The Work Productivity Burden of Opioid-Induced Constipation – A Literature Review

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Background

- Opioid analgesics are widely used in the treatment of chronic pain. For example, in the USA, ~3% of adults receive long-term opioid therapy for chronic non-cancer pain.[1]
- Of concern, however, is the occurrence of opioid-related adverse events (AEs), including gastrointestinal (GI) AEs such as constipation, nausea, vomiting, bloating, and abdominal pain.[2]
- Constipation is the most common, and often most severe, opioid-related AE. Prevalence rates range, and can be up to 90% depending on study design and patient population.[3,4]
- Importantly, the symptoms of opioid-induced constipation (OIC) (or possibly the worry of having symptoms) may compromise the ability of patients to work, leading to absenteeism, presenteeism (being less effective at work), and even job loss.

Objective of the Literature Review

- To identify and describe studies that quantified work productivity burden in patients with 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 measured the employment-related burden of OIC in adult populations taking opioids for chronic pain (cancer or non-cancer related).
- Studies included outcomes such as absenteeism, presenteeism, and job loss, and could report data either quantitatively or qualitatively.
- 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. change in work productivity associated with treatment)
  - Non-English language publications
  - Reviews, discussion papers, letters, and editorials.

Information Sources and Search Strategy

- Searches were conducted in August 2016 (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), and NHS Economic Evaluations Database (NHS EED).
- In addition, the reference lists of identified articles were checked.
- Abstract books of recent congresses (2015/2016) were also searched.
- Results were assessed for relevance by two reviewers and data extracted.

Results

Search Results

- The literature search yielded 715 de-duplicated abstracts, and a full-text review identified eight relevant studies on the work productivity burden of OIC.[3,5–11]
- There were six manuscripts[3,7–11] and two congress abstracts.[5,6]
- Data are presented according to chronic pain patient populations: cancer and non-cancer combined (n=4 studies),[3,5–7] and non-cancer only (n=4).[8–11]

Objectives and Methods of the Included Studies

- The studies varied regarding patient populations, study designs, opioid and constipation treatments, definition of constipation or OIC, and measurement of employment burden. Therefore, each study should be considered individually.
- **Table 1** summarizes the productivity-related objectives and methods in the eight studies.
- Data were sourced from:
  - Cancer and non-cancer studies: the (US) National Health and Wellness Survey (NHWS),[3] a general practitioner (GP) survey,[5] a patient survey,[6] and an observational study[7]
  - Non-cancer studies: a large international longitudinal study (two studies),[8,10] the NHWS,[9] and a patient survey.[11]
- All studies were quantitative: four used the Work Productivity and Activity Impairment (WPAI) questionnaire (measures absenteeism and presenteeism)[3,8–10] and the others focused on time off work.[5–7,11] None of the studies measured long-term sick leave or early retirement.
- Three studies compared employment burden between different patient populations:
  - Patients with versus without OIC[3], and months with versus without constipation[7]
  - Patients who had modified their opioid treatment versus those who had not.[9]
- Two studies were longitudinal;[7,10] the other studies assessed employment burden at a single point in time.[3,5,6,8,9,11]
- Two non-cancer studies were from the same international longitudinal survey: Coyne et al (2014)[8] provided a descriptive analysis of baseline data, and LoCasale et al (2015)[10] reported data for patients who were "laxative-sufficient" (at least one laxative remedy at least four times in the prior 2 weeks) at baseline and 24 weeks.

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

Reference (Country)	Study objective (productivity focus)	Study design (total patient number, OIC population)	Method to capture productivity data
Cancer and non-cancer			
Bell et al, 2009[3] (USA and Europe [France, Germany, Italy, Spain, UK])	Characterize the impact of OIC on work productivity	Cross-sectional patient survey (2004 NHWS[a]) (n=2430: OIC n=359; no OIC n=2071)	WPAI questionnaire[b]
Caekelbergh et al, 2009 [A][5] (Netherlands and Belgium)	Understand the economic burden of OIC on work productivity as estimated by GPs	Two-round Delphi panel with GPs (n=NA)	% professionally active people "unable to work" because of OIC
Dean et al, 2015 [A][6] (USA)	Understand the work productivity impact of OIC	Cross-sectional online patient survey with both qualitative and quantitative elements (n=105)	Single question on the amount of time missed work or another activity in last month due to OIC
Hjalte et al, 2010[7] (Sweden)	Estimate the indirect costs of OIC in patients being treated with strong opioids[c]	Non-interventional, 6-month, observational study (n=197)	Questionnaire designed for the study; patients were asked about their ability to work[c]
Non-cancer			
Coyne et al, 2014[8] (USA, Canada, Germany, UK)	Describe baseline work productivity burden in patients with OIC	Longitudinal patient survey[d] (n=493)	WPAI questionnaire[b]
Gupta et al, 2015[9] (USA)	Characterize productivity losses associated with modifications to opioid therapy[e] due to OIC	Cross-sectional patient survey (2004 NHWS[a]) (n=491)	WPAI questionnaire[b]
LoCasale et al, 2015[10] (USA, Canada, Germany, UK)	Understand the impact on work productivity of OIC, and the experience of constipation treatment over time in patients who were sufficient laxative users (≥1 laxative remedy 2×+ in the prior 2 weeks)	Longitudinal patient survey[d] (n=234)	WPAI questionnaire[b]
Rauck et al, 2017[11] (USA)	Understand the impact of OIC on work productivity	Patient survey in patient magazine (n=489)	11-question OIC survey with question asked about "impaired work performance/ productivity"

