from the pain medicine. It seems as though they have to stay on the pain medicine in order to get adequate relief, and yet, it's producing a side effect which is very bothersome by itself, so the whole situation gets very frustrating to the patient.
There's also concern on the parts of the patients that as they go along and try different medications, eventually nothing will work to help with their constipation, and this is a real concern for people because they are very invested in the fact that they need to have regular bowel movements, and if they lack bowel movements, they feel that something is drastically wrong. On the doctor's side, there's concern that there might be some other problem that's causing the constipation, not just the opiate that they're taking for pain relief, and that sometimes leads to a series of unprofitable investigations to try and sort out the problem further.

Dr. Allen:
Let's discuss a little bit more of the biochemistry. How does the opioid mechanism of action lead to constipation?

Dr. Schiller:
It's really quite straightforward. If one thinks about how opiates work in general, they work by interacting with receptors in the body that are normally receptors for endogenous opiates, opiate-like materials that we make within our bodies that interact with these receptors and modulate gut and other functions in the body. There are opiate receptors in the brain and central nervous system that are involved with mediation of pain, and when those opiate receptors are occupied, then pain is decreased substantially. That's the basis for the benefit that we get from using these medicines for chronic pain. On the other hand, there are opiate receptors in the gut that are involved with modulating peristalsis. These come into play normally when food rushes through the intestine and gets too far down without being absorbed. Then a series of nerve responses and hormones are released that end up causing the release of endogenous opiates from the upper gut, to slow peristalsis and reduce the amount of food that's getting distally in the small intestine. This is the so-called ileal brake. That same mechanism can be used when we give exogenous opiates and has the same effect; it slows peristalsis and prevents as much material from getting further down in the GI tract as would ordinarily be the case. So, constipation is something that typically follows pretty much anyone who gets chronic opiate dosing.

Dr. Allen:
Dr. Schiller, what steps should clinicians take when investigating potential opioid-induced constipation?

Dr. Schiller:
I think the most important thing is to make the connection. Sometimes doctors forget that the patient's on an opiate. For instance, if a patient's coming to me with a complaint of constipation, I might not realize that they're taking an opiate until I get to review their medication list. So, patients don't always make the connection in their own mind and may not bring that forward, so we have to be alert to the fact that medications may produce problems with constipation and, in particular, opiate pain medicine.

So, in terms of thinking about this, we get a history that the patient's constipated. If someone's had normal bowel habits, starts the medication and then has an abrupt change in bowel frequency or ease of defecation, then one can make a reasonable assumption it's the drug that caused the problem. On the other hand, if constipation predated the start of the opiate medication, then the doctor has to face the possibility that there's some other underlying cause for the constipation that needs to be addressed and is just being made worse, perhaps, by the use of opiates.”
that there’s some other underlying cause for the constipation that needs to be addressed and is just being made worse, perhaps, by the use of opiates. The differential diagnosis of opiate-induced constipation, therefore, becomes a differential diagnosis of constipation in general, and we have to be concerned about problems with the metabolism in the body such as hypothyroidism. We need to be concerned about a number of other processes that can cause obstruction to the colon. And we need to think about other issues such as pregnancy and the like, which can slow transit through the gut. One of the things that can help a great deal in sorting this problem out is to have patients maintain a bowel diary in which they keep track of their stool and stool form for a period of time.

**Dr. Allen:**
You outlined very clearly the importance of differential diagnosis, a proper history and also bowel function diaries. Can you discuss the type of strategies and agents that are currently available to treat opioid-induced constipation, and how do they actually work?

**Dr. Schiller:**
We think about the treatment of constipation by dividing into nonpharmacologic and pharmacologic therapy. So, amongst the non-pharmacologic therapies, an increase in dietary fiber, fluid intake and increased physical activity have all been promoted as lifestyle changes that may modify bowel habit. However, when constipation is due to the constipating effect of an opiate, these modifications rarely are effective. Then, we have to turn to pharmacologic remedies. Laxatives are often the first step that we use. Often stimulant laxatives are used with the idea that they will induce peristalsis where the opiate has reduced it, and these may work. The currently available ones that we have are bisacodyl and senna compound. These are often prescribed in anticipation of constipation when one starts an opiate regimen, and I think that’s a very reasonable approach.

Other medications that people can easily obtain over the counter include stool softeners and some of the bulk-forming or osmotic laxatives. These have a role to play as well. Stool softeners are best thought of as being very modest laxatives, but some patients report great responses to them Osmotic laxatives like polyethylene glycol may be helpful in some of the patients. In the opiate-induced constipation patients, they can modify stool form but don’t always adequately address some of these other symptoms of constipation, such as bloating or difficulty with evacuation. Finally, enemas can be used as part of a bowel treatment strategy. They often retain effectiveness into fairly advanced problems with constipation, especially opiate-induced constipation, but they’re viewed as very bothersome by many patients.

