

# Characterisation and associated costs of constipation relating to exposure to strong opioids in England: an observational study

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## Manuscript details

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Tables	6	
Figures	1	
Word count	Abstract	400
	Main body	3,423
References	21	

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CM was involved in the study design, data analysis, produced the first draft of the manuscript and contributed to subsequent versions. S J-J contributed to study design, data analysis and contributed to the interpretation of the results. RK provided data interpretation and revised the first draft of the manuscript. CC was involved in the concept of the study, study design, data interpretation and revision of the manuscript. PC was involved in the concept of the study, study design, data interpretation and revision of the manuscript. CDP

was involved in the study design, data analysis and data interpretation. EB was involved in the study design, data analysis and revision of the manuscript.

## **Abstract**

### *Purpose*

Opioid use is associated with gastrointestinal adverse events including nausea and constipation. We used a real-world dataset to characterise the healthcare burden associated with opioid induced constipation (OIC) with particular emphasis on strong opioids.

### *Methods*

This retrospective, cohort study was conducted using the Clinical Practice Research Datalink; a large UK primary care dataset linked to hospital data. Patients prescribed opioids during 2016 were selected and episodes of opioid therapy constructed. Episodes with  $\geq 84$  days exposure were classified as chronic with date of first prescription as index date. The main analysis focused on patients prescribed strong opioids who were laxative naïve. Constipation was defined by  $\geq 2$  laxative prescriptions during the opioid episode. Patients for whom initial laxative therapy escalated by switch, augmentation or dose were defined as OIC-unstable, the first three lines of OIC escalation were classified. Healthcare costs accrued in the first 12-months of the opioid episode were aggregated and compared.

### *Findings*

27,629 opioid episodes were identified; 5,916 (21.4%) involved a strong opioid for patients previously laxative naïve. Of these patients, 2,886 (48.8%) were defined as the OIC population; 941 (33.26%) were classified as stable. Of the 1,945 (67.4%) episodes classified as unstable, 849 (43.7%), 360 (18.5%) and 736 (37.8%) had one, two and three changes of laxative prescription. Patients without OIC had lower costs per patient year (£3,822; \$5,160USD/4,242 EUR) compared with OIC (£4,786; \$6,461USD/5,312 EUR). Costs increased as patients had multiple changes in therapy: £4,696 (\$6,340USD/5,213 EUR), £4,749 (\$6,411 USD/5,271 EUR and £4,981 (\$6,724 USD/5,529 EUR) for one, two and three or more changes respectively. The adjusted cost ratio relative to non-OIC was 1.14 (95% CI 1.09-1.32) for those classified as stable and 1.19 (95% CI 1.09-1.32) for those with  $\geq 3$  laxative changes. Similar patterns were observed for patients on all opioids with costs increased for those classified as having OIC (£3,727; \$5,031USD/4,137EUR versus £2,379; \$3,212 USD /2,641 EUR); higher for those patients classified as unstable versus stable (£3,931; \$5,307USD/4,363 EUR versus

£3,432; (\$4,633USD/3,810EUR); and increased with each additional line of therapy from £3,701 (\$4,996USD/4,108EUR), £3,916 (\$5,287USD/4,347EUR) and £4,318 (\$5,829USD/4,793EUR).

### *Implications*

OIC was a common adverse event of opioid treatment and for a large number of patients was poorly controlled. Poor control was associated with increased healthcare costs. The impact of OIC should be considered when prescribing opioids. These results should be interpreted with consideration of the caveats associated with the analysis of routine data.

## Introduction

Since the early 1990s, opioid prescription rates have increased sharply in UK primary care, [1–3] almost doubling for weak opioids and increasing six-fold for strong opioids between 2005 and 2012 [4]. This has been ascribed to an escalation in the use of opioids for chronic non-cancer pain [5–7]. The increase in opioid use has raised concerns due to the risk of misuse, reduced effectiveness with long term exposure and impact of adverse events including gastrointestinal disturbance [8,9,10]. Whilst opioids therefore have a place in pain management, their use needs to be carefully considered by clinicians as part of an overall treatment strategy and they should not be initiated without first trying other non-pharmacological and non-opioid strategies [11,12].

Constipation is a known side-effect of opioid exposure and opioid-induced constipation (OIC) describes a set of symptoms reflecting a change in bowel habits following initiation of opioid therapy: reduced bowel-movement frequency, sense of incomplete evacuation, hard stool consistency, and straining [13] which may cause patients to avoid or stop using opioids, thereby compromising effective pain relief and increasing the associated burden of care [14]. OIC has a significant impact on the direct and indirect costs of patient care. It has a strong negative effect on patients' quality of life (QoL) and may lead to non-adherence to opioid therapy, impairing QoL still further and increasing the associated costs of care. Several studies of healthcare resource use and cost in the USA in opioid-treated patients have demonstrated higher utilization and costs in those experiencing opioid-induced constipation [15–19].

Despite the debilitating effects of OIC, there is little awareness of this complication on the part of medical practitioners with little or no precautionary discussion of its effects and management before prescribing opioids. Recent guidelines have recommended first-line treatment options for OIC include dietary modifications (such as increased fluid and fibre intake), exercise and laxatives; with the potential for laxatives to be prescribed prophylactically [20]. Many physicians wrongly believe that OIC can be effectively treated by current laxatives (both over-the counter and prescribed), although approximately 70% of patients will not respond satisfactorily to laxatives, even after rotating and changing products. Patients, in their turn, are reluctant to discuss constipation and its symptoms with their doctors, partly because of embarrassment and partly because they worry that the opioid

treatment will be withdrawn. This can result in patients adjusting their own opioid doses to attempt manage the condition often affecting the successful management and intent of the primary prescriber. Thus, this serious complication, remains underdiagnosed, undertreated and a significant hidden burden to the health system through ineffective use of opioids for pain relief in many patients especially those being managed in primary care.

The aim of the study was to utilise a real-world dataset to characterise the healthcare burden associated with opioid use in the UK health service, in particular those prescribed laxatives with particular emphasis on strong opioids. This data will help inform treatment choices for this complex population.

## **Methods**

### *Data source*

The study used a retrospective cohort design within the UK Clinical Practice Research Datalink (CPRD) GOLD primary-care dataset. CPRD GOLD is a longitudinal, anonymized research database derived from nearly 800 primary-care practices in the UK and collected as part of the day-to-day administration of the primary care practice. Approximately 60% of the practices participate in a linkage scheme, by which their patient records are linked to other data sources, including the Hospital Episode Statistics (HES) dataset which provides data on all inpatient and outpatient contacts occurring within National Health Service hospitals in England, and the office of National Statistics (ONS) mortality dataset. Use of anonymized CPRD data is approved by the Trent Multi-Centre Research Ethics Committee (05/MRE/04/87). Individual studies using CPRD require Independent Scientific Advisory (ISAC) approval. This study was granted approval under protocol 18\_069.

### *Cohort selection*

A prevalent opioid population was selected for patients prescribed opioids during 2016. New episodes of opioid prescription were defined as  $\geq 2$  distinct opioid prescriptions with no -prior opioid exposure in the preceding 12 months. Episodes were extracted from CPRD for patients defined as being of acceptable research quality. This is a flag within CPRD to ascertain that the patient's data meets a minimum standard such as a valid age and the patient was registered after birth [21]. Patients also had to be eligible for linkage to the HES secondary care datasets. Date of first opioid prescription was the index date. Total opioid exposure was calculated as the date of the episode's last prescription plus the recorded/imputed days' supply for the last prescription. Those episodes with greater than 12 weeks ( $\geq 84$  days) exposure were defined as chronic opioid episodes. This duration was chosen to align with the generally accepted definition of chronic pain [22]. Patients for whom an exposure episode occurred either partly or wholly in 2016 formed the prevalent study population.

Opioid induced constipation was defined by prescription of laxatives on the following criteria.

- Patients with 0 or 1 laxative prescriptions prescribed during the opioid episode were classified as non-OIC. The assumption was made that patients prescribed only one laxative were prescribed it prophylactically.
- Patients with multiple prescriptions of laxatives were defined as OIC and further classified as:
  - Stable if there was no change from the initial laxative prescription in terms of augmentation, switching or dosage increase
  - Unstable if there were changes in terms of augmentation, switching or dosage increase with each change representing first, second and third line.

Patients who were admitted as an inpatient with a diagnosis for constipation (ICD-10 K59.0 in any position in the HES admitted patient care record) or those with an outpatient appointment in the gastroenterology specialty during 2016 were flagged.

