

# Recognizing and Treating Opioid-Induced Constipation in Chronically Ill Children

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**O**pioid-induced constipation (OIC) is a well-recognized sequela of opioid use for pain management across all patient populations. Some research studies suggest OIC is the most common adverse reaction to opioid use, and that OIC is one of the most detrimental adverse reactions impacting a patient's quality of life (McCarberg, 2013; Stewart & McNeilly, 2011). In pediatrics, there is no succinct definition to diagnose OIC. With no such definition, there is no universal protocol in place for nurses and other clinicians to adequately manage this condition.

Constipation, even without the use of opioids, is an issue for many chronically ill children. These children are frequently in and out of the hospital, and many undergo procedures that require opioids for analgesia. Stephens and colleagues (2017) looked at the diagnosis and treatment of constipation in children receiving Medicaid. Their study further investigated the healthcare utilization and spending for these children based on complex chronic conditions (Stephens et al., 2017). Of the 267,188 children included in the study, 6.8% had more than one chronic complex condition. This small cohort (6.8%) was identified as responsible for 33.5% (\$26.6 million) of total money spent on constipation, and 70.3% of all inpatient constipation spending (Stephens et al., 2017). Stephens and colleagues (2017) suggest that children with chronic, complex conditions need extra consideration regarding constipation because this population has a higher incidence of constipation diagnosis, which consequently results in high acuity healthcare utilization.

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Opioid-induced constipation (OIC) is a problem that plagues a large number of patients who require pain management through opioids. Research suggests about 40% of patients who are prescribed opioids experience constipation (Jitpakdee & Mandee, 2014). For hospitalized children, the most commonly used intervention for both OIC prophylaxis and treatment is a combination of different laxatives. Research suggests, however, that this treatment plan is often unsuccessful and leaves patients dissatisfied. Evidence indicates treatment modalities aimed toward OIC are not started early enough, and many do not treat the root cause of OIC (Gyawali et al., 2015). Opioid receptor antagonists are emerging in the field of OIC management. The key factor to receptor antagonists in the treatment of OIC is the inhibition of intestinal paralysis, without the disruption of the analgesic effect of the opioid medication. Education on the most effective treatment modalities for OIC in chronically ill children is important for nurses and frontline providers. An understanding of OIC, the importance of early intervention, and the most effective treatment modalities will allow providers to better advocate for and treat their patients.

**Key Words:** Opioid, constipation, pediatrics, treatment.

Constipation should be addressed in patients being treated with opioids before it even begins, but it is often unnoticed in care until it is a problem. Nurses have the opportunity to ensure that prophylaxis is implemented as a standard of care and the first line of defense against OIC. Without guidelines, physicians and pediatric teams decide prophylactic treatment preference. This leads to a delay in choice and a delay in treatment (Feudtner et al., 2014). A plan for OIC in chronically ill children at the start of opioid treatment would alleviate this burden. It is imperative that clinicians are educated about treatment options and on the mechanism of action when OIC becomes a problem. An emerging class of medications (opioid antagonists) includes medications to target the exact mechanism of action that causes OIC. The purpose of this article is to provide pediatric nurses with a better understanding of OIC so that as frontline providers, they can advocate for chronically ill children and help to prevent and treat the discomfort asso-

ciated with OIC. A specific emphasis on the understanding of OIC, the need for prophylaxis, and the treatment modalities for OIC will be addressed.

## Understanding OIC in Children

Whereas OIC has Rome III diagnostic criteria in the adult population, in pediatrics, the Rome III criteria for childhood constipation only addresses chronic constipation issues, leaving uncertainty regarding acute constipation (López et al., 2015). Rome III diagnostic criteria is helpful in diagnosing gastrointestinal disorders. Definitions of OIC vary, but they typically involve recent opioid treatment and symptoms associated with functional constipation. These symptoms often involve infrequency of bowel movements, hard stools, straining to stool, and incomplete evacuation of stool (Drewes et al., 2016). Pediatric patients are unique in that they often

manifest symptomology differently than adults. Signs and symptoms that may manifest more often in children include abdominal distension, intolerance of enteral feeds, cramps, and irritability (López et al., 2015).

