A Literature Review of the Cost of Opioid-Induced Constipation

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Background

- Opioids are the most commonly prescribed treatment for severe pain: up to 90% of chronic pain patients in the USA receive opioid therapy, and the consumption of such treatments is increasing.[1]
- Although effective in the management of pain, common side effects of opioid treatment include opioid-induced bowel dysfunction.[1,2]
- Constipation is one of the most common, and often most severe and persistent, opioid-induced adverse events.[3] The prevalence of opioid-induced constipation (OIC) varies between studies, with reported rates of up to 81%, despite laxative use.[1]
- The management of OIC involves additional physician visits to discuss side effects as well as extra physician and treatment costs, including further investigations or alternate pain relief, all of which add to the overall cost of managing chronic pain patients.[4]

Objective of the Literature Review

- To identify and describe studies that quantified the economic burden of OIC.

Methods

Literature Review Protocol

- A protocol (outlining the focus, search strategy, and data extraction methods) was developed to guide development and completion of the literature review; this reduced the potential impact of review author bias, ensured transparency and accountability, and maximized the chances of correct data extraction.

Study Selection Criteria

- Included in the review were English-language primary research studies that reported the cost of OIC in adult populations taking opioids for chronic pain (cancer or non-cancer related).
- Studies quantified the economic cost of OIC (e.g. direct medical costs, direct non-medical costs, personal costs, productivity/indirect costs).
- The following were excluded:
  - Studies not specifically in an adult population of patients taking opioids for chronic pain and reporting constipation
  - Studies that assessed the impact of treatment on OIC burden (i.e. cost-effectiveness analyses)
  - Non-English language publications
  - Reviews, discussion papers, letters, and editorials.

Information Sources and Search Strategy

- Searches were conducted in September 2015 (with no date limit) in bibliographic databases: MEDLINE, EMBASE, Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment Database (HTA), NHS Economic Evaluations Database (NHS EED), and EconLit.
- In addition, the reference lists of identified articles were checked.
- Abstract books of the most recent pain and health outcome congresses (2014/2015) were also searched.
- Results were assessed for relevance by two reviewers and data extracted.

Results

Search Results

- The literature search yielded 279 de-duplicated abstracts, and a full-text review identified 11 relevant studies that explored the economic burden of OIC.
- There were eight manuscripts and three congress abstracts, all published since 2009.
- Data are presented according to chronic pain patient populations: cancer and non-cancer combined (n=6 studies),[5–10] cancer only (n=3),[11–13] and non-cancer only (n=2).[14,15]

Objectives and Methods of the Included Studies

- The studies varied regarding patient populations, type of study, opioid and constipation treatments, definition of constipation or OIC, types of cost included, and how costs were reported. Therefore, each study should be considered individually.
- **Table 1** summarizes the cost-related objectives, methods, and patient population in the 11 studies.
- All the studies assessed direct costs associated with OIC, with two studies[5,7] also including indirect costs (productivity losses). None of the studies included costs borne by patients.
- Cost analyses were based on:
  - Retrospective claims data from third-party payer health claims databases in the USA[8,9,11,14,15] and Brazil[10]
  - Healthcare resource use (HCRU) information from patient records[6,13]
  - HCRU information from patient interviews/questionnaires[6,7]
  - HCRU estimates or information from healthcare professionals.[5,7,12,13]
- In the studies that undertook bottom-up costing, the cost was derived by multiplying units of HCRU by unit costs.
- The USA was the most common study country (five studies).[8,9,11,14,15]
- The study length varied: nine studies lasted ≤12 months, but one study[10] followed up patients for 35 months (study length not applicable in two studies[5,12]).
- A number of studies undertook comparative cost analyses:
  - Patients with versus without OIC[7–11,14,15]
  - Patients with different severity levels of OIC (from none to severe)[7]
  - Laxative responders versus non-responders[6]
  - Elderly, non-elderly, and long-term care facility patients[15]
  - Cancer versus non-cancer patients with OIC.[10]

Cost Burden of OIC

- **Table 2** summarizes the key findings regarding the economic burden in patients with OIC.
- The cost of managing patients with OIC was consistently higher than managing patients without OIC.[7–11,14,15]
- Patients with severe constipation had the highest total costs per patient-month in one study.[7]