The main analysis cohort was divided between those with a prescription for a laxative in the 90 days prior to index date (prior-laxative exposed cohort) and those without (laxative naïve cohort). This was on the basis that in the case of the former, it was not possible to attribute a constipation event evidenced by laxative prescriptions as new-onset and thus these patients were considered mixed-aetiology constipation (MAC). Those with no laxative script in the 90 days prior to index date but who subsequently were prescribed multiple laxatives were considered as having OIC.

The primary analysis considered all patients prescribed strong opioids either alone or in combination with other opioid types. The opioids classified as strong were buprenorphine, methadone, diamorphine, fentanyl, hydromorphone, morphine, oxycodone, pethidine, dextromoramide, alfentanil, dipipanone, papaveretum and pentazocine. In an additional sensitivity analysis, results for all opioid episodes were presented.

Primary and secondary costs accrued in the 12 months following index date were aggregated. Primary care contacts were identified from the consultation table of the CPRD GOLD primary care dataset and classified according to the combination of staff role and consultation type. Costs were derived from the Units Costs of Health and Social Care 2017 [23]. Inpatient



admissions were identified from the HES admitted patient care dataset. Healthcare resource groups (HRGs) were assigned to each inpatient admission and processed using HRG 4 grouper software (National Casemix Office, Winchester, UK) [24]. The allocated HRG was then linked to the 2017 National Tariff [25] adjusting for the nature of the admission (elective admissions versus emergency) and excess length of stay. Outpatient appointments were identified from the HES outpatient dataset described by specialty and processed using HRG 4 grouper software. The allocated HRG was then linked to the 2017 National Tariff [25]. Prescriptions issued in primary care, recorded in the CPRD therapy table, were attributed an estimated cost by applying the net ingredient cost (NIC) per prescription from the Prescription Cost Analysis (PCA) for England 2017 [26]. For prescriptions for discontinued products that were not listed in the PCA 2017, the most recently published cost was used and adjusted to 2017 prices using the HM Treasury GDP deflator index. Where an exact match was not made, the British National Formulary (BNF) taxonomy will be utilized to attribute an average NIC per item for the BNF sub-paragraph, section or chapter.

Total costs and cost per person year were presented. Costs were compared to the reference of non- OIC using a Gamma model adjusting for age, gender, the Charlson index and presence of either gastrointestinal or colorectal cancer. The Charlson index is a predictor of 10 year mortality based upon combination of comorbidities [27].

Due to the potential confounder that patients with gastrointestinal and colorectal cancers have an increased risk of constipation, all cost tables were replicated with patients with a diagnosis of these conditions recorded either in the primary care or secondary care sources within 12 months of index date excluded.

All costs were provided in pounds sterling with conversions to US dollars and the Euro. Exchange rates were those from December 2020; \$1.35 and 1.11 EUR to £1.00.

## Results

### ***Strong opioid episodes***

During 2016, 27,629 opioid episodes were identified (Tables and figures

Table 1. Baseline characteristics of patients prescribed opioids by opioid strength and subsets defined by constipation status for those without prior exposure to laxatives.

Table 2. Total and mean healthcare costs per patient year for patients prescribed strong opioids without prior exposure to laxatives with subsets defined by constipation status.

Table 3. Adjusted cost ratios for patients with patients prescribed strong and all opioids with and without prior exposure to laxatives defined by constipation status.

Table 4. Baseline characteristics of patients prescribed opioids by opioid strength and subsets defined by constipation status for those with prior exposure to laxatives.

Table 5. Total and mean healthcare costs per patient year for patients prescribed strong opioids with prior exposure to laxatives with subsets defined by constipation status.

Table 6. Total and mean healthcare costs per patient year for patients prescribed all opioids without prior exposure to laxatives with subsets defined by constipation status.

Table 7. Total and mean healthcare costs per patient year for patients prescribed all opioids with prior exposure to laxatives with subsets defined by constipation status.

Figure 1). Of these, 25,091 (90.8%) were defined as chronic episodes based on our defined minimum opioid exposure threshold of 84 days. Mean follow-up was 347 days (sd 55.6). 448 (1.8%) patients died during the 12-month follow-up period and a further 2,618 (10.4%) patients had incomplete follow-up due to either leaving their primary care practice or the last date of data collection for their practice and were censored at this date. 6,697 (26.7%) of these episodes were classified as comprising a strong opioid, either alone or in combination with other opioids. A large majority of these (88.3%) had no prescriptions for laxatives in the 90 days prior to index date and were considered the laxative naïve cohort; the remainder were considered laxative prior-exposed.

### **Laxative naïve cohort – strong opioids**

Of the laxative naïve cohort, 2,886 (48.8%) had multiple laxative prescriptions recorded subsequent to index date and were defined as the OIC population. Of these, 941 (33.26%) were classified as stable and 1,945 (67.4%) classified as unstable. Of the unstable patients 849

(43.7%), 360 (18.5%) and 736 (37.8%) had one, two and three changes of laxative prescription from first index laxative respectively (Table 1).

Of those patients defined as having OIC mean age at index date was 63.0 (sd 16.5) years and the majority (1,884 (65.3%)) were female. 776 (26.9%) patients had a diagnosis of cancer recorded in their patient record within 12 months of index date and estimated Charlson comorbidity score at a baseline was 1.8 (sd 2.0). Characteristics of those classified as stable and unstable were broadly similar: females 65.8% versus 65.0%, mean age 64.0 years versus 62.5 years and proportion with index cancer diagnosis 25.0 versus 27.8% respectively (Table 1).

The total estimated healthcare costs for the prevalent, chronic strong opioid cohort in 2016 was £24,491,898 (\$33,683,307 USD / 27,695,164 EUR); cost per patient year of £4,297 (\$5,877 USD / 4,832EUR). For those without evidence of OIC the costs per patient year were lower (£3,822 (\$5,160USD / 4,242 EUR) compared with £4,786 (\$6,461USD /5,312 EUR) for those with OIC. Costs were increased as patients had multiple changes in therapy with those changing once having a cost of £4,696 (\$6,340USD / 5,213 EUR) compared with £4,749 (\$6,411 USD / 5,271 EUR) for those changing twice and £4,981 (\$6,724 USD / 5,529 EUR) for those with three or more changes in therapy (

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Table ).

After adjusting for demographic and clinical covariates, there was a significant increase in costs for patients with OIC compared to those without (CR=1.14 (95% CI 1.09-1.32). For those

patients requiring three changes of laxative prescription the cost ratio was 1.19 (1.09-1.32) (Table 3).

### **Laxative prior- exposed strong opioid**

Of the 781 patients with chronic strong laxative exposure and prior history of laxative, 92 (11.8%) had no subsequent multiple laxative prescriptions. These patients were different at baseline from those that developed MAC in terms of gender (53.3% versus 68.8% female), age (65.6 versus 72.5) and index cancer diagnosis (38.0% versus 24.1%) (

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Table ). Of the remaining 689, 183 (26.6%) were considered stable on laxative therapy and 506 (73.4%) were considered unstable. The majority (298, (58.9%)) of the unstable had three or more subsequent changes in laxative therapy. The cohorts were broadly similar in terms of age, gender, cancer status and Charlson index (Table 4).

Unlike the laxative naïve population, cost per patient year were higher for the population without MAC at £7,615 (\$10,280USD /8,453EUR) versus £6,178 (\$8,340 USD /6,858 EUR). For those classified as stable, costs were lower (£5,873; \$7,929USD /6,519 EUR versus £6,282; \$8,481USD /6,973 EUR) compared with those unstable; but highest in those with only one change in laxative prescription (£6,972; \$9,412 USD /7,739 EUR), compared with £6,843 (\$9,238USD/ 7,596EUR) for those with two changes and £5,866 (\$7,919 USD/ 6,511EUR) for those with three or more changes (5).

In the models adjusting for baseline clinical and demographic characteristics, there was no significant difference between those with and without mixed-aetiology constipation (table 3).

## All opioids

### Laxative naïve cohort – all opioids

For all chronic opioid patients, 23,159 (92.3%) had no prior laxative prescription in the 90 days prior to index date. Of these, 17,030 (73.5%) had no subsequent laxative prescription and were classified as not having OIC. Of the remaining 6,129 (26.5%) were considered to have OIC, with 2,514 (41.0%) stable on laxative therapy whereas 3,615 (59.0%) defined as unstable: 1,842 (51.0%) were stabilised after one change of prescription, 673 (18.6%) after 2 changes and 1,100 (30.4%) had three or more changes (Table 1).

