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RESEARCH

Inadequate management of opioid-induced constipation in European cancer pain patients: results of a real-world, multicentre, observational study ("E-StOIC")

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Abstract

Purpose The objectives of the study were to determine the prevalence of (uncontrolled) OIC, relevant medications / interventions employed by healthcare professionals, and the additional strategies utilised by patients, amongst European patients with cancer pain.

Methods This study was a prospective observational study conducted at 24 research sites in ten European countries. Cancer patients receiving opioid analgesics for at least a week were recruited, and asked to complete a questionnaire including background information, single question (Are you constipated?), Rome IV diagnostic criteria for OIC, Bowel Function Index (BFI), and Patient Assessment of Constipation Quality of Life questionnaire (PAC-QOL).
Participants were characterised as having / not having OIC on the basis of the Rome IV diagnostic criteria.

Results 1200 participants completed the study. 59.5% met the Rome IV diagnostic criteria for OIC: only 61.5% that met these criteria self-reported constipation**.** 72% participants were prescribed a regular conventional laxative / peripherally acting mu-opioid receptor antagonist (PAMORA). However, only 66% took their prescribed laxatives every day. Many participants had utilised other strategies / interventions to manage their OIC. Furthermore, 27% had needed to use suppositories, 26.5% had needed to use an enema, and 8% had had a manual evacuation. The use of PAMORAs, and other novel effective medications, was relatively uncommon.

Conclusion The results of this study suggest that management in Europe is often inadequate, and this undoubtedly relates to a combination of inadequate assessment, inappropriate treatment, and inadequate reassessment.

Keywords Analgesics · Opioid · Opioid-induced constipation · Neoplasms · Cancer pain

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Introduction

Constipation has been defined as "slow movement of faeces through the large intestine, resulting in infrequent bowel movements and passage of dry, hard stools" [1]. However, the term "constipation" means different things to different people, and there seems to be some cultural / regional differences in interpretation [2]. For example, a survey of the Swedish population reported that only 41% of females and 21% of males considered "infrequent bowel movements" indicative of constipation, whilst only 44% of females and 43% of males considered "hard stools" indicative of constipation [3]. Constipation is a common problem in patients with cancer, and may be due to a number of factors, including many drugs used for symptom control, and especially the opioid analgesics [4].

Opioid-induced constipation (OIC) has been defined as "a change when initiating opioid therapy from baseline bowel habits that is characterized by any of the following: reduced bowel movement frequency; development or worsening of straining to pass bowel movements; a sense of incomplete rectal evacuation; and harder stool consistency" [5]. Additionally, the Rome Foundation have produced diagnostic criteria for OIC (Box 1) [6]: these diagnostic criteria are similar to those for functional constipation, although the justification for these diagnostic criteria is somewhat obscure. Recently, Davies et al. reported that these diagnostic criteria had an accuracy of 81.9% when compared with the "gold standard" of a thorough clinical assessment by an experienced clinician [7].

OIC is a common problem in patients with cancer (and other groups of patients) [8], and is associated with a diverse range of physical [7], psychological [9], and social consequences (and impaired quality-of-life) [10]. Moreover, OIC has a significant health economic impact on patients and health care services [11, 12]. Indeed, cancer pain guidelines universally recommend the co-prescription of "laxatives" with opioid analgesics [13, 14], although previous research suggest that this practice is not universal [7, 15], that clinicians often do not follow guidance about prescribing laxatives [16, 17], that patients often do not follow advice about taking laxatives (i.e. regularly) [7, 18], and that novel interventions are infrequently utilised [19, 20].

This study investigated OIC within a large cohort of "real world" European patients with cancer pain. The objectives of the study were to determine the prevalence of (uncontrolled) OIC, relevant medications prescribed by healthcare professionals, other relevant interventions employed by healthcare professionals (e.g. rectal interventions, opioid switching), and the additional strategies utilised by patients to manage constipation (e.g. lifestyle changes, over-the-counter medications).

Methods

The study was a prospective observational study conducted at 24 research sites (see Acknowledgements) in ten European countries (Denmark, Finland, France, Germany, Ireland, Italy, Netherlands, Norway, Spain, United Kingdom). The study was sponsored by Trinity College Dublin, and received ethical approval in Ireland from the St. James's Hospital / Tallaght University Hospital Joint Research Ethics Committee (reference number – 0148). It received similar ethical approval in all other countries. The study was conducted in accordance with the Declaration of Helsinki. It was registered on CancerTrials.gov registry (reference number – NCT05149833).

Participants were recruited from inpatients and outpatients at the research sites. All patients that met the criteria for the study were eligible for entry into the study (i.e. convenience sampling, consecutive recruitment). The inclusion criteria were a) age $\geq$ 18 yr; b) diagnosis of cancer; c) diagnosis of cancer pain / cancer treatment-related pain; and d) taking regular opioids for at least one week (i.e. opioid for mild-to-moderate pain, or opioid for moderate-to-severe pain). The exclusion criteria were a) inability to provide informed consent; and b) inability to complete study questionnaire. The study questionnaire was provided in the "local" language, and so participants needed to be proficient in the local language.

