Experts Answer Your Key Questions on OIC

What percentage of people with chronic pain taking opioids have bothersome constipation?

In our collective experience, most patients that are on opioids develop constipation – it is unfortunately one side effect that the patients do not become tolerant to and the reason clinicians need to consider a bowel regimen for patients on opioid therapy. Lifestyle modifications and over-the-counter agents (OTC) improve symptoms of constipation in some patients, however many patients have persistent symptoms and require the use of prescription medications.

When you look to the literature, you could find the prevalence reported anywhere from 10% to 90%. A meta-analysis review of the literature came up with a number around 40% to 50%. In a longitudinal study of 493 adults with chronic non-cancer pain and opioid-induced constipation (OIC), 83% reported straining to pass bowel movements.

Laxatives do not address the underlying mechanism of OIC. As we discussed, a majority of patients that develop constipation fail to obtain adequate relief from OTC stool softeners and laxatives, hence the need for these newer prescriptive agents.

Remember, OIC ISN'T JUST ABOUT BOWEL MOVEMENT FREQUENCY. OIC is defined as a change from baseline bowel habits upon initiation of opioid therapy, including any of the following: decreased frequency, straining, incomplete evacuation, and harder stool consistency

How long can a patient stay on one of these newer agents?

Our panelists described patients that have been stable on opioid therapy for 20 to 25 years who experience persistent symptoms of constipation. The prescription agents approved for OIC are all relatively new agents and include PAMORAs and chloride channel activators. Although these newer agents have not been studied for decades, our panelists felt that, based on the mechanism of PAMORAs blocking opioid receptors, they should be safe long term. The phase 3 efficacy trials are 12 weeks long, but the phase 3 safety assessments submitted to FDA for approval of these agents went out for one year; remember, we're talking about blocking opioid receptors in the gut, so as long as the patient remains on opioids, there's no reason they couldn't remain on a PAMORA.

Can I continue with these newer agents if I stop my patient's opioid?

The PAMORAs aren't actually laxatives per se; they inhibit the mechanism by which opioids cause constipation. So if the patient discontinues opioid therapy, there's no reason to be on a drug that blocks the receptor.

Most package inserts instruct clinicians to discontinue the PAMORA when opioid therapy is discontinued. If you lower (rather than discontinue) a patient's dose of opioid, they can certainly continue their PAMORA agent as long as OIC persists.

How long do you need to stop laxatives and stool softeners before starting a PAMORA?

In one of the PAMORA trials, patients were allowed to maintain their current laxative therapy throughout study duration. Another label instructs clinicians to discontinue all other laxative therapies when starting the PAMORA, and add them back in after a few days if needed.

One of our panelists discussed understanding the time to onset of various laxative therapies; Senna can take 8 to 10 hours to start working, while bisacodyl may be only 4 hours. If it's something like Senna, I probably would wait 8 hours.

Our panelists discussed the rationale for discontinuing OTC laxatives when starting a newer prescriptive agent, as patients may have too robust an effect, a so-called hyper-laxation response. It may be a painful (and messy) event, so the general consensus was to discontinue current laxative treatment and add it back if necessary.

What's the time to relief for some of these newer agents?

The injectable PAMORA can stimulate a bowel movement (BM) in as little as 30 minutes in some patients. With the oral formulations, time to first post-dose bowel movement in one study was 6-7 hours. It may take longer, so our panelists council patients to have access to bathroom, especially in the first few days of treatment. Once stable on these therapies, patients get to know their bowel patterns and can usually plan their day accordingly.

Can these agents be used in older frail patients or are there any special precautions I need to take?

Constipation is quite a common and bothersome condition in the elderly. It is usually multifactorial and certainly worsened by the addition of opioid analgesics. Compared with individuals <65 years of age, the literature suggests that elderly individuals with constipation often report more frequent straining, hard stools, self-digitation, sensation of rectal blockage, and usually <2 BMs per week. Treatment guidelines specifically for the management of elderly patients with OIC are not available.

Both the oral and injectable PAMORAs included elderly patients in their clinical trials, and these drugs seemed effective without any added risks; despite that, keep in mind the potential for drug:drug interactions is probably increased in the elderly population.

Although age was not specifically examined, a post-hoc analysis of one of the PAMORAs showed similar efficacy in treating OIC regardless of maintenance opioid type, dose, or duration of opioid use at baseline.