The total healthcare cost for these patients was £60,601,098 (\$81,811,482 USD /67,267,219 EUR); a cost per person year of (£2,745; \$3,706 USD /3,047 EUR) (

Table ). Costs were increased for those patients classified as having OIC (£3,727; \$5,031USD /4,137EUR) versus those without (£2,379; \$3,212 USD /2,641 EUR)) and were higher for those patients classified as unstable (£3,931; \$5,307USD /4,363 EUR) versus stable (£3,432; (\$4,633 USD /3,810 EUR); and for those classified as unstable increased with each additional line of therapy from £3,701 (\$4,996USD /4,108EUR), £3,916 (\$5,287 USD /4,347EUR) and £4,318 (\$5,829USD /4,793EUR) were for those with one, two and three lines of change (Table 6).

Relative to patients without OIC there was a significant increase in cost ratio for patients with stable OIC 1.24 ((1.16-1.33)) and 1.30 (95% CI 1.14-1.50) for those patients requiring three or more changes in laxative prescription (Table 3).

### Laxative prior-exposed all opioids

There were 1,932 chronic opioid episodes which had a prior 90-day history of laxative prescriptions; of which 1,633 (84.5%) were classified as mixed aetiology constipation. 620 (38.0%) of these were stable on treatment and 1,013 (62.0%) were unstable with 300 (29.6%) ,168 (16.6%) and 545 (53.8%) having one, two or three lines of therapy, respectively (

Table 1. Baseline characteristics of patients prescribed opioids by opioid strength and subsets defined by constipation status for those without prior exposure to laxatives.

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Table ).

In the laxative prior-exposed cohort, costs per person year for those without MAC were higher than those with (£5,420; \$7,317 USD /6,016 EUR versus £4,566; \$6,164USD /5,068EUR). For those stable on laxative treatment costs were lower (£3,866; \$5,219 USD /4,291 EUR versus £4,976; \$6,718 USD /5,523 EUR) and for those classified as unstable were lowest in those with only one change in laxative prescription (£4,748; \$6,410 USD /5,270 EUR) compared with two (£5,174; \$6,985 USD /5,743 EUR) or three (£5,039; \$6,803 USD /5,593 EUR) (

Table ).

In the models adjusting for baseline clinical and demographic characteristics, there was no significant difference between those with and without mixed-aetiology constipation (table 3).

#### **Sensitivity analysis**

After excluding patients with a recent history of either colorectal or gastrointestinal cancer, similar patterns to the main cohorts were observed (see supplementary tables 1-4). For example, in the main cohort of those patients prescribed strong opioids without prior history of laxative, those classified as not having OIC had a mean cost of £3,714 (\$5,014/€ 4,123) whereas those with OIC had cost per annum of £4,583 (\$6,187/€ 5,072) increasing to £4,813 (\$6,498/€ 5,343) for those with stable OIC requiring three changes in laxative prescription.

## Discussion

This descriptive study considered healthcare costs associated with constipation status amongst patients exposed to chronic opioid therapy. We report that almost half of patients, previously naïve to laxative, that received a strong opioid developed OIC as determined by multiple laxative prescriptions, and that of those classified with OIC only one third were maintained on their initial laxative prescription with the majority requiring multiple changes of either laxative type or dose.

Patients naïve to laxatives who developed OIC had significantly increased combined healthcare costs compared to those opioid users without OIC. Furthermore, of those patients with OIC classified as unstable on laxative treatment, healthcare costs were increased compared to those who were considered stable although this trend was not significant in the adjusted multivariate analysis. Similar patterns were observed in those patients treated with strong opioids and those treated with all opioids. The increase of healthcare costs associated with OIC has been reported previously in different settings particularly in the United States [17,18,19], but this study demonstrates increased costs from A UK perspective.

From this analysis it appears that the difference in overall costs is reflected in the individual components of healthcare costs and that there is not one element that is driving the increase. Comparing OIC and non-OIC patients costs per person year were greater for inpatient contacts (£2,078 (\$2,805/€ 2,306 versus £1,575 (\$2,126/€ 1,748), outpatients (£926(\$1,250/€ 1,028 versus £811 (\$1,095/€ 901), primary care contacts (£763(\$1,030/€ 847 versus £627 (\$847/€ 696) and prescription costs (£816(\$1,102/€ 906 versus £701 (\$946/€ 778).

For those patients with prior exposure to laxatives, who were classified with MAC, costs were lower in both the strong and all-opioid analyses but those that were classified as MAC were more costly if unstable on treatment. It should be noted that only a small proportion of patients (13.5% strong and 18.3% all-opioids) were considered non-MAC and they were noticeably different in terms of age, gender and index cancer status than those classified as MAC.

Previous studies have estimated the prevalence of OIC as between 15-90% for chronic opioid users whilst we estimated 26% overall and 48% in those receiving strong opioids [28]. We may

therefore be underestimating the prevalence based on our proxy measure of primary care prescribed laxatives. It is possible that some patients may either tolerate a certain level of constipation without seeking medical help or, alternatively, patients may be non-compliant with their opioid therapy thereby receiving sub-optimal pain management. Exposure to opioids can only be taken as an intention-to-treat on the part of the prescriber. We have no data as to whether the patient actually filled the prescription at the pharmacy or, further, as to whether they took the medicine at the recorded dosage.

Prescription data, which was used to characterise patients with opioid exposure and OIC based on receipt of laxatives, is generated automatically by primary care software and thus should be recorded accurately. However, prescriptions emanating from secondary care or in the case of laxative, bought 'over-the-counter' would not be identified through CPRD and thus we were not able to capture where patients have opted for self-management of symptoms. In England, patients pay a fixed charge for each prescription and although many groups such as those aged over 60 or those treated for cancer are exempt, there may be a financial disincentive for some patients to have laxative issued through their primary care practice. This is also a consideration in the estimation of duration of opioid exposure as it is likely in many situations, for example, post-operative pain, the initial opioids will be prescribed in the first instance by a tertiary specialist and therefore their first prescriptions may not be recorded in the primary care data.

There are acknowledged drawbacks of observational studies using routine data sources including issues of data quality. Routine data in the CPRD is collected for reasons other than research and predominantly for the administration of the patient system. As such the individual practitioner may or may not choose to enter diagnoses or other data.

The CPRD is considered broadly representative of the United Kingdom as a whole with practices reflecting the demographics of the background population. For the main analyses in this study, we only used HES linked practices and so restricted our analysis to practices within



England. However, we believe that these results would be generalizable to a broader population.

To conclude this study has identified a population exposed to chronic opioid therapy and reports high levels of OIC especially amongst those receiving strong opioids. It is important that OIC is recognized as a common adverse event of opioid therapy and that in addition to the impact upon the individual, OIC has healthcare cost implications. The consequences of OIC should be considered when initiating opioid therapy and effective strategies for recognizing and managing the condition implemented.

## Tables and figures

Table 1. Baseline characteristics of patients prescribed opioids by opioid strength and subsets defined by constipation status for those without prior exposure to laxatives.

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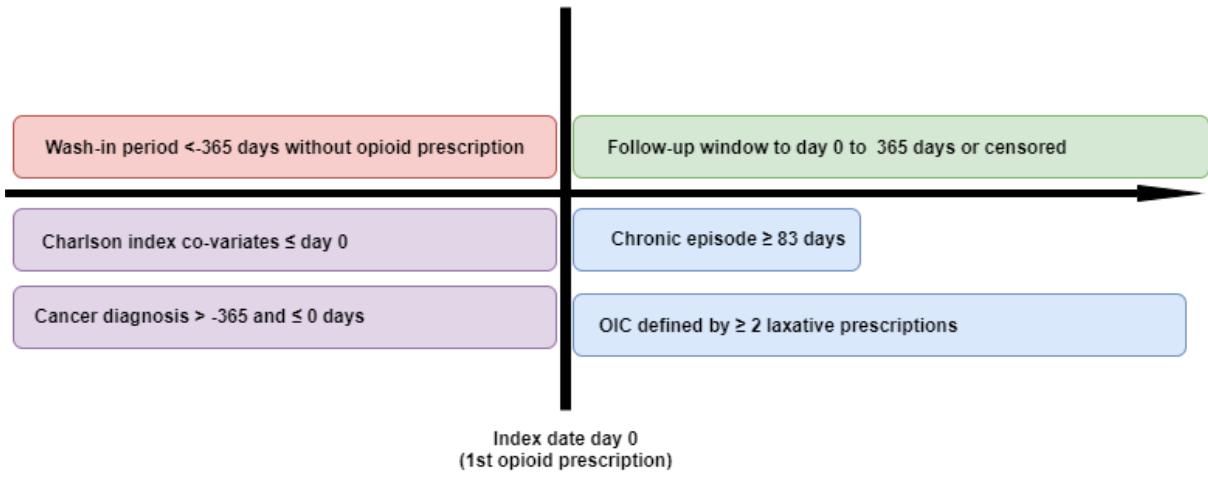
Figure 1. Derivation of stable and unstable opioid induced constipation cohort treated with strong opioids.