Informed consent was obtained from participants prior to entry into the study, which involved collection of demographic information, current prescribed opioid regimen, current prescribed "laxative" regimen, as well as assessment of Eastern Co-operative Oncology Group (ECOG) performance status (participant assessed) [21], completion of Rome IV diagnostic criteria for OIC [6], completion of the Bowel Function Index (BFI) [22], and completion of the Patient Assessment of Constipation Quality of Life questionnaire (PAC-QOL) [23]. In addition, patients were asked about their opinion about their bowel habit ("Are you constipated?"), their perceptions about their prescribed "laxative" regimen, their adherence with their prescribed laxative regimen, and what other strategies they used / had used to manage their constipation.

The Rome IV diagnostic criteria for OIC consists of six statements relating to constipation-related symptoms, and one "exclusion" statement relating to the co-existence of diarrhoea in the absence of laxatives (Box 1) [6]. Patients were required to answer "yes" or "no" to each statement, and those that answer positively to $\geq$ 2 statements (and negatively to the exclusion statement) meet the Rome IV diagnostic criteria for OIC. It should be noted that the statements relate to "new or worsening symptoms of constipation when initiating, changing, or increasing opioid therapy".

The Rome IV diagnostic criteria for OIC do not relate to a specific period of time.

Box 1 Rome IV diagnostic criteria for opioid-induced constipation [6]

Rome IV diagnostic criteria for opioid-induced constipation
1. New, or worsening, symptoms of constipation when initiating, changing, or increasing opioid therapy, that must include two or more of the following:
a) Straining during more than ¼ (25%) of defecations
b) Lumpy or hard stools (Bristol Stool Form Scale 1–2) more than ¼ (25%) of defecations
c) Sensation of incomplete evacuation more than ¼ (25%) of defecations
d) Sensation of anorectal obstruction / blockage more than ¼ (25%) of defecations
e) Manual maneuvers to facilitate more than ¼ (25%) of defecations (e.g. digital evacuation, support of pelvic floor)
f) Fewer than three spontaneous bowel movements per week
2. Loose stools are rarely present without the use of laxatives

The BFI is a validated patient-reported outcome measure (PROM), and consists of three questions (and was used to assess the adequacy of treatment) [22]. It relates to the previous seven days. The BFI provides an overall score (range 1–100), and a score of > 28.8 indicates inadequate treatment. The PAC-QOL is a validated PROM, and consists of 28 questions (and was used to assess constipation-related quality-of-life) [23]. It relates to the previous two weeks. The PAC-QOL provides a series of scores (range 0–4), and a higher score indicates a greater impact: the scores include a physical subscale score, a psychosocial subscale score, a worries / concerns subscale score, a satisfaction subscale score, and there is also an overall score.

The study questionnaire was initially written in English, and then translated into the other local languages. The official translations of the Rome IV diagnostic criteria, the BFI, the PAC-QOL were utilised in the study (with permission of the copyright holders). The rest of the case report form was translated by a commercial medical translation company, and was then checked for accuracy / meaning by the Principal Investigators in the relevant countries.

The sample size was pragmatic, and reflected the need to collect data from a large / heterogeneous cohort of patients. In terms of determining the prevalence of OIC, and assuming a similar prevalence to that suggested by an Expert Working Group of European Association of Palliative Care [24], then a sample size of 1200 would provide a 95% confidence interval of ± 2.70% for the estimate of the prevalence percentage. It was decided in advance to replace patients that were recruited to the study but did not complete relevant sections of the questionnaire.

For the purposes of the analysis, participants were characterised as either having OIC, or not having OIC, on the basis of the Rome IV diagnostic criteria [6]. The dose of opioid analgesic was converted into the mean equivalent daily dose (MEDD) of morphine primarily using the opioid conversion chart developed by the Pharmacy Department at Our Lady's Hospice and Care Services (Dublin) [25]. However, other sources were required for specific opioid analgesic (e.g. tapentadol, tildine). It should be noted that patients receiving methadone, or an opioid / naloxone combination, were excluded from analyses relating to the MEDD ($n = 71$).

Descriptive statistics were primarily used to explain the data derived from study questionnaire (numbers, percentages; mean, standard deviation / SD; median, range or interquartile range—the latter was used where there appeared to be a marked departure from normality). Standard statistical methods were used in the analysis. Chi-squared tests were used to assess the association between categorical data, with Yates continuity corrections employed as needed for nominal binary (2 × 2) categorical variables, and test for trend employed as needed for ordered categorical variables; Mann–Whitney U tests or Student t tests were used to assess the association between continuous data. An alpha 5% two-sided cut-off was used to determine a significant association between the two groups of patients.

Results

One thousand two hundred patients completed the study, although 1204 patients were enrolled in the study: 4 participants were excluded, as they did not complete relevant sections of the questionnaire (e.g. Rome IV diagnostic criteria, BFI). The participant's characteristics are shown in Table 1. All of the countries recruited 120 patients, except for Ireland ($n = 177$), Denmark ($n = 113$), and Norway ($n = 70$).

