Opioid-Induced Constipation: Considerations for Health Care and Comprehensive Pain Management
Opioid therapy for chronic pain management may lead to side effects, including constipation.

Opioids are a commonly selected treatment for patients with a variety of chronic pain conditions who have not adequately responded to other treatment options.\(^1\)-\(^3\)

- Common conditions necessitating opioid treatment for chronic, non-cancer pain include muscle, joint, and limb pain.\(^4\)

**Common side effects of opioids include\(^5,\)\(^6\):**

- Constipation
- Sedation
- Nausea
- Vomiting

- OIC is one of the most common side effects of opioids.\(^5\)
- OIC can occur at the initiation of opioid therapy.\(^6,\)\(^7\)
- Unlike some other opioid-induced side effects, OIC may persist for the duration of opioid use\(^6,\)\(^7\).
Mechanism of condition for opioid-induced constipation

Activation of mu-opioid receptors in the bowel may affect motility and lead to OIC

Mu-opioid receptors are widely distributed in the central nervous system (CNS) and the gastrointestinal (GI) tract. Opioids relieve pain by binding mu-receptors in the CNS, but also bind mu-receptors in the bowel, which can result in OIC.

<table>
<thead>
<tr>
<th>Altered GI motility</th>
<th>Disruption of peristalsis and GI spasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased fluid absorption</td>
<td>Increased passive absorption of fluids</td>
</tr>
<tr>
<td>Reduced intestinal secretions</td>
<td>Overall decreased bowel secretions</td>
</tr>
<tr>
<td>Sphincter dysfunction</td>
<td>Increased pyloric and anal sphincter tone</td>
</tr>
</tbody>
</table>

CNS
Opioid activation of mu-receptors in the CNS primarily mediates analgesia.

GI
Opioid activation of mu-receptors in the bowel may lead to OIC.
OIC symptom burden for patients

Common OIC symptoms of moderate or greater severity (≥25%), as reported on the Patient Assessment of Constipation-Symptoms (PAC-SYM)* questionnaire, are shown below.11

The baseline analysis of a multinational, longitudinal study of 242 patients with chronic non-cancer pain and clinician-identified, patient confirmed OIC found that among patients who saw their HCP in the last month, 37% did not discuss OIC.11,12,†

Why did you not talk to your doctor about your problems with constipation? n=78

<table>
<thead>
<tr>
<th>Reason</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discussed with doctor in the past</td>
<td>43 (55%)</td>
</tr>
<tr>
<td>Concerned about need to change/reduce pain medication</td>
<td>11 (14%)</td>
</tr>
<tr>
<td>Embarrassed</td>
<td>6 (8%)</td>
</tr>
<tr>
<td>Constipation not a problem</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Ran out of time</td>
<td>6 (8%)</td>
</tr>
<tr>
<td>Other</td>
<td>10 (13%)</td>
</tr>
</tbody>
</table>

* A 12-item measure with 3 subscales (ie, stool, rectal, and abdominal symptoms) to assess patient-reported symptoms.11

† Results from the US cohort (n=242) of a prospective, longitudinal, multinational study in adult patients with chronic non-cancer pain and self-reported OIC (n=493); the burden of OIC was assessed using a combination of a patient survey, retrospective data abstraction from medical records, and a physician survey. A total of 493 participants with self-reported OIC and confirmed daily opioid therapy for ≥4 weeks were included in the study. The most frequently utilized OIC treatments were natural or behavioral therapies (84%), 60% used at least one over-the-counter laxative, 24% used two or more over-the-counter laxatives, and 19% used one or more prescription laxatives.11

BM=bowel movement.
Current management of OIC

OIC: an underrecognized condition in patients with chronic non-cancer pain

There is a lack of standard guidelines on appropriate diagnosis, assessment, and treatment of OIC. This contributes to underrecognition and undertreatment of OIC. 13–16