A, conference abstract.
[a] NHWS is a large, comprehensive, self-administered, international, cross-sectional healthcare Internet survey.
[b] The WPAI is a 6-item validated instrument, with three of the four outcomes specific to work: absenteeism (percentage of work time missed in last 7 days), presenteeism (percentage of impairment at work over last 7 days due to poor health), overall work productivity (combined estimate of absenteeism and presenteeism), and activity impairment.
[c] Indirect cost data used to calculate time off work.[7]
[d] Two publications are from the same international longitudinal survey assessing OIC burden.[8,10]
[e] Opioid "modifiers" reported making modifications to their opioid medication due to OIC in the past 6 months (reduced dose, changed medication, skipped doses, discontinued).[9]

Employment Burden of OIC

- There was a low level of employment in the studies: most reported that only about one-third of patients were working.
- **Table 2** shows the key findings related to employment burden in patients with OIC.

Table 2. Key Findings Regarding Employment Burden in Patients with OIC[a]

Reference	Key findings
Cancer and non-cancer combined populations	
Bell et al, 2009[3]	• Patients with OIC had higher rates of time missed from work, impairment while working, and overall work impairment vs those without OIC
Caekelbergh et al, 2009 [A][5]	• GPs estimated that the proportion of professionally active patients with OIC who could not work because of their condition was 20% (Netherlands) and 30% (Belgium)
Dean et al, 2015 [A][6]	• 30% of respondents reported that they had missed work (or ≥1 activity) at least once over the past month; 1% had missed ≥7 days
Hjalte et al, 2010[7]	• Inferred days off work per patient-month for patients:[b] – 2.99 days in those with no constipation – 4.1 days in those with mild constipation – 3.07 days in those with moderate constipation – 4.51 days in those with severe constipation
Non-cancer only populations	
Coyne et al, 2014[8]	• Overall (pooled) results in patients with OIC were: – 8.9% time missed from work (absenteeism) – 32.2% impairment while working (presenteeism) – 29.0% overall work impairment • There were differences between countries, with the highest rates seen in the UK for absenteeism (13.1%), and in the USA for presenteeism (38.3%) and overall work impairment (33.8%)
Gupta et al, 2015[9]	• Opioid modifiers reported greater presenteeism than non-modifiers (adjusted means 49.75% vs 38.28%; p=0.038) • There were no significant differences in adjusted means for absenteeism (p=0.586) or overall work impairment (p=0.051)
LoCasale et al, 2015[10]	• Work productivity remained relatively constant over 24 weeks in patients with OIC and sufficient laxative use • At Week 24, the average number of work hours missed per week because of constipation-associated problems was 0.9 h • Among these patients at Week 24: – 6% mean work time missed due to constipation – 24% impairment experienced while working because of constipation – 23% overall work impairment because of constipation
Rauck et al, 2017[11]	• 38.17% of respondents indicated that impaired work performance/ productivity had impacted their QOL

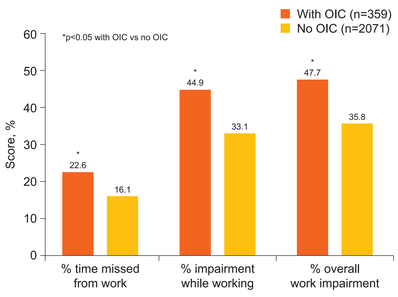
A, conference abstract.
[a] Note that there was a low level of employment in the studies: most reported that only about one-third of patients were working.
[b] Indirect cost (production loss) data were used to infer the time off work data.[7]