Table 1. Cost-Related Objectives and Methods in the Included Studies of Patients with Chronic Pain

Reference (Country)	Study objective related to cost (study length)	Comparisons	Type of study (cost year)	Patient population (n)
Cancer and non-cancer				
Caekelbergh et al, 2009 [A][5] (Belgium and the Netherlands)	Describe the direct medical and indirect per-patient costs of OIC (constipation episode and cost of specific complications) (study length NA)	–	2-round Delphi panel of 24 GPs (NR)	Patients with OIC taking opioids (n=NA)
Guijarro et al, 2009 [A][6] (Spain)	Analyze direct medical per-patient costs of an OIC event (2 months)	Laxative responders vs non-responders	Retrospective, multicenter, observational study using NHS patient records and patient interviews (2009)	Patients with OIC who had previously not responded to laxatives (n=744[a])
Hjalte et al, 2010[7] (Sweden)	Estimate the direct medical and indirect societal per-patient monthly costs of OIC (by severity) in patients being treated with strong opioids (6 months)	OIC vs non-OIC (severity of OIC: none, mild, moderate, severe)	Non-interventional database study (2008)	Patients with mild, moderate, or severe OIC taking strong opioids (n=197)
Iyer et al, 2010[8] (USA)	Compare direct medical per-patient costs in patients on opioid therapy who have constipation vs those who do not (12 months)	OIC vs non-OIC	Retrospective, multicenter, observational matched cohort study using a health insurance database (1999–2005)	Patients with constipation (n=2519)
Suh et al, 2011[9] (USA)	Estimate direct per-patient hospital-based treatment costs for patients with OIC (identified as those being treated with constipation medication) vs the cost of patients who did not receive medication for nausea, vomiting, or constipation (14 days)	OIC vs non-OIC (patients with constipation treatment vs without NVC medication)	Retrospective, multicenter, observational matched cohort study using an inpatient health insurance database (2007)	Hospitalized patients on opioid and constipation medication (oral opioid n=2493; injectable opioid n=47,122)
Takemoto et al, 2011[10] (Brazil)	Compare direct medical per-patient monthly costs in opioid-treated patients with vs without constipation (35 months)	OIC vs non-OIC	Retrospective, multicenter, observational matched cohort study using a health insurance database (2009)	Patients with OIC (n=6678) (29.0% among opioid-treated patients)[b]
Cancer				
Candrilli et al, 2009[11] (USA)	Compare direct medical per-patient costs in patients with opioid use with vs without constipation (12 months)	OIC vs non-OIC	Retrospective, multicenter, observational matched cohort study using a health insurance database (NR)	Patients with OIC (n=821)
Ovanfors et al, 2009 [A][12] (Sweden)	Estimate the direct medical per-patient costs of treating OIC (constipation episode) (study length NA)	–	Survey-based interviews with nurses from 3 hospices and home care centers informing HCRU (NA)	Patients with OIC who had previously failed laxatives (n=NA)
Wee et al, 2010[13] (UK)	Evaluate the direct medical costs of managing constipation (per admission and cost over 6 months) in patients taking opioids in a specialist palliative care unit (6 months)	–	Retrospective review of medical records of HCRU for constipation in single palliative care center. Prospective time-in-motion study also conducted to estimate bottom-up costing of HCRU (2006)	Patients with OIC (n=58)
Non-cancer				
Kwong et al, 2010[14] (USA)	Estimate the direct medical per-patient costs associated with GI events coincident with oral short-acting opioid treatment vs those without GI events (90 days)	OIC vs non-OIC (patients with vs without GI event medical or prescription claim)	Retrospective, multicenter, observational cohort study using a health insurance database (2002–2005)	Patients with constipation medical claim (n=1972) Patients with laxative use, without GI event medical claim (n=3303)
Wan et al, 2015[15] (USA)	Analyze the direct medical per-patient costs in non-cancer patients taking long-term (≥90 days) opioids, comparing those with vs without OIC (12 months)	OIC vs non-OIC Elderly, non-elderly, and long-term care facility patients	Retrospective, multicenter, observational, matched cohort study using a health insurance database to capture HCRU and cost data (2011)	Patients with OIC (elderly n=194; non-elderly n=401; long-term care n=85)

A, conference abstract; GI, gastrointestinal; GP, general practitioner; HCRU, healthcare resource utilization; NA, not applicable; NHS, National Health Service; NR, not reported; NVC, nausea, vomiting, constipation.