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**Table 1. Baseline characteristics of patients prescribed opioids by opioid strength and subsets defined by constipation status for those without prior exposure to laxatives.**

	Number	Females (%)	Mean age (sd)	Cancer (%)	Mean CI (sd)
<b>Strong opioids</b>					
All episodes	6,147	3,894 (63.3%)	61.3 (16.6)	1,392 (22.6%)	1.8 (2.0)
Chronic	5,916	3,771 (63.7%)	60.9 (16.5)	1,270 (21.5%)	1.7 (1.9)
Non-OIC	3,030	1,887 (62.3%)	58.9 (16.3)	494 (16.3%)	1.6 (1.9)
OIC	2,886	1,884 (65.3%)	63.0 (16.5)	776 (26.9%)	1.8 (2.0)
Stable	941	619 (65.8%)	64.0 (16.1)	235 (25.0%)	1.9 (2.0)
Unstable	1,945	1,265 (65.0%)	62.5 (16.7)	541 (27.8%)	1.8 (2.0)
1st line	849	550 (64.8%)	61.6 (17.0)	223 (26.3%)	1.9 (2.1)
2nd line	360	231 (64.2%)	64.8 (16.3)	117 (32.5%)	1.9 (2.0)
3rd line	736	484 (65.8%)	62.5 (16.5)	201 (27.3%)	1.7 (1.9)
<b>All opioids</b>					
All episodes	25,458	15,051 (59.1%)	59.2 (16.3)	2,813 (11.0%)	1.4 (1.7)
Chronic	23,159	13,789 (59.5%)	59.3 (16.0)	2,560 (11.1%)	1.4 (1.7)
Non OIC	17,030	9,893 (58.1%)	57.9 (15.7)	1,367 (8.0%)	1.3 (1.6)
OIC	6,129	3,896 (63.6%)	63.3 (16.3)	1,193 (19.5%)	1.6 (1.9)
Stable	2,514	1,572 (62.5%)	64.1 (15.9)	409 (16.3%)	1.6 (1.9)
Unstable	3,615	2,324 (64.3%)	62.7 (16.5)	784 (21.7%)	1.6 (1.9)
1st line	1,842	1,177 (63.9%)	62.4 (16.4)	358 (19.4%)	1.6 (1.9)
2nd line	673	426 (63.3%)	64.2 (16.2)	171 (25.4%)	1.7 (1.8)
3rd line	1,100	721 (65.5%)	62.3 (16.8)	255 (23.2%)	1.6 (1.8)

sd Standard deviation, CI Charlson Co-morbidity Index

**Table 2. Total and mean healthcare costs per patient year for patients prescribed strong opioids without prior exposure to laxatives with subsets defined by constipation status.**

	Combined costs		Inpatients		Outpatients		Primary care		Prescription costs	
	Total cost (cost ppy)		Total cost (cost ppy)		Total cost (cost ppy)		Total cost (cost ppy)		Total cost (cost ppy)	
<b>All episodes</b>	£24,950,598	(£4,353)	£11,044,476	(£1,927)	£5,329,132	(£930)	£4,110,200	(£717)	£4,466,790	(£779)
Equivalent USD (\$)	\$33,683,307	(\$5,877)	\$14,910,043	(\$2,601)	\$7,194,328	(\$1,256)	\$5,548,770	(\$968)	\$6,030,167	(\$1,052)
Equivalent Euro (€)	€ 27,695,164	(€ 4,832)	€ 12,259,368	(€ 2,139)	€ 5,915,337	(€ 1,032)	€ 4,562,322	(€ 796)	€ 4,958,137	(€ 865)
<b>Chronic</b>	£24,491,898	(£4,297)	£10,829,815	(£1,900)	£5,229,862	(£918)	£4,018,239	(£705)	£4,413,982	(£774)
Equivalent USD (\$)	\$33,064,062	(\$5,801)	\$14,620,250	(\$2,565)	\$7,060,314	(\$1,239)	\$5,424,623	(\$952)	\$5,958,876	(\$1,045)
Equivalent Euro (€)	€ 27,186,007	(€ 4,770)	€ 12,021,095	(€ 2,109)	€ 5,805,147	(€ 1,019)	€ 4,460,245	(€ 783)	€ 4,899,520	(€ 859)
<b>Non OIC (£)</b>	£11,062,529	(£3,822)	£4,680,211	(£1,617)	£2,477,635	(£856)	£1,837,540	(£635)	£2,067,143	(£714)
Equivalent USD (\$)	\$14,934,414	(\$5,160)	\$6,318,285	(\$2,183)	\$3,344,807	(\$1,156)	\$2,480,679	(\$857)	\$2,790,643	(\$964)
Equivalent Euro (€)	€ 12,279,407	(€ 4,242)	€ 5,195,034	(€ 1,795)	€ 2,750,175	(€ 950)	€ 2,039,669	(€ 705)	€ 2,294,529	(€ 793)
<b>OIC</b>	£13,429,369	(£4,786)	£6,149,604	(£2,192)	£2,752,227	(£981)	£2,180,699	(£777)	£2,346,839	(£836)
Equivalent USD (\$)	\$18,129,648	(\$6,461)	\$8,301,965	(\$2,959)	\$3,715,506	(\$1,324)	\$2,943,944	(\$1,049)	\$3,168,233	(\$1,129)
Equivalent Euro (€)	€ 14,906,600	(€ 5,312)	€ 6,826,060	(€ 2,433)	€ 3,054,972	(€ 1,089)	€ 2,420,576	(€ 862)	€ 2,604,991	(€ 928)
<b>Stable</b>	£4,288,221	(£4,725)	£1,891,872	(£2,085)	£964,111	(£1,062)	£676,050	(£745)	£756,188	(£833)
Equivalent USD (\$)	\$5,789,098	(\$6,379)	\$2,554,027	(\$2,815)	\$1,301,550	(\$1,434)	\$912,668	(\$1,006)	\$1,020,854	(\$1,125)
Equivalent Euro (€)	€ 4,759,925	(€ 5,245)	€ 2,099,978	(€ 2,314)	€ 1,070,163	(€ 1,179)	€ 750,416	(€ 827)	€ 839,369	(€ 925)
<b>Unstable</b>	£9,141,148	(£4,815)	£4,257,732	(£2,243)	£1,788,116	(£942)	£1,504,649	(£793)	£1,590,651	(£838)
Equivalent USD (\$)	\$12,340,550	(\$6,500)	\$5,747,938	(\$3,028)	\$2,413,957	(\$1,272)	\$2,031,276	(\$1,071)	\$2,147,379	(\$1,131)
Equivalent Euro (€)	€ 10,146,674	(€ 5,345)	€ 4,726,083	(€ 2,490)	€ 1,984,809	(€ 1,046)	€ 1,670,160	(€ 880)	€ 1,765,623	(€ 930)
<b>1st line</b>	£3,857,270	(£4,696)	£1,798,718	(£2,190)	£779,795	(£949)	£638,131	(£777)	£640,626	(£780)
Equivalent USD (\$)	\$5,207,315	(\$6,340)	\$2,428,269	(\$2,957)	\$1,052,723	(\$1,281)	\$861,477	(\$1,049)	\$864,845	(\$1,053)
Equivalent Euro (€)	€ 4,281,570	(€ 5,213)	€ 1,996,577	(€ 2,431)	€ 865,572	(€ 1,053)	€ 708,325	(€ 862)	€ 711,095	(€ 866)
<b>2nd line</b>	£1,656,803	(£4,749)	£823,972	(£2,362)	£308,796	(£885)	£262,921	(£754)	£261,114	(£748)
Equivalent USD (\$)	\$2,236,684	(\$6,411)	\$1,112,362	(\$3,189)	\$416,875	(\$1,195)	\$354,943	(\$1,018)	\$352,504	(\$1,010)
Equivalent Euro (€)	€ 1,839,051	(€ 5,271)	€ 914,609	(€ 2,622)	€ 342,764	(€ 982)	€ 291,842	(€ 837)	€ 289,837	(€ 830)
<b>3rd line</b>	£3,627,075	(£4,981)	£1,635,042	(£2,246)	£699,525	(£961)	£603,597	(£829)	£688,911	(£946)
Equivalent USD (\$)	\$4,896,551	(\$6,724)	\$2,207,307	(\$3,032)	\$944,359	(\$1,297)	\$814,856	(\$1,119)	\$930,030	(\$1,277)
Equivalent Euro (€)	€ 4,026,053	(€ 5,529)	€ 1,814,897	(€ 2,493)	€ 776,473	(€ 1,067)	€ 669,993	(€ 920)	€ 764,691	(€ 1,050)
<b>Patients seen in gastroenterology outpatients</b>	£4,167,618	(£4,676)	£1,929,273	(£2,165)	£846,327	(£950)	£642,722	(£721)	£749,296	(£841)
Equivalent USD (\$)	\$5,626,284	(\$6,313)	\$2,604,519	(\$2,923)	\$1,142,541	(\$1,283)	\$867,675	(\$973)	\$1,011,550	(\$1,135)
Equivalent Euro (€)	€ 4,626,056	(€ 5,190)	€ 2,141,493	(€ 2,403)	€ 939,423	(€ 1,055)	€ 713,421	(€ 800)	€ 831,719	(€ 934)
<b>Patients admitted with constipation related diagnosis</b>	£3,445,526	(£6,589)	£1,785,843	(£3,415)	£684,936	(£1,310)	£468,147	(£895)	£506,600	(£969)
Equivalent USD (\$)	\$4,651,460	(\$8,895)	\$2,410,888	(\$4,610)	\$924,664	(\$1,769)	\$631,998	(\$1,208)	\$683,910	(\$1,308)
Equivalent Euro (€)	€ 3,824,534	(€ 7,314)	€ 1,982,286	(€ 3,791)	€ 760,279	(€ 1,454)	€ 519,643	(€ 993)	€ 562,326	(€ 1,076)