Our panelists reminded us that not all 70-year-olds are alike and agreed that they have not experienced any different or greater side effects with these agents in the elderly. With elderly or frail patients, there may be other comorbid conditions or concomitant medications that worsen OIC. For example, if an elderly patient is on amitriptyline or other anticholinergic agent, NSAIDs, antihypertensives, or has longstanding diabetes – these can certainly contribute to constipation caused by opioids.

One of our panelists commented that he may be more concerned about the use of Senna, fleets, bisacodyl, and osmotic laxatives in his elderly patients. Clinicians need to be familiar with the general contraindications and warnings for their younger and older patients alike.

Which of the PAMORAs have an indication specifically for OIC in cancer patients?

As it turns out, one of the first PAMORAs out, which was methylnaltrexone, was indicated for OIC in patients with advanced illness requiring palliative care, including cancer patients. That was (and remains) formulated as subcutaneous, although now it is available orally as well. The clinical trials for the more recent orally administered PAMORAs looked at OIC in non-cancer patients because their doses of opioids are pretty consistent and they are not burdened with the comorbidities of active oncology patients. The studying of a non-cancer population that is more stable is an easier study to enroll, and because that was the population studied, that's the indication on the label.

The label (package insert) for PAMORAs notes the indication for opioid-induced constipation for adults with chronic non-cancer pain, but also state that you may include patients with chronic pain related to prior cancer or prior cancer treatment as long as they are stable, ie, those patients who do not require frequent opioid dosage escalation. It's not that they can't be used in patients with a history of cancer, it's that these patients need to be stable. One of our panelists noted that it is very difficult to enroll cancer patients in clinical trials for non-oncology-based therapies, as so many of them are in clinical trials for chemotherapeutic and other anti-cancer agents – it's hard to get them to enroll in laxative or constipation studies.

One panelist noted that although clinicians should follow the label, there's no scientific reason in his practice why these laxatives cannot be used off-label for stable cancer patients, but again noted because they weren't studied in that population that they don't have the official indication.

We also reminded our audience that there are certain scenarios where you would not want to give an agent that promotes forward flow inside the GI tract; any patient with the potential for bowel obstruction or perforation, anybody whose competency of the bowel wall might be compromised, like active Crohn's or ulcerative colitis, or similar GI disorders.

Are there any specific education instructions I need to tell patients or caregivers when we prescribe any of these newer agents?

One of our panelists stressed the importance of compliance, not only with their analgesics, but with their laxative regimen as well. In addition, patients need to take note of how quickly and reliably these agents work, as they may need to stay close to home (or a bathroom).

Another panelist agreed and wanted to make sure that patients understand that this is something that they need to take every day, as presumably they are taking opioids on a regular basis. Patients are used to taking laxatives on a prn basis, so they need to understand that this is something that they take to prevent constipation and not necessarily to chase after it, so that it is a medication for daily – not prn use. Also if there is any cramping or other adverse effects that may suggest obstruction or perforation, I ask them to let the doctor know right away.

Are there any contraindications for using the newer agents?

We already discussed the warning in patients with known or suspected GI obstruction and those who are at increased risk of recurrent obstruction. We

are also concerned about inducing opioid withdrawal in patients who potentially have some underlying problem with the central nervous system (CNS), perhaps traumatic brain injury, dementia, or Alzheimer's, because of the potential passage of the opioid antagonist through the blood brain-barrier. In addition, some of the PAMORAs are metabolized via the hepatic cytochrome P450 enzyme system; there are warnings and contraindications for patients taking moderate to strong P450 inhibitor medicines.

One of our panelists reminded us about potential obstruction in cancer patients. Clinicians should consider flat plate or other radiological assessment to rule out obstruction when suspected in this challenging population.

What is the maximum dose that you would offer for peripherally activating mu-opioid receptor antagonist and chloride channel agonists?

Our panelists concurred to prescribe within the recommended instructions but did note that although there may have been minor efficacy benefits in early trials with escalated doses, there were clearly more adverse effects as well. One panelist mentioned that going above a dose higher than FDA approved could be necessary in certain situations. For example, with lubiprostone, we know that the concentrations are decreased in the presence of methadone, so I supposed you could make that argument theoretically, but in general we recommend sticking to the dosing guidelines in the package insert.

Do you always discontinue stool softeners and laxatives when using PAMORAs or is there a role for combination therapy?