[a] Number calculated as not provided in abstract.[6]

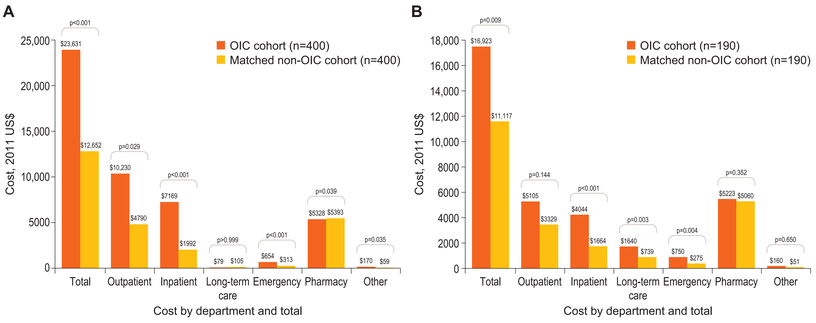
[b] In supplementary tables, this is stated as 6768. It is unclear what the correct number is, as 29% of opioid-treated patients is 6761.[10]

Table 2. Key Findings Regarding Economic Burden in Patients with OIC

Reference	Population	Key findings
OIC vs non-OIC		
Hjalte et al, 2010[7]	Cancer and non-cancer	• Patients with severe constipation had the highest total costs per patient-month: – Severe OIC, €1525 (SD 1711) – Moderate OIC, €1088 (SD 1489) – Mild OIC, €1196 (SD 1544) • The largest cost component across OIC severity levels was indirect costs, followed by costs of outpatient care
Iyer et al, 2010[8]	Cancer and non-cancer	• Over 12 months, OIC patients had significantly ($p≤0.003$) higher mean costs than non-OIC patients in all examined categories, including emergency, physician visits, nursing facility, home health, and prescription drug services (values in the paper)
Suh et al, 2011[9]	Cancer and non-cancer	• Patients receiving constipation medications had significantly higher mean inpatient healthcare costs than those without NVC medication: the difference was $1668 overall, and was higher for oral ($2723) than injectable ($1500) opioids (all p<0.0001)
Takemoto et al, 2011[10]	Cancer and non-cancer	• The average cost per month was significantly higher for opioid-treated patients with constipation vs those without constipation (BRL 787.84 vs 526.66; p<0.001) • Cancer patients had, on average, higher costs than did non-cancer patients; however, the absolute difference between patients with vs without constipation was relatively similar in the entire study population and in those with cancer (BRL 261.18 vs 263.21)
Candrilli et al, 2009[11]	Cancer	• OIC was associated with an increase in total costs of >109% vs non-OIC ($138,605 vs $66,188; p<0.0001) • OIC patients also had significantly (p<0.05) increased inpatient, outpatient, emergency, nursing home, home health service, laboratory service, pharmacy, and other outpatient or ancillary care costs (but not hospice costs) (values in the paper)
Kwong et al, 2010[14]	Non-cancer	• The adjusted mean total healthcare cost was $3981 (range 3385–4577) for patients with no GI event medical or prescription claim, and was significantly higher (all p<0.001) for: – Patients with a constipation medical claim during the 90 days following opioid prescription: $11,726 (range 10,529–12,923) (incremental cost $7745) – Patients identified through prescription claims for laxatives: $8861 (range 7798–9924) (incremental cost $4880) • There was at least a doubling of total healthcare cost in managing a patient following a constipation or laxative claim in the 90 days following opioid therapy • Specific service costs are given in the paper (inpatient, emergency care, office visit, pharmacy)
Wan et al, 2015[15]	Non-cancer	• After 12 months, and after matching by key covariates, OIC patients had significantly (p<0.05) higher total healthcare costs vs non-OIC patients in elderly and non-elderly cohorts (**Figure 1**) as well as long-term care patients • The additional cost in patients with OIC (vs non-OIC) was highest in non-elderly, followed by elderly, and lowest in long-term care patients
Laxative responders vs non-responders		
Guijarro et al, 2010 [A][6]	Cancer and non-cancer	• The mean total cost of constipation management was €271.08 (SD 621.22) • The mean per-patient cost was significantly higher for laxative non-responders than for responders: €442 (SD 810) vs €115 (SD 230); p<0.001
No comparisons		
Caekelbergh et al, 2009 [A][5]	Cancer and non-cancer	• When a societal perspective was taken, the mean cost of a constipation episode was €130.37 (Belgium) and €102.16 (Netherlands) • When only HCP costs were included, the mean cost was €101.54 in Belgium and €102.14 in the Netherlands • Healthcare visits were the main cost driver • The paper provides societal and HCP costs of managing specific complications (hemorrhoids, anal fissures, defecation incontinence, external peri-anal thrombosis, rectal prolapse, bladder prolapse). For example, in Belgium, the mean total cost of managing anal fissures was €125.14 (societal) and €74.87 (HCP)
Ovanfors et al, 2009 [A][12]	Cancer	• The average cost per OIC episode was estimated at SEK 1700 • Direct healthcare costs in Sweden of OIC in patients who had previously failed laxatives was estimated at SEK 40 million per year
Wee et al, 2010[13]	Cancer	• The total per-patient cost of managing OIC was £29.81 per admission, 85% of which was the cost of staff time • A relatively small proportion of the total cost was from drug expenditure (13%) • The authors noted that the cost results were highly skewed: in 71% of admissions, the cost of managing constipation was £30, but in 5% of admissions the cost exceeded £100