**Table 3. Adjusted cost ratios for patients with patients prescribed strong and all opioids with and without prior exposure to laxatives defined by constipation status.**

<b>Population</b>	<b>Cost ratio</b>	<b>95% CI</b>	<b>p-value</b>
<b>Without prior opioid exposure</b>			
<b>Strong opioids</b>			
Non-OIC	1.00		
Stable OIC	1.14	(1.05-1.24)	0.0031
Unstable OIC 1 <sup>st</sup> line	1.09	(0.99-1.19)	0.0721
Unstable OIC 2 <sup>nd</sup> line	1.10	(0.97-1.26)	0.1420
Unstable OIC 3 <sup>rd</sup> line	1.19	(1.09-1.32)	0.0003
<b>All opioids</b>			
Non-OIC	1.00		
Stable OIC	1.24	(1.16-1.33)	<0.0001
Unstable OIC 1 <sup>st</sup> line	1.29	(1.19-1.41)	<0.0001
Unstable OIC 2 <sup>nd</sup> line	1.31	(1.13-1.52)	0.0004
Unstable OIC 3 <sup>rd</sup> line	1.30	(1.14-1.50)	0.0002
<b>With prior opioid exposure</b>			
<b>Strong opioids</b>			
Non-OIC	1.00		
Stable OIC	0.85	(0.66-1.10)	0.2176
Unstable OIC 1 <sup>st</sup> line	0.96	(0.73-1.27)	0.7885
Unstable OIC 2 <sup>nd</sup> line	0.94	(0.70-1.27)	0.6868
Unstable OIC 3 <sup>rd</sup> line	0.85	(0.66-1.08)	0.1734
<b>All opioids</b>			
Non-OIC	1.00		
Stable OIC	0.86	(0.69-1.07)	0.1631
Unstable OIC 1 <sup>st</sup> line	0.83	(0.64-1.07)	0.1427
Unstable OIC 2 <sup>nd</sup> line	0.88	(0.64-1.23)	0.4443
Unstable OIC 3 <sup>rd</sup> line	1.03	(0.81-1.31)	0.8164

**Table 4. Baseline characteristics of patients prescribed opioids by opioid strength and subsets defined by constipation status for those with prior exposure to laxatives.**

	Number	Females (%)	Mean age (sd)	Cancer (%)	Mean CI (sd)
<b>Strong opioids</b>					
All episodes	875	572 (65.4%)	72.1 (16.8)	256 (29.3%)	2.8 (2.3)
Chronic	781	523 (67.0%)	71.7 (16.7)	201 (25.7%)	2.7 (2.2)
Non MAC	92	49 (53.3%)	65.6 (18.9)	35 (38.0%)	2.7 (2.3)
MAC	689	474 (68.8%)	72.5 (16.2)	166 (24.1%)	2.6 (2.2)
Stable	183	129 (70.5%)	74.0 (15.7)	41 (22.4%)	2.6 (2.1)
Unstable	506	345 (68.2%)	71.9 (16.4)	125 (24.7%)	2.7 (2.3)
1st line	120	81 (67.5%)	72.3 (17.0)	32 (26.7%)	2.5 (2.1)
2nd line	88	52 (59.1%)	71.3 (16.2)	30 (34.1%)	2.7 (2.2)
3rd line	298	212 (71.1%)	72.0 (16.3)	63 (21.1%)	2.7 (2.3)
<b>All opioids</b>					
All episodes	2,171	1,432 (66.0%)	70.1 (16.8)	388 (17.9%)	2.4 (2.2)
Chronic	1,932	1,294 (67.0%)	69.5 (16.8)	318 (16.5%)	2.3 (2.2)
Non MAC	299	181 (60.5%)	62.3 (18.7)	60 (20.1%)	2.0 (2.2)
MAC	1,633	1,113 (68.2%)	70.8 (16.1)	258 (15.8%)	2.4 (2.2)
Stable	620	434 (70.0%)	71.4 (16.1)	82 (13.2%)	2.2 (2.1)
Unstable	1,013	679 (67.0%)	70.4 (16.1)	176 (17.4%)	2.5 (2.2)
1st line	300	203 (67.7%)	69.5 (16.8)	52 (17.3%)	2.3 (2.1)
2nd line	168	105 (62.5%)	70.8 (15.5)	38 (22.6%)	2.7 (2.2)
3rd line	545	371 (68.1%)	70.8 (15.9)	86 (15.8%)	2.5 (2.3)

sd Standard deviation, CI Charlson Co-morbidity Index

**Supplementary table 1. Total and mean healthcare costs per patient year for patients prescribed strong opioids without prior exposure to laxatives with subsets defined by constipation status excluding patients with prior history of gastrointestinal and colorectal cancer**