Among all patient populations, at least 40% of patients experience constipation related to treatment with opioids (Jitpakdee & Mandee, 2014). Because the definition of acute constipation in children differs by source, the identification of pediatric patients experiencing OIC is difficult to pinpoint. Constipation can vary depending on multiple factors, such as whether the patient has a medical or surgical diagnosis, whether constipation issues existed before hospital admission, and what other medications patients may be taking. Many chronically ill children spend a great deal of time in the hospital, and opioids are often a mainstay of their pain treatment. Research suggests constipation is not well-controlled for hospitalized children. López and colleagues (2015) found that 46.7% of critically ill children admitted to a pediatric ICU experienced constipation while in the hospital. A different study assessing constipation in pediatric orthopedic patients found that 77.7% of patients experienced constipation (Mantegazzi, Seliner, & Imhof, 2016). After implementing a regimen for constipation in post-operative orthopedic patients, these researchers found close to a 27% decrease in constipation, with only 50.8% of patients experiencing constipation. Identifying OIC in children is a challenge, which contributes to the problem of inadequate treatment.

## Pathophysiology of OIC

Opioids act on the central and peripheral nervous systems. They target three types of receptors: mu, kappa, and delta receptors. The analgesic effect of opioids is achieved by receptor activation in the central nervous system (CNS) (Stewart & McNeilly, 2011). When opioids reach mu receptors in the peripheral nervous system, specifically in the gastrointestinal tract, the normal functioning of the gastrointestinal tract is compromised. Opioid action on mu receptors in the gastrointestinal tract can cause decreased peristalsis, inhibition of water and electrolyte secretions, constriction of the pyloric sphincter, and an increase in anal

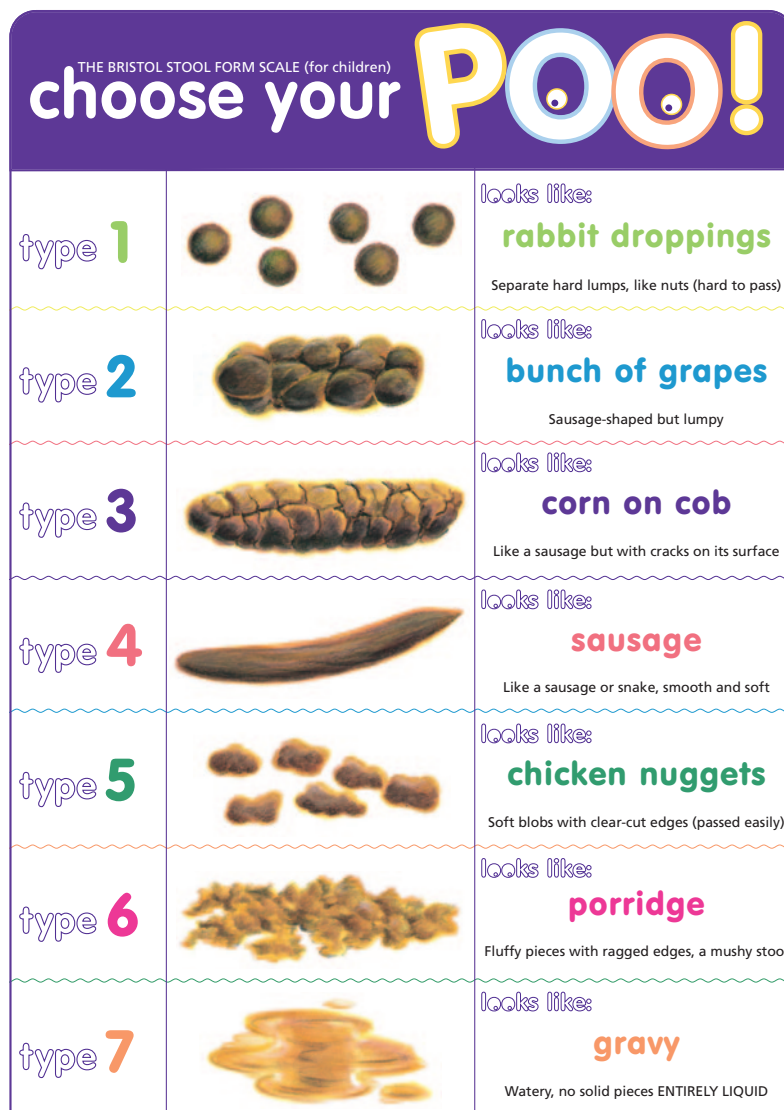
sphincter tone. These changes in gastric functioning result in a delay in gastric emptying, dry and hard feces, a decrease in rectal sensitivity, and ultimately, constipation (Gyawali et al., 2015; Stewart & McNeilly, 2011).

