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Opioid-Induced Constipation

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Abstract

Introduction. Opioid-induced constipation (OIC) is common in people treated with opioids and poses risks for physical sequelae, analgesic discontinuation, and decreased quality of life.

Methods. Targeted literature review of evidence- and consensus-based data on appropriate diagnosis, concise definition, and conventional and newer management strategies for OIC.

Results. OIC may develop early and need early treatment. To address gaps in consistent definitions and treatment recommendations, a consensus panel organized through the American Academy of Pain Medicine Foundation set diagnostic criteria and endorsed the Bowel Function Index for OIC assessment. The panel further proposed management strategies for OIC, including a proposed threshold for prescriptive therapies.

Discussion. OIC results from action exerted on opioid receptors in the gastrointestinal tract, a mechanism distinct from idiopathic constipation. Lifestyle changes and over-the-counter drugs are first-line treatments but leave refractory constipation in many opioid-treated patients. Newer therapeutic modalities that are available and in development are highlighted.

Summary. Physicians need a better understanding of the negative impacts of OIC for patients and better OIC-specific methods to assess, treat, and monitor it.

Key Words. Opioids; Side Effects; Constipation

Introduction

Opioid bowel dysfunction (OBD) is a common side effect of opioid therapy for pain as a result of the action exerted via mu-opioid receptors throughout the gastrointestinal (GI) tract [1]. Opioid-induced constipation (OIC) is the most common OBD and may persist throughout the treatment period [1–3]. The economic burden of OIC in higher total healthcare costs is significant compared with nonopioid-treated patients [4], and pain management, productivity, and health-related quality of life also suffer [5,6].

Close to one-half of patients on long-term opioids experience OIC and, of those, fewer than half get adequate relief from conventional treatment with laxatives [7–10]. In a systematic review of eight studies, opioid-treated patients with noncancer pain reported constipation as the most frequent adverse effect, experienced by 41% compared with 11% of placebo-treated patients [8]. In palliative care, OIC is suffered by 30–50% of patients [9]. Among 520 cancer patients who answered using the Knowles–Eccersley–Scott symptom score questionnaire, 61.7% reported a

degree of constipation that was problematic for the patient [10].

Some literature suggests morphine is the opioid most commonly associated with constipation [11], and a systematic review of literature comparing the adverse effects of transdermal opioids, including fentanyl, with modified-release oral morphine found less OIC with transdermal opioids [12]. It unclear whether this is due to a unique property of the molecule or the delivery route that avoids contact with the GI mucosa; furthermore, the opioid dosage, the amount and type of constipation therapy used, and variable study and reporting methods also likely affect prevalence reports [9].

Treatment of OIC is often hampered by a number of factors, including clinician failure to appreciate the potential for morbidity and even mortality; by breakdowns in communication between physicians and patients; and, until recently, by the lack of clear, consensus-built guidelines for assessment and treatment [1]. This manuscript reports on evidence- and consensus-based data on appropriate diagnosis, concise definition, and available management strategies for OIC, including conventional and newer therapeutics.

Risk/Benefit Analysis for Long-Term Opioid Therapy

Clinicians who treat pain are tasked with considering alternatives to opioids, weighing the risks and benefits of opioids and, if judged necessary, performing risk stratification and periodic reassessment [3]. Risks with opioid therapy include misuse, addiction, respiratory depression, opioid-related endocrine dysfunction and hypogonadism, sleep-related breathing disorders worsened by opioids, opioid tolerance, and opioid-induced hyperalgesia [3,13].

Diagnosis

Diagnostic criteria for constipation include at least two of the following symptoms over three months: fewer than three bowel movements per week, straining, lumpy, or hard stools, a sensation of anorectal obstruction, a sensation of incomplete defecation, and manual maneuvering to accomplish defecation [9]. However, difficulty arises in that the complaints must be present for at least 6 months, yet OIC may develop within days or weeks of treatment initiation and need fast treatment. Further exacerbating the difficulty of diagnosis, clinical trials frequently exclude patients with constipation, and current outcome measures underestimate how many patients suffer from OIC in palliative care [14].