Once these readily available over-the-counter materials have been utilized, we can turn to some of the prescription drugs that have been approved by the FDA for use in treating opiate-induced constipation. One of these is the medication lubiprostone, which works by opening up chloride C2 channels in the intestine to cause increased fluid entry into the intestine and stimulation of motility. Studies have shown that this agent, when given in a dose of 24 mcg twice a day, is effective and has been deemed to be safe in patients with opiate-induced constipation. One of the problems that develops, as happened in our case history, is nausea.

Other medications have been designed to try and block the access of the opiate pain medicine from the mu receptors in the intestine. Now, these are so-called peripherally-acting mu opiate receptor antagonists, or PAMORAs. One of these that has been marketed is an injection medicine, methylnaltrexone. This medication is effective in mitigating opiate-induced constipation and can be given as often as every other day for this purpose. The dose is partially related to body weight with patients who are more than 50 kg getting 12 mg subcutaneously every other day and those weighing less than 50 kg getting 8 mg every other day. Another medicine of this type is naloxegol. This is a tablet medicine and can be taken daily. It offers advantages to patients in that they don’t have to take an injection.

With any of these peripherally-acting mu opiate receptor antagonists, problems with the blood-brain barrier may
allow some of the medicine to get into the central nervous system where they will impact on the effectiveness of the opiate and may induce withdrawal symptoms. This happens infrequently. And, the medicine should be limited in their use to patients who have problems with the blood-brain barrier such as those who have advanced brain diseases, epilepsy or the like.

When we think about these different medications, we have to always weigh the benefit versus the risk, and for many of these medications, we have clear evidence of benefit and risk seems management. For instance, with lubiprostone, if the patient develops nausea, we can reduce the dose or stop the medication. With the peripherally-acting mu opiate receptor antagonists, if the patient develops withdrawal problems, again we can reduce the dose or try a different approach to the problem, so we can usually get the benefit and mitigate the risk with these problems.

We have some drug-drug interactions that can occur with naloxegol in that it is metabolized in the liver by the cytochrome 3A4 enzyme system. Medications that reduce the metabolism by inhibiting this receptor, such as ketoconazole, may result in higher blood levels of the medication. So, one needs to check for drug-drug interactions when prescribing the medication.

Also, these medications have been authorized for treating opiate-induced constipation in non cancer pain. They have not been studied in cancer patients receiving opiate drugs for pain treatment. And although there’s no reason to think that they would work differently, that’s something that we have to keep in mind.

Dr. Allen:
Are there any limited efficacy of laxatives, Dr. Schiller?

Dr. Schiller:
Yes, I think if we look at laxatives in general, they have a tremendous hurdle to overcome when used in a patient with opiate-induced constipation; that is, the potency of opiates in inducing constipation may be more than what laxatives can easily reverse. And so, for instance, sometimes with polyethylene glycol, as was seen in our case history, the medication does not effectively reverse the constipation and may end up causing bloating as the fluid is retained in the gut and not passed further down. So, that's a big problem towards the traditional therapy of this problem, which has been the use of laxatives.

Dr. Allen:
Can you speak a little bit further about opioid withdrawal syndrome?

Dr. Schiller:
This is a problem that can be seen whenever one gives an opiate receptor antagonist to a patient. The peripherally-acting mu opioid receptor antagonists are designed not to penetrate the central nervous system and in most patients do not produce any evidence of withdrawal. However, there are patients who have damage to the blood-brain barrier that may allow greater permeation of the drug into the brain or the blood level may be high in the case of impaired metabolism of the drug so that enough medicine gets into the brain to induce some mild withdrawal syndrome. This is usually manifested by anxiety, sweating, cramps and the other symptoms that we associate with opiate withdrawal.
Dr. Allen:
Okay. So, now I’m curious, and I’m sure that our listeners are too. Let’s go back to our case. What actually happened to Charles, the 45-year-old roofer?

Dr. Schiller:
Well, I ended up seeing Charles in the office, and he had a normal physical examination. On assessing his situation, it was fairly clear that the timing of his symptoms coincided with the start of his opiate therapy, and so we tried him on naloxegol 25 mg daily and had good results. He had bowel movements every one or two days without straining and he developed no side effects. He’s continued the medicine now for about two months with continued efficacy.

Dr. Allen:
If you are just tuning in, you are listening to Continuing Medical Education on ReachMD, and I am your host, Dr. Renee Allen. It is my pleasure to be speaking with Dr. Lawrence Schiller today about the treatments and strategies that are available to clinicians when treating and managing opioid-induced constipation or OIC. Dr. Schiller, what is the best method for preventing OIC in patients who are newly prescribed opioid medications?

Dr. Schiller:
Because the doses of opiates that are commonly used to treat pain have profound effects on the intestine, we need to think about how we’re going to manage the constipation that develops in many of these patients. I think that most clinicians tell patients to consider a stimulant laxative or one of the osmotic laxatives, such as polyethylene glycol, when they’re starting opiate therapy should they develop constipation that is symptomatic and bothersome to them. Other points that might be considered are to use the lowest effective dose of the opiate since the effect on the gut will be dose dependent.