## Addressing OIC in Children

The ultimate goal of OIC management is to prevent constipation from the initiation of opioid treatment (Johnson & Argoff, 2015). Constipation induced by opioids is predictable. Providers know that it is a frequent problem, and clear preemp-

tive measures are available (Feudtner et al., 2014). The first step in prophylaxis of OIC is patient assessment. In assessing children, the patient and parents can use a visual scale, such as the Bristol Stool Form Scale (see Figure 1), to appropriately identify the consistency of their stool (Stewart & McNeilly, 2011). It is important to have a baseline knowledge of a patient's bowel function and frequency. Every patient being treated with opioids is a presumed risk for constipation (McCarberg, 2013); therefore, all patients should have a baseline bowel assessment.

**Figure 1.**  
**The Bristol Stool Form Scale for Children: Choose Your Poo!**  
**A Visual Guide for Assessing Children's Stool**



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Traditional non-medical intervention for constipation prevention involves increasing physical activity and fluid intake, as well as dietary modification. Although these interventions aid in peristalsis, they are not necessarily realistic for children who will often need medical intervention due to their conditions (Feudtner et al., 2014; Stewart & McNeilly, 2011). In 2005, in collaboration with the Institute for Health Improvement (IHI), the Child Health Corporation of America (CHCA) implemented an improvement initiative designed to reduce narcotic-related adverse drug events across the 42 children's hospitals within their organization (Sharek et al., 2008). Together, IHI and CHCA acknowledged constipation related to narcotics as an adverse drug event. After implementing their improvement initiative, they reported a 68.9% decrease in constipation. Based on these findings, CHCA recommended laxatives and stool softeners should be used proactively when narcotics are prescribed (Sharek et al., 2008). This recommendation has not become a standard of care across pediatric inpatient treatment as evidenced by the lack of a consistent prophylactic regimen. For example, in a study of children with sickle cell disease across 29 hospitals, one-third of patients who were prescribed narcotics did not have a laxative or stool softener prescription (O'Brien, Fan, & Kelleher, 2009).

One key component to prophylactically treating OIC at the time of opioid prescription is to change the clinician behavior (Chen, Nguyen, Schrager, & Russell, 2016). In a retrospective study performed at the Children's Hospital of Los Angeles (CHLA) of 6,682 patients over a 16-month period, only 14.5% were prescribed a prophylactic medication for OIC (Chen et al., 2016). Recommendations and research exist, yet there is no standardized protocol for addressing OIC prophylaxis in chronically ill hospitalized children. Furthermore, prophylaxis would likely reduce the large amount of money spent on constipation treatment for chronically ill children described by Stephens and colleagues (2017). Prophylaxis for constipation should be a requirement for opioid prescription, but the best and most cost-effective option has not been established (O'Brien et al., 2009).

A major component in the difficulty of managing and preventing OIC lies in the choice of which medication to use both prophylactically and in treatment. With so many options and varying data on the effectiveness of these medications, there is no clear choice of medication to prescribe. Providers are still the ultimate decision makers on what medication to prescribe, and therefore, need to have a knowledge and understanding of all options.

### Laxatives

Laxatives work to loosen stools and stimulate bowel movements. There are multiple forms of laxatives: osmotic, stimulant, bulk forming, and stool softeners. Osmotic laxatives pull water into the gut lumen. Lactulose, sorbitol, and magnesium citrate are all examples of osmotic laxatives (Sharma & Jamal, 2013). Because these laxatives work osmotically, it is important to pay close attention to electrolytes.

