

The Impact of Opioid-Induced Constipation (OIC) in Patients Receiving Opioids

Clinical and Economic Considerations in Chronic Pain Management

Opioids are commonly prescribed to treat patients who suffer from a variety of chronic pain conditions which have not adequately responded to other treatment options.^{1, 2, 3} Common conditions which necessitate opioid treatment for chronic non-cancer-related pain include muscle, joint, and limb pain.⁴ While opioids are effective in alleviating pain, they can produce unpleasant side effects including constipation, sedation, nausea, and vomiting.^{5, 6} Opioid-induced constipation (OIC) is one of the most common side effects of opioid use and can occur at the beginning of opioid therapy. Unlike other opioid-related side effects, OIC does not usually abate over time and it may persist for the duration of therapy.^{6, 7} Therefore, it must be anticipated, monitored, and addressed throughout the course of opioid treatment.⁶

Estimates of the rate of OIC vary.¹ This is due to variations in studies, including differences in study design, population heterogeneity, definition of constipation, type/route/duration/dose of opioid used, and patient-reported

Constipation is one of the most common side effects of opioid therapy.

vs clinician-reported data. A meta-analysis of randomized controlled trials by Kalso et al reported rates of OIC as high as 41%,⁸ whereas a survey-based study by Bell et al reported the rate of OIC as high as 81%.⁹ Despite the variation in estimates, OIC is common and should always be included in a discussion of the potential side effects of opioids.

OIC is Caused by the Binding of Mu Receptors in the GI Tract

Opioid receptors are found throughout the central nervous system (CNS), peripheral nervous system, gastrointestinal (GI) tract, and other tissues.¹⁰ There are different types of opioid receptors in the body including mu, kappa, and delta.^{10, 11} Activation of the mu-opioid receptors by opioids in the CNS leads to analgesia.¹¹ On the other hand, activation of the mu-opioid receptors by opioids in the GI tract can result in GI side effects such as OIC.

OIC is Associated with a High Symptom Burden

OIC can be a bothersome side effect and have a high symptom burden.^{9, 12} Coyne et al reported baseline results from a longitudinal, multinational study to assess the burden of OIC in adult patients with non-cancer pain using a combination of a patient survey, retrospective data abstraction from medical records, and a physician survey.¹² Participants (N=493; mean age 52.6±11.6 years) with self-reported OIC and confirmed daily opioid therapy (≥30 mg of oral morphine or equivalent) for at least 4 weeks were included in the study. Participants completed the Patient Assessment of Constipation-Symptoms (PAC-SYM) to assess patient-reported symptoms and severity of symptoms over the previous 2 weeks. In the US cohort (N=242), the most common symptoms of moderate or greater severity included: straining/squeezing to pass bowel movement (BM) (83%), BMs too hard (79%), painful BMs (71%), incomplete BM (68%), BMs too small (68%), abdominal discomfort (65%), abdominal bloating (62%), and feeling the need to pass a BM but unable to do so (60%). Patients in this study also experienced rectal burning during or after BMs (45%) and rectal bleeding or tearing during or after BMs (25%), which contributed to the overall symptom burden.

Current Management of OIC

OIC is often under-recognized and undertreated by physicians. Patients may feel uncomfortable discussing their OIC with their health care provider resulting in lack of awareness.¹² This may be further complicated by the lack of standard definition and guidelines on appropriate diagnosis, assessment and treatment of OIC.^{1, 11, 13-15} Therefore, OIC is typically managed like general constipation.¹³

OIC May Interfere with Pain Management

Data from a patient survey and a study indicate that OIC can hinder pain management.^{9, 12, 16} OIC may cause patients to modify, change, or discontinue opioid therapy in order to find relief from OIC but at the risk of experiencing increased pain.^{9, 12, 16} The Patient Reports of Opioid-related Bothersome Effects (PROBE 1) study was an Internet-based survey of patients with chronic pain in Europe and the United States who were taking opioids and laxatives.⁹ The survey was designed to evaluate the prevalence, frequency, and severity of opioid bowel dysfunction symptoms. Of the 703 patients who completed the 45-item questionnaire, 322 patients took daily oral opioids. Results revealed that

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33% (105/322) of patients reported missing, decreasing, or stopping opioids to make it easier to have a BM.

Patients with chronic non-cancer pain may modify, change, or discontinue opioid therapy in order to find relief from OIC, at the cost of experiencing more pain.