BRL, Brazilian Real; GI, gastrointestinal; NVC, nausea, vomiting, constipation; SD, standard deviation; SEK, Swedish Krona.

Figure 1. Costs in Non-Elderly (A) and Elderly (B) Patients, by OIC Status (cost year: 2011)[15]



- The mean cost of OIC was 3.8 times higher in laxative non-responders than in laxative responders in one study.[6]
- In one study, cancer patients had higher costs than did non-cancer patients; however, the absolute difference between patients with versus without OIC was similar in the entire study population and in those with cancer.[10]
- In the study that compared OIC cost in three patient cohorts, the additional cost in patients with OIC (vs non-OIC) was highest in non-elderly, followed by elderly, and lowest in long-term care patients.[15]
- One study is summarized in more detail below.[15]

With versus without OIC: Example of one of the comparative studies[15]

- The US study by Wan et al (2015)[15] analyzed the direct per-patient cost in non-cancer patients taking long-term (≥90 days) opioids, comparing those with OIC versus those without OIC, and comparing three cohorts: elderly, non-elderly, and long-term care facility patients.
- Patients with OIC had significantly (p<0.05) higher total healthcare costs versus patients without OIC, in all three cohorts. The additional cost in patients with OIC (vs non-OIC) was $10,979 (non-elderly), $5806 (elderly patients), and $1563 (long-term care patients).
- **Figure 1** summarizes the total cost and cost components in the non-elderly and elderly patients, by OIC status.
- In multivariate analysis, OIC was associated with significantly higher total costs (vs non-OIC) in the elderly (89% higher) and non-elderly cohorts (52% higher) but not in the long-term care cohort. Predictors of increased total cost for both elderly and non-elderly were: baseline hospitalization, nausea/vomiting, and high Charlson comorbidity score.
- The authors concluded that, in managed care patients receiving long-term opioid therapy, OIC is associated with increased healthcare costs in elderly, non-elderly, and patients in long-term care facilities.[15]

Conclusions

- This review identified 11 studies on the economic impact of OIC. The studies almost exclusively focused on direct healthcare costs, and suggest – consistent with previous reviews – that OIC poses a significant economic burden on healthcare systems.[16,17] This burden appears to increase with the severity of constipation.
- Further research across geographies is needed to fully understand the costs incurred over time by healthcare systems, employers, and patients. It is also important to better understand the difference in costs between cancer and non-cancer patients.
- The role of treatment compliance should also be explored, as the presence of OIC can cause patients to reduce their opioid dose.[18] When using claims data, it is not clear if patients adhered to their pain medications. If this is the case, then the results on the cost of OIC may have been underestimated.
- More effective treatment that reduces the incidence or severity of OIC could lessen its economic burden.

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