OIC is typically managed like general constipation, with OTC laxative therapy as the mainstay of treatment15

Inadequate symptom control and dissatisfaction with current constipation treatment in many patients with OIC

Despite sufficient¹ use of OTC and/or prescription laxatives, 32% of US patients² with OIC had an inadequate response³ to treatment with ≥2 laxatives from ≥2 different classes in the past 2 weeks.¹¹

Inadequate response to treatment with 2 or more different laxatives in the past 2 weeks

³ Defined as usual of at least one laxative ≥4 times over the last 2 weeks.
¹ US patients with sufficient laxative use (n=88).
² Defined as <3 BMs and 1 or more PAC-SYM symptom scored moderate, severe, or very severe.

79% of US patients with OIC reported dissatisfaction with their current constipation treatment¹¹
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OIC may impact pain management therapy

Patient alteration of opioid therapy

**33%** of patients reported altering use of pain medication to make it easier to have a BM over the course of their treatment.

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**PROBE 1 Survey**

*The Patient Reports of Opioid-related Bothersome Effects (PROBE 1) study was an Internet-based survey of patients in western Europe and the United States to evaluate the prevalence, frequency, and severity of opioid bowel-dysfunction symptoms. Patients with chronic pain receiving opioids (at least 2 days per week) and taking laxatives completed a 45-item questionnaire. Of the 703 patients who completed the survey, 322 patients took daily oral opioids and were included in the main analysis.*

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- In a second study of chronic non-cancer pain patients with OIC by Coyne et al, 23 patients (10%) in the US cohort (n=242) reported that they changed how they used their opioid in the prior 7 days in order to have a BM.

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<table>
<thead>
<tr>
<th>Patient change in opioid medication as result of OIC in the last week</th>
<th>% of Patients (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interrupted pain medication use</td>
<td>61</td>
</tr>
<tr>
<td>Reduced pain medication use</td>
<td>48</td>
</tr>
<tr>
<td>Switched to different pain medication</td>
<td>4</td>
</tr>
</tbody>
</table>

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1 Results from the US cohort (n=242) of a prospective, longitudinal, multinational study in adult patients with chronic non-cancer pain and self-reported OIC (n=493), the burden of OIC was assessed using a combination of a patient survey, retrospective data abstraction from medical records, and a physician survey. A total of 493 participants with self-reported OIC and confirmed daily opioid therapy for ≥4 weeks were included in the study.
OIC may decrease quality of life (QoL) and productivity

Impact on QoL

PROBE 1 SURVEY\textsuperscript{17,*}

- Approximately 55\% of patients reported that constipation had a “moderate-to-great” or “great” impact on QoL\textsuperscript{4,5}

\textsuperscript{4}3 or 4 on a 0–4 scale, where 0 is “no impact” and 4 is “greatly impacts.”

\textsuperscript{5}Number of patients who reported constipation: 262/322.

NATIONAL HEALTH AND WELLNESS SURVEY\textsuperscript{i}

OIC led to reported impairment in both physical and mental components of health-related quality of life (HRQoL)\textsuperscript{18}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{chart.png}
\caption{Mean SF-8 Score for OIC (n=359) vs No OIC (n=2071)}
\end{figure}

\textsuperscript{i}The National Health and Wellness Survey (NHWS) is a comprehensive, annual, cross-sectional survey of adults in different health care settings in the United States and Europe. These results are based on 2004 data in 2430 patients receiving opioids for at least 6 months to treat pain (median duration of opioid use was approximately 4 years). Patients were grouped according to those who reported OIC (n=359) and those who did not report OIC (n=2071). Health-related QoL was evaluated using the Short-Form 8 Health Survey. The SF-8 survey is made up of physical and mental health components, on which a lower score reflects greater impairment in HRQoL\textsuperscript{14}.

\textsuperscript{¶}P<0.05, OIC vs no OIC.