In a previously mentioned study by Coyne et al in patients with chronic non-cancer pain and OIC, 23 patients (10%) in the US cohort (n=242) reported that they changed how they took their opioid in the preceding 7 days in an effort to have a BM.¹² Of those, 61% temporarily interrupted their pain medication use, 48% reduced their dose, and 4% switched to a different pain medication. Patients in this group were then asked how severe their pain was following opioid use modification: 52% reported that their pain was much worse, and 39% reported that their pain was a little worse. The remaining 9% reported a little improvement in their pain.¹⁶

OIC May Contribute to Increased Healthcare Resource Use

In patients receiving chronic opioid therapy who have constipation, data suggest that OIC is associated with increased healthcare utilization.¹⁷ The National Health and Wellness Survey (NHWS) is a comprehensive, annual, cross-sectional web-based survey of adults in different healthcare settings in the United States and Europe. The results of this survey are based on data from 2,430 patients who received opioids for at least 6 months (median duration was approximately 4 years). Patients were grouped according to those who reported OIC (n=359) and those who did not report OIC (n=2,071). Patients with OIC had significantly ($p < 0.05$) more physician office visits (mean difference of 3.8 visits) and alternative care provider visits (mean difference of 1.73 visits) in the previous 6 months versus respondents without OIC. There was no difference in the number of emergency room visits or the number of days hospitalized between the two groups.

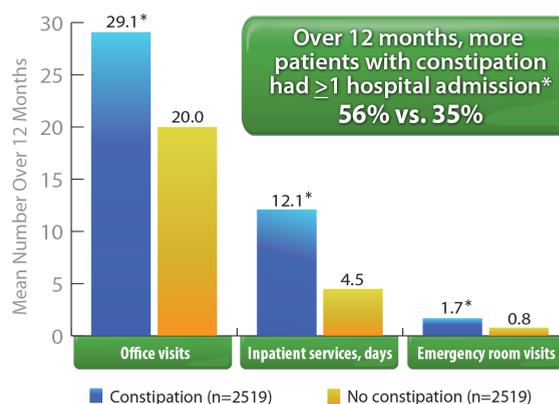
Constipation Following Opioid Use May Contribute to Increased Yearly Healthcare Resource Use

Iyer et al conducted a retrospective, observational, matched cohort study of US insurance claims of 39,485 patients with an opioid prescription or procedure code for IV-adminis-

tered opioid for at least 30 days and found that 2,519 (6.4%) patients had constipation.¹⁸ Constipation was determined in patients with at least one ICD-9-CM diagnosis code, pri-

Patients with constipation following opioid administration had significantly greater health care utilization compared with patients without constipation.

12- Month Retrospective Claims Analysis



mary or non-primary, in the range of 564.0x. Subjects with constipation were matched to a cohort without constipation. In the 12 months following opioid initiation there was significantly more healthcare resource use among patients with constipation vs those without constipation. More patients had at least 1 hospital admission compared to those without constipation (56% vs 35%). Patients with constipation following opioid prescription, compared to those without constipation, also had significantly greater annual:

- Number of office visits (29.1 vs 20)
- Length of hospitalization (12.1 vs 4.5 days)
- Number of emergency department visits (1.7 vs 0.8)

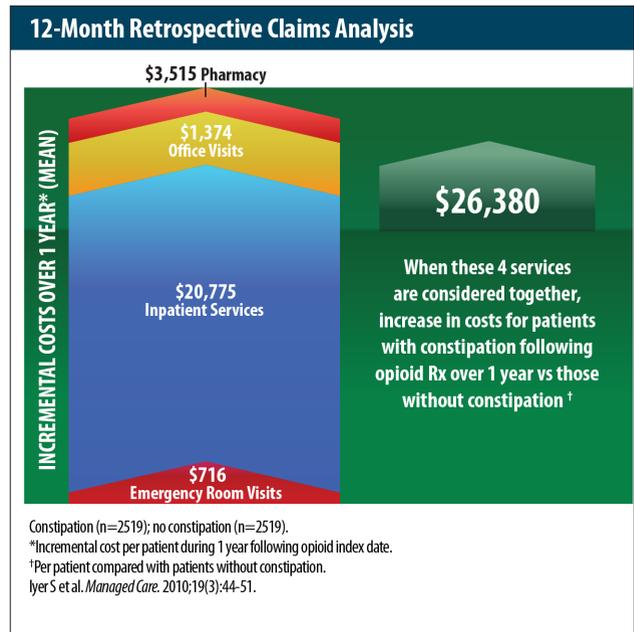
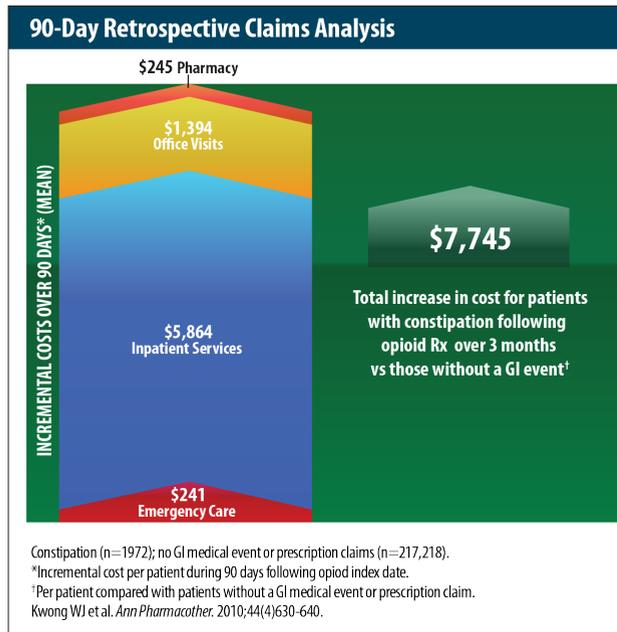
As is inherent in retrospective, observational studies, causality was not assessed for the various endpoints. In addition, the etiology of the constipation was not assessed; constipation may not have been attributable to opioid use in all subjects.