Some of the ways that people approach this problem are a little bit more exotic. One is the use of combination opiate and the antagonist drugs. There are several of these that have been marketed mainly to try to reduce the risk of opiate abuse by converting an oral medicine to an intravenous form. Use of the opiate antagonist blocks the high that the patient might experience by this abuse of the medication, but they also may be less constipating in certain patients and might be considered if a patient needs to have chronic opiate therapy.

Currently, prescription agents that we have for treating opiate-induced constipation such as lubiprostone, methylnaltrexone and naloxegol, have not been labeled for use in an expectant fashion, and I would suggest to our audience that they not be used in that way until studies are done showing their effectiveness for that indication.

Dr. Allen:
What important safety and efficacy data should we clinicians keep in mind when selecting therapies to treat opioid-induced constipation?

Dr. Schiller:
I think we need to keep side effects in mind whenever we utilize medicines because fundamentally, the choice of therapies comes down to estimation of the benefit-to-risk ratio in a given patient. One of the medicines that’s been approved for treating opiate-induced constipation, lubiprostone, is associated with nausea. This nausea can be difficult to manage, and reducing the dose of medicine only works in selected patients to mitigate the problem so that sometimes we have to switch to another agent. Another medication that is used for treating opiate-induced constipation, naloxegol, sometimes will produce problems with a mild opiate withdrawal syndrome. If one looks at the prevalence of this in patients treated with 25 mg daily, you’ll see that this occurs
approximately 3% of the time. Patients sometimes develop an increase in abdominal pain after naloxegol that was more prevalent with the active drug than with placebo in controlled trials, and that’s another side effect that patients should be warned about.

Dr. Allen:
Dr. Schiller, each patient is unique and has their own personal medical history, so with that in mind, what other patient and drug factors should clinicians consider when tailoring therapies to treat opioid-induced constipation?

Dr. Schiller:
In part it depends on what the underlying opiate therapy is for and how long it is anticipated that it will continue. In patients who are receiving short-term opiate therapy, say after an operation, it is probably only necessary to make sure that the patient is following a reasonable diet and activity and hydration schedule and then treat constipation if and when it develops. For those who are taking medications on a chronic basis, it is more important to think about what agent is being used for treating the pain. There is some evidence that patients treated with methadone tend to be more difficult to treat for opiate-induced constipation with naloxegol than some of the other opiate therapies, so that that becomes a consideration as to choice of medication as well. In the end, though, it really depends on what medicine can be used safely in an individual patient.

Dr. Allen:
Dr. Schiller, we, as clinicians, all have those cases that are difficult and at times perplexing. What is the best way to manage treatment-refractory opioid-induced constipation or otherwise adjust the treatment strategy when it's not really that effective?

Dr. Schiller:
We’ve had fairly good success over the years, although it's not all that well documented in the scientific literature, with the use of stimulant laxatives, other laxatives and lifestyle changes in dealing with opiate-induced constipation. The difficulty comes when these things don’t work or produce side effects that the patient finds alarming. For most patients who have not responded to traditional therapies, the three prescription drugs that have been approved by the FDA for treating opiate-induced constipation include lubiprostone, methylnaltrexone and naloxegol, and these can be tried to manage the problem. It will depend, in part, on patient’s individual differences as to which of these might be the preferred one to start with. For example, some patients may have an aversion to receiving subcutaneous injections every other day, and if that were the case, then methylnaltrexone would not be a good choice. Some other patients have preexisting problems with nausea, and in that case lubiprostone would not be a good choice, so that the ultimate selection of agents depends on the individual patient.

There is some evidence from the constipation literature that other drugs may be useful in taking care of constipation. These have not been specifically tried in opioid-induced constipation, and so it’s not recommended that they be used for that indication. But drugs that increase the dose of acetylcholine that’s effective at synapses in the gut, such as acetylcholine esterase inhibitors or bethanechol can be used in some patients with chronic constipation. Misoprostol, a prostaglandin analog, which has diarrhea as a common side effect when it’s used for its approved use for mitigating ulcer disease, has also been tried in some patients with constipation. The old medicine, colchicine, which fairly typically produces diarrhea in patients, has been used in some refractory patients with constipation.
One of the approaches that some people use is to give a more general opioid antagonist, such as naloxone, to patients who are suffering with constipation due to opiates. While this has an effect on the gut and will reverse the opiate effect in the gut as it does in the brain, it also has significant effects in the central nervous system and will reduce pain control, so this is often not a good chronic way of dealing with the problem but can be used in urgent situations such as someone who has a fecal impaction.

Alvimopan was one of the first drugs that would now be recognized as a peripherally-acting mu opioid receptor antagonist drug, and it was originally trialed for use in opioid-induced constipation but had significant side effects. Its use now is limited to prevention of postoperative ileus in hospitalized patients, and so it's not available and is not approved for treating opioid-induced constipation in the United States.

Dr. Allen:

I would like to thank Dr. Lawrence Schiller for joining us today and discussing Opioid-Induced Constipation, Improving Outcomes with Individualized Evidence-Based Treatment. Thanks again, Dr. Schiller, for your time.

Dr. Schiller:

You’re very welcome, Dr. Allen. Thank you.

REFERENCES