Stimulant laxatives trigger colonic contractions. These address the issue of impaired peristalsis (Sharma & Jamal, 2013). Bisacodyl and senna are commonly used stimulant laxatives. Senna in particular increases peristalsis and intestinal secretion. In one study, in comparison to other oral bowel regimen medications, senna was found to reduce the likelihood of problematic constipation (Feudtner et al., 2014).

Bulk-forming laxatives are indigestible fibers that pull water to make the stool more "bulky" (Sharma & Jamal, 2013). The most commonly used pediatric bulk-forming laxative is polyethylene glycol. Bulk-forming laxatives are not recommended with OIC because the increased stool bulk can cause pain and obstruction (Feudtner et al., 2014; Sharma & Jamal, 2013).

The last type of laxatives is known as stool softeners. Stool softeners work by softening the stool so patients are not straining and experiencing pain while attempting to evacuate stool. Stool softeners are often used in tandem with other laxatives. These medications aid in the mixing of aqueous and fatty substances, which in turn softens the stool (Poulsen, Brock, Olesen, Nilsson, & Drewes, 2015). The most common stool softener used with children is docusate sodium.

Laxatives are very common in treatment and prophylaxis of OIC,

but patients are often not satisfied with laxatives for their constipation treatment (Feudtner et al., 2014). This method of treatment is often not successful for OIC because laxatives do not target the mu-receptors (Sharma & Jamal, 2013).

### Opioid Antagonists

The pathophysiology of OIC involves the mu receptors in the peripheral nervous system (PNS), specifically in the gastrointestinal (GI) tract. Recently, newer medications that target the cause of OIC have become available. This class of medications is known as opioid antagonists. The goal of peripheral-acting mu-opioid receptor antagonists (PAMORAs) is to peripherally provide inhibition of intestinal paralysis without disrupting the analgesic effect of the opioid medication acting on the CNS mu receptors. Table 1 summarizes the different opioid antagonists and their effect on OIC.

#### Naloxone

Naloxone is a well-known opioid antagonist, but research suggests it does not necessarily distinguish between CNS and PNS mu receptors. Naloxone stimulates peristalsis in the PNS GI tract, but it impairs the analgesic effect of the opioid in the CNS (Drewes et al., 2016; Sharma & Jamal, 2013). For chronically ill children who require additional pain management, this is not the best choice. Additionally, patients who rely on opioids can experience withdrawal with medications like naloxone.

#### Naltrexone

Naltrexone, another opioid antagonist, is similar to naloxone in that it does not exclusively go to peripheral mu receptors. It crosses the blood-brain barrier, which again leads to reversing the action of the opioid on the CNS, and in turn, can cause pain (Stewart & McNeilly, 2011).

#### Methylnaltrexone

Adding "methyl-" to naltrexone causes a change in the polarity of the drug. Methylnaltrexone is positively charged and typically does not cross the blood-brain barrier into the CNS. Thus, methylnaltrexone strictly competes with peripheral mu receptors (Flerlage & Baker, 2015).

Methylnaltrexone obtained approval by the U.S. Food and Drug Administration (FDA) in 2008 for OIC

**Table 1.**  
**Opioid Antagonists in the Treatment of Opioid-Induced Constipation**

Medication	Opioid Receptor Activation	Effect on Opioid-Induced Constipation
Naloxone	CNS + PNS	Does not exclusively target peripheral nervous system opioid receptors; can experience reverse of analgesia.
Naltrexone	CNS + PNS	Does not exclusively target peripheral nervous system opioid receptors; can experience reverse of analgesia.
Methylnaltrexone	PNS	Exclusively targets peripheral nervous system opioid receptors; proven to induce defecation.

**Notes:** CNS = central nervous system, PNS = peripheral nervous system.

in palliative care. More recently it has been approved for OIC in adults suffering from chronic non-cancer pain (Johnson & Argoff, 2015). Methylnaltrexone can be administered both orally and subcutaneously, but its subcutaneous administration has gained attention for its use in patients who are unable to tolerate oral bowel regimens (Flerlage & Baker, 2015). In one research study involving adults, methylnaltrexone injection elicited laxation within 4 hours for 48% of patients with OIC in advanced illness (Johnson & Argoff, 2015).