The need is for a consensus definition of OIC [15]. In March 2015, a multidisciplinary consensus panel organized through the American Academy of Pain Medicine Foundation (AAPMF) met in Washington, D.C., to consider available OIC assessment and diagnostic tools. The panel set criteria for the definition of OIC to include a set of objective measures (e.g., stool frequency and consistency), one or more patient-reported outcomes, such as ease of defecation, and changes in those measures following opioid initiation. After reviewing the evidence the panel endorsed the work of a previous multidisciplinary consensus group, which met in 2014, and defined OIC as a change from baseline bowel habits upon initiation of opioids that is characterized by any of the following symptoms [1]:

- Reduced bowel movement frequency.
- Development or worsening of straining to pass stool.
- A sense of incomplete rectal evacuation.
- Harder stool consistency.

Tools to diagnose OIC make use of objective measures (e.g., bowel movement frequency and stool consistency) and subjective patient report. Two constipation-specific instruments available to assess impact and severity are the Patient Assessment of Constipation Quality of Life (PAC-QOL) [16] and the Patient Assessment of Constipation Symptoms (PAC-SYM) [17] questionnaires. After a review of the clinical application of available tools, some of which are limited in terms of clinical utility by their length, the AAPMF consensus panel endorsed the Bowel Function Index (BFI) [18–21], a patient-reported outcome tool containing only three items (pertaining to ease of defecation, incomplete evacuation, and patients' judgment of constipation) as the method best suited for assessing OIC in most clinical settings [19].

A differential diagnosis should be performed to exclude comorbid conditions that can cause or exacerbate constipation or problems with rectal evacuation. These include: obstructing colon cancer, any obstruction, Parkinson's disease, diabetes, constipating medications (e.g., iron supplements, antidepressants), or an underlying condition such as dyssynergic defecation or large rectocele [1]. Thus is it important for the clinician to evaluate the extent to which the constipation followed and was definitely caused by the initiation of opioid therapy and to consider eliminating or reducing doses of concomitant medications that can also contribute to constipation during opioid therapy. A consultation with a knowledgeable gastroenterologist may form part of the differential diagnosis. The OIC definition proposed by Camilleri et al is useful in this regard because it does not require a timeframe for symptoms to appear and relies on subjectively reported changes from baseline [1].

Morbidity

Physicians have not long recognized many adverse effects, including OIC, with long-term opioid administration [13], and patients may resist discussing their bowel habits with healthcare providers. However, it is important to facilitate such discussion, because a number of complications and adverse effects can occur with OIC, including dyspepsia, reflux, bloating, spasm, cramping

[22], fecal impaction [23], urinary obstruction or infection [24], pain, hospitalizations, lessened quality of life, and interference with the pain treatment regimen [10].

Treatment Options

Most treatment for constipation begins with encouraging exercise, activity, fluid intake, and dietary fiber and the use of stool softeners and laxatives. The European Association for Palliative Care recommends prophylactic laxatives for OIC in cancer patients [25]. No evidence exists to recommend one laxative over another [1].

A stool softener to ease passage of stool may be prescribed in combination with a laxative [26]. Laxatives include osmotic agents (e.g., polyethylene glycol solution), which retain water in the gut, and stimulant laxatives (e.g., senna, bisacodyl), which are designed to increase intestinal motility [1,26]. Osmotic agents may be mixed with electrolytes to avoid dehydration. Bulk laxatives are not recommended for OIC [27]. These agents along with behavioral modifications can be considered first-line treatments for OIC due to their convenience, low cost, and favorable risk profile. Many patients will improve after adjusting doses of OTC laxatives; however, because the mechanism of OIC differs from that of idiopathic or functional constipation, many first-line treatments for constipation may not be effective for OIC [1,2], leaving patients with refractory constipation.

Newer OIC therapies target the underlying mechanism of OIC by displacing opioids from the receptors in the GI tract without affecting the centrally activated mechanism that gives rise to analgesia. These peripherally acting mu-opioid receptor antagonist (PAMORA) drugs and other OIC-specific therapeutics may benefit patients who do not respond to first-line treatment. Two FDA-approved drugs in the PAMORA class are subcutaneous methylnaltrexone (MNTX) and naloxegol [28–30]. An oral MNTX is also in development for OIC [31]. These drugs demonstrated efficacy over placebo, but not all patients tested responded.