	Combined costs		Inpatients		Outpatients		Primary care		Prescription costs	
	Total cost (cost ppy)		Total cost (cost ppy)		Total cost (cost ppy)		Total cost (cost ppy)		Total cost (cost ppy)	
<b>Chronic</b>	£23,191,806	(£4,140)	£10,203,146	(£1,822)	£4,859,940	(£868)	£3,887,473	(£694)	£4,241,247	(£757)
Equivalent USD (\$)	\$31,308,938	(\$5,590)	\$13,774,247	(\$2,459)	\$6,560,919	(\$1,171)	\$5,248,089	(\$937)	\$5,725,683	(\$1,022)
Equivalent Euro (€)	€ 25,742,905	(€ 4,596)	€ 11,325,492	(€ 2,022)	€ 5,394,533	(€ 963)	€ 4,315,095	(€ 770)	€ 4,707,784	(€ 840)
<b>Non OIC (£)</b>	£10,598,899	(£3,714)	£4,494,254	(£1,575)	£2,315,307	(£811)	£1,790,200	(£627)	£1,999,138	(£701)
Equivalent USD (\$)	\$14,308,514	(\$5,014)	\$6,067,243	(\$2,126)	\$3,125,664	(\$1,095)	\$2,416,770	(\$847)	\$2,698,836	(\$946)
Equivalent Euro (€)	€ 11,764,778	(€ 4,123)	€ 4,988,622	(€ 1,748)	€ 2,569,991	(€ 901)	€ 1,987,122	(€ 696)	€ 2,219,043	(€ 778)
<b>OIC</b>	£12,592,907	(£4,583)	£5,708,892	(£2,078)	£2,544,633	(£926)	£2,097,273	(£763)	£2,242,109	(£816)
Equivalent USD (\$)	\$17,000,424	(\$6,187)	\$7,707,004	(\$2,805)	\$3,435,255	(\$1,250)	\$2,831,319	(\$1,030)	\$3,026,847	(\$1,102)
Equivalent Euro (€)	€ 13,978,127	(€ 5,087)	€ 6,336,870	(€ 2,306)	€ 2,824,543	(€ 1,028)	€ 2,327,973	(€ 847)	€ 2,488,741	(€ 906)
<b>Stable</b>	£4,059,493	(£4,570)	£1,780,414	(£2,004)	£905,252	(£1,019)	£655,626	(£738)	£718,201	(£808)
Equivalent USD (\$)	\$5,480,316	(\$6,169)	\$2,403,559	(\$2,706)	\$1,222,090	(\$1,376)	\$885,095	(\$996)	\$969,571	(\$1,091)
Equivalent Euro (€)	€ 4,506,037	(€ 5,072)	€ 1,976,260	(€ 2,225)	€ 1,004,830	(€ 1,131)	€ 727,745	(€ 819)	€ 797,203	(€ 897)
<b>Unstable</b>	£8,533,414	(£4,590)	£3,928,478	(£2,113)	£1,639,381	(£882)	£1,441,647	(£775)	£1,523,908	(£820)
Equivalent USD (\$)	\$11,520,109	(\$6,196)	\$5,303,445	(\$2,852)	\$2,213,164	(\$1,190)	\$1,946,223	(\$1,047)	\$2,057,276	(\$1,106)
Equivalent Euro (€)	€ 9,472,090	(€ 5,094)	€ 4,360,611	(€ 2,345)	€ 1,819,713	(€ 979)	€ 1,600,228	(€ 861)	€ 1,691,538	(€ 910)
<b>1st line</b>	£3,602,701	(£4,474)	£1,664,403	(£2,067)	£712,777	(£885)	£610,197	(£758)	£615,324	(£764)
Equivalent USD (\$)	\$4,863,646	(\$6,040)	\$2,246,944	(\$2,790)	\$962,249	(\$1,195)	\$823,766	(\$1,023)	\$830,687	(\$1,032)
Equivalent Euro (€)	€ 3,998,998	(€ 4,966)	€ 1,847,487	(€ 2,294)	€ 791,182	(€ 983)	€ 677,319	(€ 841)	€ 683,010	(€ 848)
<b>2nd line</b>	£1,493,659	(£4,393)	£720,352	(£2,119)	£277,191	(£815)	£251,235	(£739)	£244,881	(£720)
Equivalent USD (\$)	\$2,016,440	(\$5,931)	\$972,475	(\$2,860)	\$374,208	(\$1,101)	\$339,167	(\$998)	\$330,589	(\$972)
Equivalent Euro (€)	€ 1,657,961	(€ 4,877)	€ 799,591	(€ 2,352)	€ 307,682	(€ 905)	€ 278,871	(€ 820)	€ 271,818	(€ 800)
<b>3rd line</b>	£3,437,054	(£4,813)	£1,543,723	(£2,162)	£649,413	(£909)	£580,215	(£813)	£663,703	(£929)
Equivalent USD (\$)	\$4,640,023	(\$6,498)	\$2,084,026	(\$2,919)	\$876,708	(\$1,228)	\$783,290	(\$1,097)	\$895,999	(\$1,255)
Equivalent Euro (€)	€ 3,815,130	(€ 5,343)	€ 1,713,533	(€ 2,400)	€ 720,848	(€ 1,009)	€ 644,039	(€ 902)	€ 736,710	(€ 1,032)

**Supplementary table 1. Total and mean healthcare costs per patient year for patients prescribed strong opioids without prior exposure to laxatives with subsets defined by constipation status excluding patients with prior history of gastrointestinal and colorectal cancer**

	Combined costs		Inpatients		Outpatients		Primary care		Prescription costs	
	Total cost (cost ppy)		Total cost (cost ppy)		Total cost (cost ppy)		Total cost (cost ppy)		Total cost (cost ppy)	
<b>Chronic</b>	£23,191,806	(£4,140)	£10,203,146	(£1,822)	£4,859,940	(£868)	£3,887,473	(£694)	£4,241,247	(£757)
Equivalent USD (\$)	\$31,308,938	(\$5,590)	\$13,774,247	(\$2,459)	\$6,560,919	(\$1,171)	\$5,248,089	(\$937)	\$5,725,683	(\$1,022)
Equivalent Euro (€)	€ 25,742,905	(€ 4,596)	€ 11,325,492	(€ 2,022)	€ 5,394,533	(€ 963)	€ 4,315,095	(€ 770)	€ 4,707,784	(€ 840)
<b>Non OIC (£)</b>	£10,598,899	(£3,714)	£4,494,254	(£1,575)	£2,315,307	(£811)	£1,790,200	(£627)	£1,999,138	(£701)
Equivalent USD (\$)	\$14,308,514	(\$5,014)	\$6,067,243	(\$2,126)	\$3,125,664	(\$1,095)	\$2,416,770	(\$847)	\$2,698,836	(\$946)
Equivalent Euro (€)	€ 11,764,778	(€ 4,123)	€ 4,988,622	(€ 1,748)	€ 2,569,991	(€ 901)	€ 1,987,122	(€ 696)	€ 2,219,043	(€ 778)
<b>OIC</b>	£12,592,907	(£4,583)	£5,708,892	(£2,078)	£2,544,633	(£926)	£2,097,273	(£763)	£2,242,109	(£816)
Equivalent USD (\$)	\$17,000,424	(\$6,187)	\$7,707,004	(\$2,805)	\$3,435,255	(\$1,250)	\$2,831,319	(\$1,030)	\$3,026,847	(\$1,102)
Equivalent Euro (€)	€ 13,978,127	(€ 5,087)	€ 6,336,870	(€ 2,306)	€ 2,824,543	(€ 1,028)	€ 2,327,973	(€ 847)	€ 2,488,741	(€ 906)
<b>Stable</b>	£4,059,493	(£4,570)	£1,780,414	(£2,004)	£905,252	(£1,019)	£655,626	(£738)	£718,201	(£808)
Equivalent USD (\$)	\$5,480,316	(\$6,169)	\$2,403,559	(\$2,706)	\$1,222,090	(\$1,376)	\$885,095	(\$996)	\$969,571	(\$1,091)
Equivalent Euro (€)	€ 4,506,037	(€ 5,072)	€ 1,976,260	(€ 2,225)	€ 1,004,830	(€ 1,131)	€ 727,745	(€ 819)	€ 797,203	(€ 897)
<b>Unstable</b>	£8,533,414	(£4,590)	£3,928,478	(£2,113)	£1,639,381	(£882)	£1,441,647	(£775)	£1,523,908	(£820)
Equivalent USD (\$)	\$11,520,109	(\$6,196)	\$5,303,445	(\$2,852)	\$2,213,164	(\$1,190)	\$1,946,223	(\$1,047)	\$2,057,276	(\$1,106)
Equivalent Euro (€)	€ 9,472,090	(€ 5,094)	€ 4,360,611	(€ 2,345)	€ 1,819,713	(€ 979)	€ 1,600,228	(€ 861)	€ 1,691,538	(€ 910)
<b>1st line</b>	£3,602,701	(£4,474)	£1,664,403	(£2,067)	£712,777	(£885)	£610,197	(£758)	£615,324	(£764)
Equivalent USD (\$)	\$4,863,646	(\$6,040)	\$2,246,944	(\$2,790)	\$962,249	(\$1,195)	\$823,766	(\$1,023)	\$830,687	(\$1,032)
Equivalent Euro (€)	€ 3,998,998	(€ 4,966)	€ 1,847,487	(€ 2,294)	€ 791,182	(€ 983)	€ 677,319	(€ 841)	€ 683,010	(€ 848)
<b>2nd line</b>	£1,493,659	(£4,393)	£720,352	(£2,119)	£277,191	(£815)	£251,235	(£739)	£244,881	(£720)
Equivalent USD (\$)	\$2,016,440	(\$5,931)	\$972,475	(\$2,860)	\$374,208	(\$1,101)	\$339,167	(\$998)	\$330,589	(\$972)
Equivalent Euro (€)	€ 1,657,961	(€ 4,877)	€ 799,591	(€ 2,352)	€ 307,682	(€ 905)	€ 278,871	(€ 820)	€ 271,818	(€ 800)
<b>3rd line</b>	£3,437,054	(£4,813)	£1,543,723	(£2,162)	£649,413	(£909)	£580,215	(£813)	£663,703	(£929)
Equivalent USD (\$)	\$4,640,023	(\$6,498)	\$2,084,026	(\$2,919)	\$876,708	(\$1,228)	\$783,290	(\$1,097)	\$895,999	(\$1,255)
Equivalent Euro (€)	€ 3,815,130	(€ 5,343)	€ 1,713,533	(€ 2,400)	€ 720,848	(€ 1,009)	€ 644,039	(€ 902)	€ 736,710	(€ 1,032)