Like most research, studies involving methylnaltrexone injection for OIC in children are far less prevalent than those involving adults. Thus, studies and case presentations seen in pediatrics demonstrate that methylnaltrexone injection is a plausible treatment for OIC in children. One case presentation involving an 8-year-old with terminal neuroblastoma recounts the multiple opioids used for pain control, as well as the absence of a bowel movement for 25 days (Kissling, Mohassel, & Heintz, 2012). On day 25, methylnaltrexone was prescribed based on the recommended prescribing information. Within 10 minutes of the subcutaneous injection, the patient defecated (Kissling et al., 2012). Another article addressing OIC in a critically ill child showed similar results. This patient, a 9-year-old boy with stage IV intestinal graft versus host disease, was experiencing severe abdominal pain that required treatment with high doses of morphine (López et al., 2016). He experienced severe constipation due to the morphine, refractory to standard treatment modalities, and was then given a methylnaltrexone injection; he defecated within 2 hours. These case studies highlight the efficacy of methylnaltrexone injection for children with OIC.

Flerlage and Baker (2015) performed a retrospective analysis of children, adolescents, and young adults with progressive incurable cancer, and consequently OIC, at St. Jude's Children's Research Hospital. The research over a 5-year period looked at children who were deceased. All patients in the study ultimately received methylnaltrexone. Flerlage and Baker (2015) point out that each of the 9 children included in the study had documented OIC, and previous attempts to treat their OIC with enteral preparations and suppositories had failed. In 7 of these 9 children, methylnaltrexone successfully produced laxation within one hour of subcutaneous administration. The other 2 children did not have laxation with the first dose but responded to methylnaltrexone injection with successive doses.

### Nursing Implications

Research on OIC in children clearly emphasizes the need for better planning and recognition of OIC from clinicians. Embedded in the definition of professional nursing is the objective of "prevention of illness and injury, alleviation of suffering through the diagnosis and treatment of human response, and advocacy in the care of individuals, families, communities, and populations" (American Nurses Association, 2010, p. 10). Nurses are trained to be a patient's greatest advocate and to approach care with the driving goal of patient health and well-being. As front-line providers caring for pediatric patients with OIC, nurses have the opportunity to achieve this goal through improved recognition, understanding, prophylaxis, and appropriate treatment.

Nurses also have the opportunity to educate parents. Voepel-Lewis,

Zikmund-Fisher, Smith, Zyzanski, and Tait (2015) performed a study surveying parents of children receiving opioids to assess parental response to their child's pain and adverse drug events related to opioid use. Parents were more concerned with alleviating their child's pain than they were with the opioid-associated adverse drug events that could occur (Voepel-Lewis et al., 2015). Nurses can teach parents that pain control can be achieved, and adverse drug events can be avoided or adequately treated as well.

Pediatric nurses need to fully grasp OIC and why it occurs in their patient population. They need to be aware of the necessity to assess all patients taking opioids, and must be alert for signs and symptoms of OIC. It is essential that in addition to advanced practice providers, nurses have a strong knowledge base of commonly used treatment modalities for OIC and issues that occur with these treatments (Stewart & McNeilly, 2011). Nurses can advocate for the best medication choice and the introduction of opioid antagonists when they feel alternate medications are not working.

### Opportunity for Improvement

Chronically ill children continue to suffer from OIC. Current commonly used treatment modalities are not targeting the cause of OIC, and consequently, are not the most effective in OIC management. Emerging medications, such as opioid antagonists, target the cause of OIC. Methylnaltrexone in particular exclusively targets peripheral nervous system opioid receptors, which does not affect the analgesic actions of the opioid itself. With better clinician education and implemented prophylaxis there is potential to prevent OIC and avoid

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#### Learning Outcome

After completing this learning activity, the learner will be able to assess and identify how to prevent and/or treat the discomfort associated with opioid-induced constipation in children with chronic conditions.

#### Learning Engagement Activity

Review Table 1 to identify how different opioid antagonists affect opioid-induced constipation. Identify which antagonists inhibit intestinal paralysis without disrupting the analgesic effect of the opioid medication.

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patient suffering. Nurses can make an impact, advocate for prophylaxis, and encourage the use of the best treatment modalities for the health and well-being of their patients.

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