Clinical effectiveness of MNTX, defined as the ability to induce spontaneous bowel movement, was 50–60% in clinical trials [32]. The most common drug-associated adverse effects with MNTX were abdominal pain, flatulence, and nausea. Reduction of dose with MNTX is advised in patients on methadone, who demonstrate high sensitivity to the side effects of peripheral opioid antagonists [13]. An advantage of MNTX is that it has not induced abstinence syndrome in clinical trials.

The clinical evidence for naloxegol shows greatest efficacy at a dose of 25 mg but also greater risk for adverse effects [33–36]. In a Phase 2 trial, naloxegol efficacy, defined as increase in weekly bowel movement frequency, was greater than placebo for patients treated with 25 mg (2.9 vs 1.0 [$P = 0.0020$]) and 50 mg (3.3 vs 0.5 [$P = 0.0001$]) of once-daily oral naloxegol and was maintained over 4 weeks [34]. The most frequent adverse events were abdominal pain, diarrhea, and nausea and were mostly mild and transient at doses of 5 mg and 25 mg, increasing in frequency and severity at 50 mg [34]. In two identical Phase 3 trials, 12.5 mg and 25 mg doses of naloxegol demonstrated statistical treatment response over placebo measured over 12 weeks without loss of analgesia [36]. Adverse events were most frequently reported in the 25 mg group. In a 52-week Phase 3 trial with 804 patients, the most common treatment-emergent adverse events with 25 mg nalaxegol compared with usual care were abdominal pain (17.8% vs 3.3%), diarrhea (12.9% vs 5.9%), nausea (9.4% vs 4.1%), headache (9.0% vs 4.8%), flatulence (6.9% vs 1.1%), and upper abdominal pain (5.1% vs 1.1%) [35]. Most were mild or moderate, occurred early, and resolved during treatment or after discontinuation.

PAMORA drugs act peripherally and are without evidence thus far of central nervous system involvement. However, use should be avoided in patients with conditions that compromise the blood brain barrier until safety can be demonstrated due to potential for serious withdrawal and reversal of analgesia.

Other medications utilize different mechanisms of action. Lubiprostone is a locally acting chloride channel activator [37,38], and prucalopride, approved for use in several countries but not the United States, is a high-affinity serotonin type-4 receptor agonist [39]. There are additional OIC-specific drugs, including several PAMORA drugs, now in development [40–45]. The most common adverse events (>5%) were diarrhea, nausea, vomiting, and abdominal pain for lubiprostone [38].

In addition, the effects of lubiprostone are reduced in a dose-dependent manner by the diphenylheptane opioids (e.g., methadone, propoxyphene), and so lubiprostone is not recommended in patients treated with these opioids [38].

Threshold for Prescription Therapies

Prophylactic constipation treatment at opioid initiation is recommended [1]. Evidence does not support one OTC treatment over another, and OIC may improve or remain refractory. Consideration of prescription therapies is recommended by the AAPMF consensus panel in patients whose BFI score is $\geq$30 points [19] with previous or current use of first-line therapies. There is no consensus on choice of appropriate prescription agent, but cost, efficacy, and side effect comparisons are factors to consider. Additional assessment is part of ongoing clinical monitoring of opioid adverse effects, based on clinical judgment and individual patient need, particularly in regard to bowel movement frequency, if the patient can recall it. The Bristol Stool Form Scale may be useful for patients with advanced illness, cognitive difficulties, or other challenges in communication [46].

More invasive therapies may be necessary for refractory constipation and fecal impaction, which requires prompt treatment [23,26]. Manual disimpaction, enemas, and suppositories are sometimes necessary but are embarrassing and painful to patients, and can also lead to complications that include rectal bleeding, bowel perforation, and infection [32,47]. Given that OIC is common with opioid administration, every effort should be made to institute preventive care that avoids the subsequent need for more invasive remedies.

Summary

Many patients on long-term opioids for pain experience OIC and related risk for significant morbidity. The mechanism of OIC differs from idiopathic constipation and requires prompter assessment, preferably with a validated tool such as the BFI. Consensus-based recommendations for clinical diagnosis and treatment options encompass behavioral modifications and OTC agents as first-line therapies, and OIC-specific formulations for patients whose constipation remains refractory.

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