**Supplementary table 2. Total and mean healthcare costs per patient year for patients prescribed strong opioids with prior exposure to laxatives with subsets defined by constipation status excluding patients with prior history of gastrointestinal and colorectal cancer**

	Combined costs		Inpatients		Outpatients		Primary care		Prescription costs	
	Total cost (cost ppy)		Total cost (cost ppy)		Total cost (cost ppy)		Total cost (cost ppy)		Total cost (cost ppy)	
<b>Chronic</b>	£4,308,379	(£6,084)	£1,809,440	(£2,555)	£763,211	(£1,078)	£756,222	(£1,068)	£979,506	(£1,383)
Equivalent USD (\$)	\$5,816,312	(\$8,213)	\$2,442,744	(\$3,449)	\$1,030,335	(\$1,455)	\$1,020,900	(\$1,442)	\$1,322,333	(\$1,867)
Equivalent Euro (€)	€ 4,782,301	(€ 6,753)	€ 2,008,478	(€ 2,836)	€ 847,164	(€ 1,196)	€ 839,406	(€ 1,185)	€ 1,087,252	(€ 1,535)
<b>Non OIC (£)</b>	£494,763	(£7,152)	£219,366	(£3,171)	£116,658	(£1,686)	£77,980	(£1,127)	£80,759	(£1,167)
Equivalent USD (\$)	\$667,930	(\$9,655)	\$296,144	(\$4,281)	\$157,488	(\$2,277)	\$105,273	(\$1,522)	\$109,025	(\$1,576)
Equivalent Euro (€)	€ 549,187	(€ 7,939)	€ 243,496	(€ 3,520)	€ 129,490	(€ 1,872)	€ 86,558	(€ 1,251)	€ 89,642	(€ 1,296)
<b>OIC</b>	£3,813,616	(£5,968)	£1,590,074	(£2,488)	£646,553	(£1,012)	£678,242	(£1,061)	£898,747	(£1,406)
Equivalent USD (\$)	\$5,148,382	(\$8,057)	\$2,146,600	(\$3,359)	\$872,847	(\$1,366)	\$915,627	(\$1,433)	\$1,213,308	(\$1,899)
Equivalent Euro (€)	€ 4,233,114	(€ 6,625)	€ 1,764,982	(€ 2,762)	€ 717,674	(€ 1,123)	€ 752,849	(€ 1,178)	€ 997,609	(€ 1,561)
<b>Stable</b>	£898,397	(£5,554)	£332,944	(£2,058)	£160,780	(£994)	£181,318	(£1,121)	£223,355	(£1,381)
Equivalent USD (\$)	\$1,212,836	(\$7,499)	\$449,474	(\$2,779)	\$217,053	(\$1,342)	\$244,779	(\$1,513)	\$301,529	(\$1,864)
Equivalent Euro (€)	€ 997,221	(€ 6,165)	€ 369,568	(€ 2,285)	€ 178,466	(€ 1,103)	€ 201,263	(€ 1,244)	€ 247,924	(€ 1,533)
<b>Unstable</b>	£2,915,219	(£6,108)	£1,257,130	(£2,634)	£485,773	(£1,018)	£496,924	(£1,041)	£675,392	(£1,415)
Equivalent USD (\$)	\$3,935,546	(\$8,246)	\$1,697,126	(\$3,556)	\$655,794	(\$1,374)	\$670,847	(\$1,406)	\$911,779	(\$1,910)
Equivalent Euro (€)	€ 3,235,893	(€ 6,780)	€ 1,395,414	(€ 2,924)	€ 539,208	(€ 1,130)	€ 551,586	(€ 1,156)	€ 749,685	(€ 1,571)
<b>1st line</b>	£683,864	(£6,425)	£293,544	(£2,758)	£119,188	(£1,120)	£111,871	(£1,051)	£159,261	(£1,496)
Equivalent USD (\$)	\$923,216	(\$8,674)	\$396,284	(\$3,723)	\$160,904	(\$1,512)	\$151,026	(\$1,419)	\$215,002	(\$2,020)
Equivalent Euro (€)	€ 759,089	(€ 7,132)	€ 325,834	(€ 3,061)	€ 132,299	(€ 1,243)	€ 124,177	(€ 1,167)	€ 176,780	(€ 1,661)
<b>2nd line</b>	£540,191	(£6,756)	£294,579	(£3,684)	£72,220	(£903)	£77,623	(£971)	£95,769	(£1,198)
Equivalent USD (\$)	\$729,258	(\$9,121)	\$397,682	(\$4,974)	\$97,497	(\$1,219)	\$104,791	(\$1,311)	\$129,288	(\$1,617)
Equivalent Euro (€)	€ 599,612	(€ 7,500)	€ 326,983	(€ 4,090)	€ 80,164	(€ 1,003)	€ 86,162	(€ 1,078)	€ 106,304	(€ 1,330)
<b>3rd line</b>	£1,691,164	(£5,814)	£669,007	(£2,300)	£294,365	(£1,012)	£307,430	(£1,057)	£420,362	(£1,445)
Equivalent USD (\$)	\$2,283,071	(\$7,849)	\$903,159	(\$3,105)	\$397,393	(\$1,366)	\$415,031	(\$1,427)	\$567,489	(\$1,951)
Equivalent Euro (€)	€ 1,877,192	(€ 6,454)	€ 742,598	(€ 2,553)	€ 326,745	(€ 1,123)	€ 341,247	(€ 1,173)	€ 466,602	(€ 1,604)

**Supplementary table 3. Total and mean healthcare costs per patient year for patients prescribed opioids without prior exposure to laxatives with subsets defined by constipation status excluding patients with prior history of gastrointestinal and colorectal cancer**