Constipation Following Opioid Use May Contribute to Increased Healthcare Costs in the 90 Days Following Opioid Prescription

A retrospective analysis of medical and prescription claims was conducted by Kwong et al to assess the economic

burden of 3 GI events (including constipation) over 90 days in patients treated with an oral short-acting opioid using medical and prescription claims.¹⁹ The analysis in-

partment and office visits, inpatient services, and pharmacy for patients with constipation following opioid treatment compared to patients without constipation.¹⁸ When these 4



cluded patients in the US with an outpatient prescription claim for an oral immediate-release oxycodone- or hydrocodone-containing product. The date on which the opioid was first filled was the opioid index date. Medical claims were evaluated to identify patients with a medical claim associated with nausea/vomiting, constipation (ICD-9-CM code 564.0x), or bowel obstruction during the 90 days following opioid index date. Prescription claims were also examined for anti-emetics and laxatives. Overall, 237,447 patients were included in the analysis, of which 2,412 patients had a constipation claim. Of the 2,412 patients, 1,972 had constipation without occurrence of another GI event and were used in the analysis of the claims.

In patients with constipation, there were increases in mean costs associated with emergency department and office visits, inpatient services, and pharmacy compared with patients without a GI event, resulting in a total mean increase in cost of \$7,745 over 90 days for patients with constipation following opioid prescription compared with those without a GI event (no medical or prescription claim). As is inherent in retrospective, observational studies, causality was not assessed for the various endpoints.

Constipation Following Opioid Use May Contribute to Increased Annual Healthcare Costs

In the previously mentioned Iyer et al study, there were increases in annual costs associated with emergency de-

partment and office visits, inpatient services, and pharmacy for patients with constipation following opioid treatment compared to patients without constipation. When these 4

OIC May Have a Negative Impact on Work Productivity and Daily Activities

Findings from a patient survey and a study indicate that OIC may have a negative impact on patients' work productivity and daily activities.^{12,17} In the National Health and Wellness Survey, participants completed the Work Productivity and Activity Impairment (WPAI) Questionnaire, which consists of questions regarding employment status, time spent away from work, time spent at work, and the effect of the respondent's condition on work productivity and daily activity within the previous 7 days.¹⁷ Of 2,430 patients receiving opioids for at least 6 months, those experiencing OIC (n=359) were more likely to miss time from work, experience work impairment, and have activity impairment than patients without OIC (n=2,071).

In the overall US cohort (n=242) of the study by Coyne et al, patients with chronic non-cancer pain and OIC reported daily activity impairment due to constipation.¹² Among patients who were working and who had WPAI Constipation Score information available (n=78-79), patients reported that constipation symptoms resulted in missed time from work, impairment while working, and impairment on overall work productivity.

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OIC May Impair Health-Related Quality of Life

OIC may have an impact on quality of life. In the aforementioned National Health and Wellness Survey, the Short-Form 8 (SF-8) Health Survey was used to evaluate health-related quality of life, including physical and mental health.¹⁷ Of patients 2,430 patients receiving opioids for at least 6 months, those with OIC (n=359) had impairment in both physical and psychological components of health-related quality of life compared to opioid-treated

patients without OIC (n=2,071). Additionally, results from the PROBE 1 Internet-based survey of patients with chronic pain who were taking opioids and laxatives, approximately 55% of patients with OIC reported that constipation had a moderate-to-great or great negative impact on quality of life.⁹

Summary

In summary, OIC is associated with a high symptom burden which may impact quality of life, daily activities, and work productivity. OIC may also impact pain management if patients modify their opioid regimen in order to make it easier to have a bowel movement. Constipation following opioid use may increase healthcare resource use. OIC is common side effect of opioid therapy that should be anticipated and addressed throughout the course of opioid treatment. ■

Patients with OIC reported missing time from work as well as work and/or activity impairment.

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