Impact on productivity

OIC symptoms may also impact patients who are employed. In the overall US cohort (n=242) of a prospective longitudinal study,\textsuperscript{11} patients with chronic non-cancer pain and OIC reported daily activity impairment due to constipation. Among patients who were working and who had Work Productivity and Activity Impairment Questionnaire, Specific Health Problem (WPAI-SHP) Constipation score information available, patients reported missing time from work, impairment while working, and impact on overall work productivity.

- In the US cohort of patients who were currently working (n=81), patients reported that they missed a mean of 6 hours of work in the past 7 days

<table>
<thead>
<tr>
<th>Survey outcomes\textsuperscript{4}</th>
<th>WPAI-Constipation scores (mean %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Work time missed</td>
<td>10</td>
</tr>
<tr>
<td>Impairment while working</td>
<td>38</td>
</tr>
<tr>
<td>Impaired overall work productivity</td>
<td>33</td>
</tr>
<tr>
<td>Daily activity impairment</td>
<td>43</td>
</tr>
</tbody>
</table>

\textsuperscript{4}Productivity was assessed using the WPAI-SHP, a self-reported quantitative assessment of the effect of specific health problems, such as constipation in this case, on work productivity, daily activities, and classroom impairment over the past 7 days. WPAI-Constipation outcomes are expressed as impairment percentages, with higher scores indicating greater impairment and less productivity (ie, worse outcomes).\textsuperscript{11}
OIC may lead to increased health care utilization

NATIONAL HEALTH AND WELLNESS SURVEY\textsuperscript{18,*}

Patients experiencing OIC had significantly greater physician and alternative care\textsuperscript{†} visits in the previous 6 months compared with patients receiving opioid therapy, but without OIC.

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|}
\hline
 & OIC (n=359) & No OIC (n=2071) \\
\hline
Physician visits & 13.5\textdagger & 9.7 \\
Alternative care provider visits & 6.2\textdagger & 4.4 \\
No. of days hospitalized & 1.6\$ & 1.8 \\
Emergency room visits & 0.5\$ & 0.5 \\
\hline
\end{tabular}
\caption{Mean Number in Prior 6 Months}
\end{table}

\textsuperscript{*}The National Health and Wellness Survey (NHWS) is a comprehensive, annual, cross-sectional survey of adults in different health care settings in the United States and Europe. These results are based on 2004 data in 2430 patients receiving opioids for at least 6 months to treat pain (median duration of opioid use was approximately 4 years). Patients were grouped according to those who reported OIC (n=359) and those who did not report OIC (n=2071). Health care utilization was assessed through the number of emergency room visits, days hospitalized, physician visits, and alternative health care provider visits.\textsuperscript{18}

\textsuperscript{†}Alternative care providers included acupuncturists, chiropractors, and physical therapists, among others.\textsuperscript{18}

\textsuperscript{\$}P<0.05; OIC vs no OIC.

\textsuperscript{\$}Not significant.
Patients with constipation following opioid administration had significantly greater health care utilization compared with patients without constipation.

Over 12 months, more patients with constipation had ≥1 hospital admission.

This study was a retrospective, observational matched cohort study of US insurance claims of 39,485 patients with an opioid prescription or procedure code for IV-administered opioid for at least 30 days found that 2519 (6.4%) patients had constipation. A patient was considered to have constipation if his or her medical information contained at least one ICD-9-CM diagnosis code, primary or nonprimary, in the range of 564.0x (inclusive of all fifth-digit modifiers) in the 12 months following the index date. Subjects with constipation were matched to a cohort without constipation. In the 12 months following opioid initiation, there was significantly more health care resource use among patients with constipation vs those without constipation.

Data were extracted from the LifeLink Health Plan database (formerly PharMetrics Integrated Outcomes Database), which contains 2 billion health care transactions in the form of computerized administrative claims from more than 40 million unique patients from 75 private health plans. The average patient enrollment time is greater than 2 years. The data are gathered from all 4 geographic regions of the United States. Patient age and gender distributions within the database are representative of national managed care enrollment. Matching was 1:1 based on age (±3 years), gender, and payer type (commercial vs noncommercial).