- Overall, the studies generally show that, in the patients who are still able to work, the impact of OIC on work productivity is substantial, including both time off work and reduced effectiveness at work.
- Respondents with OIC reported significantly (all p<0.05) higher percentages for time off work, impairment while working, overall work impairment, and activity impairment, versus those without OIC (WPAI questionnaire, part of the 2004 NHWS) (**Figure 1**).[3]
- Data from a large longitudinal (24-week) study showed that, even with sufficient laxative use, OIC persists and can have a negative impact on work productivity in patients with chronic non-cancer pain and OIC (WPAI questionnaire).[10]
- Patients with chronic non-cancer pain who modified their opioid dose reported greater presenteeism than non-modifiers (adjusted means 49.75% vs 38.28%; p=0.038) (WPAI questionnaire, part of the 2012 NHWS).[9]
- As many as 30% of patients (cancer and non-cancer pain) had missed work or at least one activity due to OIC in the last month (patient survey).[6]
- GPs estimated high proportions of professionally active OIC patients who could not work because of their condition: 20% in the Netherlands, 30% in Belgium.[5]
- Two studies are summarized in more detail below.[3,10]

Patients with versus without OIC[3]

- The study by Bell et al (2009)[3] was the only one to compare the productivity burden of chronic pain patients with versus without OIC.
- This large US survey used the validated WPAI questionnaire that formed part of the 2004 NHWS in a combined cancer and non-cancer chronic pain population (n=2430: with OIC n=359, without OIC n=2071).
- As shown in **Figure 1**, patients with OIC had ~25% greater time off work, impairment while working, and overall work impairment than those without OIC.

Figure 1. Results from the WPAI questionnaire comparing patients with OIC versus no OIC in a large US survey (2004 NHWS) of a cancer and non-cancer chronic pain population[3]

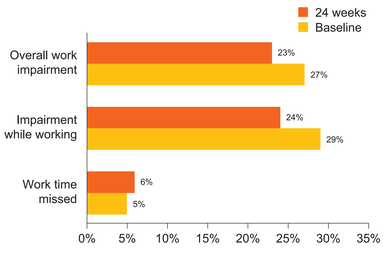


- In multiple regression analysis, significant differences in impairment while working between respondents with versus without OIC were maintained after adjustment for potential confounders (age, gender, number of comorbid conditions, health insurance, education).
- The authors concluded that OIC limited work activity, and that this was largely independent of confounders.

Patients with OIC and sufficient laxative use[10]

- The study by LoCasale et al (2015)[10] assessed employment burden in OIC patients who reported sufficient laxative use (one remedy at least four times in the prior 2 weeks).
- This large international (USA, Canada, Germany, and UK), longitudinal (24-week), web-based patient survey used the validated WPAI questionnaire in non-cancer chronic pain patients (baseline n=234; Week 24 n=157).
- The percentage of patients employed was 21% at baseline, and 19% at Week 24.
- In OIC patients who were employed and reported sufficient laxative use, the average number of work hours missed per week was 1.6 h at baseline, and 0.9 h at Week 24.
- Data showed that patients had high rates of work time missed, impairment while working, and overall work impairment because of OIC (**Figure 2**).
- The authors concluded that, even with sufficient laxative use, OIC persists and can have a negative impact on work productivity.

Figure 2. Results from the WPAI questionnaire in OIC patients with sufficient laxative use in a large international, 24-week, Internet-based patient survey in non-cancer chronic pain patients[10]



P-values not reported in the paper.

Conclusions

- This review identified a small number of studies on the productivity impact of OIC. The findings from these studies suggest that OIC has a detrimental impact on both absenteeism and presenteeism.
- There is a lack of data outside the USA, and a paucity of longitudinal studies; more research is warranted to address these gaps. Only one study[3] included a non-OIC control group, and undertook multivariate regression analysis to compare patients with versus without OIC: OIC significantly limited work activity, and this was largely independent of confounders. In the other studies, some of the productivity burden attributed to OIC could be due to constipation from other causes (e.g. mobility issues or dietary habits). Therefore, more comparative studies are needed.
- Importantly, OIC persists and can have a negative impact on work productivity despite sufficient laxative use, and despite patients modifying their opioid dose.
- There is a need for treatment options that target the underlying cause of OIC, i.e. opioid binding to the mu-receptors in the GI system.
- Studies in which patients describe their personal experience of OIC in a work context would be valuable in understanding the ways in which work life is impacted by OIC and the reasons why productivity is impacted.

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