	Combined costs		Inpatients		Outpatients		Primary care		Prescription costs	
	Total cost (cost ppy)		Total cost (cost ppy)		Total cost (cost ppy)		Total cost (cost ppy)		Total cost (cost ppy)	
<b>Chronic</b>	£58,754,287	(£2,682)	£23,452,424	(£1,070)	£12,667,909	(£578)	£11,564,784	(£528)	£11,069,170	(£505)
Equivalent USD (\$)	\$79,318,287	(\$3,620)	\$31,660,772	(\$1,445)	\$17,101,677	(\$781)	\$15,612,458	(\$713)	\$14,943,380	(\$682)
Equivalent Euro (€)	€ 65,217,259	(€ 2,977)	€ 26,032,191	(€ 1,188)	€ 14,061,379	(€ 642)	€ 12,836,910	(€ 586)	€ 12,286,779	(€ 561)
<b>Non OIC (£)</b>	£37,421,154	(£2,340)	£14,256,172	(£891)	£8,331,199	(£521)	£7,674,862	(£480)	£7,158,921	(£448)
Equivalent USD (\$)	\$50,518,558	(\$3,159)	\$19,245,832	(\$1,203)	\$11,247,119	(\$703)	\$10,361,064	(\$648)	\$9,664,543	(\$604)
Equivalent Euro (€)	€ 41,537,481	(€ 2,597)	€ 15,824,351	(€ 989)	€ 9,247,631	(€ 578)	€ 8,519,097	(€ 533)	€ 7,946,402	(€ 497)
<b>OIC</b>	£21,333,133	(£3,606)	£9,196,252	(£1,555)	£4,336,710	(£733)	£3,889,922	(£658)	£3,910,249	(£661)
Equivalent USD (\$)	\$28,799,730	(\$4,869)	\$12,414,940	(\$2,099)	\$5,854,559	(\$990)	\$5,251,395	(\$888)	\$5,278,836	(\$892)
Equivalent Euro (€)	€ 23,679,778	(€ 4,003)	€ 10,207,840	(€ 1,726)	€ 4,813,748	(€ 814)	€ 4,317,813	(€ 730)	€ 4,340,376	(€ 734)
<b>Stable</b>	£8,089,089	(£3,348)	£3,338,497	(£1,382)	£1,757,609	(£727)	£1,477,953	(£612)	£1,515,030	(£627)
Equivalent USD (\$)	\$10,920,270	(\$4,520)	\$4,506,971	(\$1,865)	\$2,372,772	(\$982)	\$1,995,237	(\$826)	\$2,045,291	(\$847)
Equivalent Euro (€)	€ 8,978,889	(€ 3,716)	€ 3,705,732	(€ 1,534)	€ 1,950,946	(€ 807)	€ 1,640,528	(€ 679)	€ 1,681,683	(€ 696)
<b>Unstable</b>	£13,244,044	(£3,785)	£5,857,755	(£1,674)	£2,579,101	(£737)	£2,411,969	(£689)	£2,395,219	(£685)
Equivalent USD (\$)	\$17,879,459	(\$5,110)	\$7,907,969	(\$2,260)	\$3,481,786	(\$995)	\$3,256,158	(\$931)	\$3,233,546	(\$924)
Equivalent Euro (€)	€ 14,700,889	(€ 4,201)	€ 6,502,108	(€ 1,858)	€ 2,862,802	(€ 818)	€ 2,677,286	(€ 765)	€ 2,658,693	(€ 760)
<b>1st line</b>	£6,322,363	(£3,563)	£2,786,349	(£1,570)	£1,259,156	(£710)	£1,173,777	(£662)	£1,103,081	(£622)
Equivalent USD (\$)	\$8,535,190	(\$4,811)	\$3,761,571	(\$2,120)	\$1,699,861	(\$958)	\$1,584,599	(\$893)	\$1,489,159	(\$839)
Equivalent Euro (€)	€ 7,017,823	(€ 3,955)	€ 3,092,847	(€ 1,743)	€ 1,397,663	(€ 788)	€ 1,302,892	(€ 734)	€ 1,224,420	(€ 690)
<b>2nd line</b>	£2,414,608	(£3,713)	£1,111,141	(£1,709)	£464,062	(£714)	£433,965	(£667)	£405,440	(£623)
Equivalent USD (\$)	\$3,259,721	(\$5,013)	\$1,500,040	(\$2,307)	\$626,484	(\$963)	\$585,853	(\$901)	\$547,344	(\$842)
Equivalent Euro (€)	€ 2,680,215	(€ 4,122)	€ 1,233,367	(€ 1,897)	€ 515,109	(€ 792)	€ 481,701	(€ 741)	€ 450,038	(€ 692)
<b>3rd line</b>	£4,507,073	(£4,194)	£1,960,265	(£1,824)	£855,883	(£796)	£804,227	(£748)	£886,698	(£825)
Equivalent USD (\$)	\$6,084,549	(\$5,662)	\$2,646,358	(\$2,463)	\$1,155,442	(\$1,075)	\$1,085,706	(\$1,010)	\$1,197,042	(\$1,114)
Equivalent Euro (€)	€ 5,002,851	(€ 4,655)	€ 2,175,894	(€ 2,025)	€ 950,030	(€ 884)	€ 892,692	(€ 831)	€ 984,235	(€ 916)

**Supplementary table 4. Total and mean healthcare costs per patient year for patients prescribed opioids with prior exposure to laxatives with subsets defined by constipation status excluding patients with prior history of gastrointestinal and colorectal cancer**

	Combined costs		Inpatients		Outpatients		Primary care		Prescription costs	
	Total cost (cost ppy)		Total cost (cost ppy)		Total cost (cost ppy)		Total cost (cost ppy)		Total cost (cost ppy)	
<b>Chronic</b>	£8,112,435	(£4,550)	£3,190,511	(£1,789)	£1,494,396	(£838)	£1,453,961	(£815)	£1,973,567	(£1,107)
Equivalent USD (\$)	\$10,951,787	(\$6,143)	\$4,307,190	(\$2,416)	\$2,017,435	(\$1,132)	\$1,962,847	(\$1,101)	\$2,664,315	(\$1,494)
Equivalent Euro (€)	€ 9,004,803	(€ 5,051)	€ 3,541,467	(€ 1,986)	€ 1,658,780	(€ 930)	€ 1,613,897	(€ 905)	€ 2,190,659	(€ 1,229)
<b>Non OIC (£)</b>	£1,280,642	(£5,161)	£554,978	(£2,236)	£299,059	(£1,205)	£191,533	(£772)	£235,072	(£947)
Equivalent USD (\$)	\$1,728,867	(\$6,967)	\$749,220	(\$3,019)	\$403,730	(\$1,627)	\$258,570	(\$1,042)	\$317,347	(\$1,279)
Equivalent Euro (€)	€ 1,421,513	(€ 5,728)	€ 616,026	(€ 2,482)	€ 331,955	(€ 1,338)	€ 212,602	(€ 857)	€ 260,930	(€ 1,051)
<b>OIC</b>	£6,831,793	(£4,451)	£2,635,533	(£1,717)	£1,195,337	(£779)	£1,262,428	(£823)	£1,738,495	(£1,133)
Equivalent USD (\$)	\$9,222,921	(\$6,009)	\$3,557,970	(\$2,318)	\$1,613,705	(\$1,051)	\$1,704,278	(\$1,110)	\$2,346,968	(\$1,529)
Equivalent Euro (€)	€ 7,583,290	(€ 4,941)	€ 2,925,442	(€ 1,906)	€ 1,326,824	(€ 865)	€ 1,401,295	(€ 913)	€ 1,929,729	(€ 1,257)
<b>Stable</b>	£2,129,424	(£3,756)	£749,039	(£1,321)	£389,338	(£687)	£432,068	(£762)	£558,979	(£986)
Equivalent USD (\$)	\$2,874,722	(\$5,070)	\$1,011,203	(\$1,783)	\$525,606	(\$927)	\$583,292	(\$1,029)	\$754,622	(\$1,331)
Equivalent Euro (€)	€ 2,363,661	(€ 4,169)	€ 831,433	(€ 1,466)	€ 432,165	(€ 762)	€ 479,595	(€ 846)	€ 620,467	(€ 1,094)
<b>Unstable</b>	£4,702,369	(£4,859)	£1,886,494	(£1,949)	£805,999	(£833)	£830,360	(£858)	£1,179,516	(£1,219)
Equivalent USD (\$)	\$6,348,198	(\$6,560)	\$2,546,767	(\$2,632)	\$1,088,099	(\$1,124)	\$1,120,986	(\$1,158)	\$1,592,347	(\$1,645)
Equivalent Euro (€)	€ 5,219,630	(€ 5,393)	€ 2,094,008	(€ 2,164)	€ 894,659	(€ 924)	€ 921,700	(€ 952)	€ 1,309,263	(€ 1,353)
<b>1st line</b>	£1,232,974	(£4,455)	£475,292	(£1,717)	£223,625	(£808)	£220,410	(£796)	£313,647	(£1,133)
Equivalent USD (\$)	\$1,664,515	(\$6,014)	\$641,644	(\$2,318)	\$301,894	(\$1,091)	\$297,554	(\$1,075)	\$423,423	(\$1,530)
Equivalent Euro (€)	€ 1,368,601	(€ 4,945)	€ 527,574	(€ 1,906)	€ 248,224	(€ 897)	€ 244,655	(€ 884)	€ 348,148	(€ 1,258)
<b>2nd line</b>	£785,852	(£5,073)	£377,142	(£2,435)	£116,876	(£755)	£130,014	(£839)	£161,820	(£1,045)
Equivalent USD (\$)	\$1,060,900	(\$6,849)	\$509,142	(\$3,287)	\$157,783	(\$1,019)	\$175,519	(\$1,133)	\$218,457	(\$1,410)
Equivalent Euro (€)	€ 872,296	(€ 5,631)	€ 418,628	(€ 2,703)	€ 129,732	(€ 838)	€ 144,316	(€ 932)	€ 179,620	(€ 1,160)
<b>3rd line</b>	£2,683,543	(£5,006)	£1,034,060	(£1,929)	£465,498	(£868)	£479,936	(£895)	£704,049	(£1,313)
Equivalent USD (\$)	\$3,622,783	(\$6,758)	\$1,395,981	(\$2,604)	\$628,422	(\$1,172)	\$647,914	(\$1,209)	\$950,466	(\$1,773)
Equivalent Euro (€)	€ 2,978,733	(€ 5,556)	€ 1,147,807	(€ 2,141)	€ 516,703	(€ 964)	€ 532,729	(€ 994)	€ 781,494	(€ 1,458)