Mean duration of opioid therapy was approximately 155 days, and approximately 30% of subjects had taken 2 or more concurrent opioid prescriptions at any point during the 12-month follow-up period.

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

\( P < 0.0001 \), constipation vs no constipation.
OIC may lead to increased health care costs

Constipation following opioid use may contribute to increased health care costs

The table below shows results of 2 retrospective claims analyses for OIC over 90 days and 1 year, respectively.

<table>
<thead>
<tr>
<th>Health care services</th>
<th>Incremental costs over 90 days&lt;sup&gt;a&lt;/sup&gt; (mean)&lt;sup&gt;20&lt;/sup&gt;</th>
<th>Incremental costs over 1 year&lt;sup&gt;†&lt;/sup&gt; (mean)&lt;sup&gt;19&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergency care</td>
<td>$241</td>
<td>$716</td>
</tr>
<tr>
<td>Inpatient services</td>
<td>$5864</td>
<td>$20,775</td>
</tr>
<tr>
<td>Office visits</td>
<td>$1394</td>
<td>$1374</td>
</tr>
<tr>
<td>Pharmacy</td>
<td>$245</td>
<td>$3515</td>
</tr>
<tr>
<td><strong>Total increase in costs for patients with constipation following opioid use</strong></td>
<td><strong>$7745</strong></td>
<td><strong>$26,380</strong></td>
</tr>
</tbody>
</table>

<sup>a</sup>A retrospective analysis of medical and prescription claims was conducted to assess the economic burden of 3 GI events (including constipation) over 90 days in patients treated with an oral short-acting opioid using the PharMetrics Patient-Centric Database. The PharMetrics Patient-Centric Database includes integrated medical and prescription claims from more than 80 health plans and more than 60 million patients in the United States. It is representative of individuals covered by commercial health insurance in the United States.<sup>20</sup>

The analysis included patients with an outpatient prescription claim for an oral immediate-release oxycodone- or hydrocodone-containing product. 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 antiemetics and laxatives.<sup>20</sup>

Overall, 237,447 patients were included in the analysis, of which 2412 patients had a constipation claim. Of the 2412 patients, 1972 had constipation without occurrence of another GI event and were used in the analysis of claims above. Patients with medical claims of >1 GI event were reported as a separate group. In patients with constipation, there were increases in mean costs associated with ED and office visits, inpatient services, and pharmacy compared with patients without a GI event, resulting in a total mean increase in cost of $7745 for patients with constipation following opioid prescription compared with those without a GI event (no medical or prescription claim).<sup>20</sup>

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References


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OIC can be a burdensome condition for patients that can impact health care utilization and costs

Opioids play an important role in chronic pain relief by binding to mu-receptors in the CNS, but they also bind to mu-receptors in the bowel, which can lead to opioid-induced constipation, or OIC. OIC is one of the most common side effects of opioids.

It is important to recognize that patients with OIC face a burden. Patients with OIC may alter their opioid regimen in order to have a BM. Patients with constipation following opioid therapy may be likely to require more health care resources, and incur greater costs than patients taking opioids without constipation.

Take a proactive stand to improve patient lives in your organization by considering these steps to help address OIC.

1. Identify patients at risk for OIC
   - Develop a series of OIC-related questions for physicians and other health care providers who manage patients with chronic pain who are receiving opioid treatment

2. Educate physicians
   - Provide training for physicians and other health care providers to diagnose and treat OIC in patients receiving opioid treatment

3. Standardize OIC
   - Adopt standard practices for OIC definition, diagnosis, and management based on leading expert clinical guidance across your organization. Standardization may help the consistency of physician treatment across your patient population

Address OIC in your chronic pain management plan