Our panelists mentioned that they tend to stop stool softeners and laxatives when starting prescriptive laxatives, and that one or more of the package inserts recommend doing so when starting the PAMORA and assess the patient's response. And if after a few days, you think they still need the additional OTC stool softeners and laxatives, you can then restart them. One speaker reminded us that not all constipation is opioid induced, and that multimodal laxative therapies may be beneficial.

Can you switch between PAMORAs if one fails to work or if a patient has an issue with the drug, maybe I assume some drug interaction or may be access through managed care?

Most clinicians consider OTC interventions for OIC as first-line therapy; however, failure of these options to provide adequate relief should be determined quickly to facilitate consideration of further intervention with PAMORAs or other prescription laxatives. Our panelists agreed that there were no studies that they knew of that addressed switching from one prescription agent to another. They agreed – other than specified

contraindications – there is probably no reason why you can't. Most reasons behind switching has to do with insurance coverage. Some may change an insurance plan and one of these agents is preferred over the other.

When patients have constipation, prescribers may think about treatment the way they do opioid rotation – that each one of the agents might work a little bit different at the receptors; so there may be some theoretical rationale to switching agents. Also, if you are having issues with access to the drug or some weird drug-drug interaction or side effects of a particular drug, you want to make sure it is not because of the class of drug, and then you might consider using another PAMORA in the class.

As a reminder, although we have mentioned constipation throughout our lecture, that not every patient defines constipation the same. There is an expert GI group that rates functional gastrointestinal disorders and define criteria for each – they are called the Rome Criteria. They are up to their fourth iteration. Constipation is not just infrequent bowel movements. That's what many of us think it is, but it also has to include straining or hard lumpy stools or a sense of incomplete evacuation, a sense of obstruction, and manual maneuvers to facilitate defecation. So remember, it's not just the number of bowel movements that patients have when you query them about constipation. You need to ask about some of those other symptoms that go along with the definition of constipation as well.

Are there any significant adverse drug reactions of the PAMORAs?

One of our panelists opined that despite the package insert warning about drug interactions, he was not overly concerned as, even if the plasma levels of PAMORAs were to increase, these are pretty safe drugs because, again, they're acting as antagonists on the receptors in the gut. Unless there is some kind of problem with the blood-brain barrier, we don't expect they are going pass into the CNS, so the likelihood of adverse effects is low. Now, there are adverse effects that are obviously listed in the insert; one for example is hypohidrosis, which is a kind of a sweating that can happen if someone is having a normal bowel movement and GI cramping. It's hard to know whether these side effects are from the actual PAMORA or they're from the stool moving through the bowel. But, in any case, the side effects listed are usually minor side effects that tend to abate over time.

Another panelist reminded us that at least two of these products warn about the potential for drug-drug interactions because of P450 metabolic pathway. So, if you're going to use some of the classic antifungals, antibiotics like clarithromycin, or some of the antiretrovirals, you need to worry about inhibiting the P450 system and raising your plasma levels of these drugs. As mentioned above, if anything, you would probably have a more robust bowel

response – but clearly, we want to avoid any type of drug-drug interactions if we can.

Is there any evidence of tolerance to PAMORAs?

Recall that that these are antagonists that bind to the opioid receptors; our clinicians related this question back to tolerance related to opioid analgesics which, if you think about, once you achieve your therapeutic dose in the chronic pain setting, we really don't see tolerance; patient doses just don't progressively escalate for years and years on end. They reach a point where a stable dose remains effective. As we discussed, there are some studies with the PAMORAs that suggest effectiveness at the end of 52 weeks, and our panelists have had patients on them for years at this point without evidence of tolerance.

The pharmacist on our panel opined that with PAMORAs, all you do is occupy the receptor. The efficacy is by disallowing another drug linking with the receptor, so he could not imagine physiologically or pharmacologically there would be a way to become tolerant to this.

Why start with over-the-counter options? Is it safe to prophylactically start my patients on one of the newer agents?

Our panelists affirmed and noted that they have asked themselves this same question about these newer prescriptive agents. In practice, they still are doing the same thing as we did 25 years ago, the same OTC stool softener and laxative regimen. When you consider the patients who enroll in OIC clinical trials, they seem to have failed these agents, so why not go right to one of the newer agents?

They also noted that when you start a patient on a laxative regimen, they don’t often fully comply with it or it’s not effective, and so they get very discouraged. An agent that is going to provide them a better chance of relief/laxation is probably a better option than having them go through a series of trial and errors and dealing with extreme constipation.