All participants were receiving regular opioid analgesics (Table 2), with 57 (4.5%) taking more than one opioid analgesic, and 30 (2.5%) of these taking methadone with either fentanyl, morphine, or oxycodone. The median morphine equivalent daily dose (MEDD) was 70 mg (interquartile range: 40–120 mg; absolute range: $3–6 \times 10^4$ mg). Eight hundred and sixty seven (72%) participants were prescribed a regular conventional laxative / peripherally acting mu-opioid receptor antagonist (PAMORA). In addition, 40 participants were receiving an oxycodone / naloxone combination preparation, with 24 prescribed additional regular conventional laxatives (included in the previous figures); one participant was receiving a buprenorphine / naloxone combination preparation.

Of the participants prescribed a regular conventional laxative / PAMORA, 578 (67%) received a single drug, 244 (28%) two drugs, 40 (4.5%) three drugs, four (0.5%) four drugs, and a single person five drugs. Macrogols were the

Table 1 Characteristics of study participants

Characteristic	All participants (n = 1200)	Participants with OIC* (n = 713)	Participants without OIC* (n = 487)
Age			
Median (range)	65 yr (23-96 yr)	64 yr (23-94 yr)	67 yr (24-96 yr)
Gender			
Female	611 (51%)	362	249
Male	589 (49%)	351	238
Cancer primary location			
Breast	137 (11.5%)	97	40
Endocrine	28 (2.5%)	14	14
Gastrointestinal	309 (25.5%)	158	151
Gynaecological	89 (7.5%)	45	44
Haematological	74 (6%)	39	35
Head & neck	60 (5%)	34	26
Lung	227 (19%)	144	83
Neurological	6 (0.5%)	4	2
Ophthalmic	1 (0%)	1	0
Skin	39 (3%)	29	10
Soft tissue & bone	40 (3.5%)	23	17
Unknown primary	21 (2%)	10	11
Urological & male genital	168 (14%)	114	54
No data	1 (0)	1	0
ECOG performance status (participant determined)			
0	65 (5.5%)	40	25
1	357 (30%)	208	149
2	391 (32.5%)	242	149
3	332 (27.5%)	190	142
4	55 (4.5%)	33	22

*Based on Rome IV diagnostic criteria

most commonly prescribed conventional laxative (45.5% participants). PAMORAs were regularly prescribed in 127 (10.5%) participants, with 73 of these participants co-prescribed conventional laxatives. It should be noted that the opioid / naloxone formulations are included in these figures. Per rectum interventions (i.e. suppositories, enemas) were regularly prescribed in 14 (1%) participants. One participant was prescribed regular loperamide (and no medication for constipation).

In answer to the question *"Are you constipated?"*, 549 (45.5%) participants replied "yes", 588 (49%) replied "no", and 59 (5%) were "unsure" (with missing data in four cases—0.5%). However, 713 (59.5%) participants met the Rome IV diagnostic criteria for OIC: only 61.5% (439) participants that met these criteria self-reported constipation (Fig. 1).

Rome IV diagnostic criteria positivity was associated with younger age (Mann–Whitney U-test: $p = 0.003$), and certain cancer diagnoses (Chi-square test: $\chi^2 = 31.12$; $p = 0.001$). Thus, OIC was more frequent in patients with breast cancer, lung cancer, skin cancer (melanoma), and urological / male genital cancer. However, it was not associated with sex (Chi-square test: $p = 0.950$), or ECOG performance status (Chi-square test: $p = 0.754$). Rome IV diagnostic positivity was associated with higher MEDD (Mann–Whitney U-test: $p = 0.018$), and was less frequent in patients receiving transdermal buprenorphine as their background opioid analgesic (Chi-square test: $\chi^2 = 4.32$; $p = 0.038$).

Only 66% (570) participants took their prescribed laxatives every day (with five patients "unsure", and missing data for another five patients). The remaining (n = 287) participants either took their laxatives "regularly but not every day" ($n = 94$), "only when my bowel movements are less than normal" ($n = 83$), or "only when I am constipated" ($n = 100$), with no data for 10 participants. The reasons for not taking laxatives regularly were (multiple options allowed): a) "I do not need the laxatives every day" (73%); b) "I forget to take the laxatives" (8.5%); c) "I have to take too many medications" (8.5%); d) "Difficulty / unpleasantness of taking laxatives" (7.5%); e) "Side effects of laxatives" (5%); and

Table 2 Regular medication of study participants

Regular medication	Number of participants (n = 1200)
Opioid analgesic (regular prescription)*	
Alfentanil	3 (0%)
Buprenorphine	44 (3.5%)
Buprenorphine / naloxone	1 (0%)
Codeine	8 (0.5%)
Dihydrocodeine	1 (0%)
Fentanyl	267 (22%)
Hydromorphone	37 (3%)
Methadone	105 (8.5%)
Morphine	361 (30%)
Oxycodone	356 (29.5%)
Oxycodone / naloxone	40 (3.5%)
Tapentadol	14 (1%)
Tildine	7 (0.5%)
Tramadol	14 (1%)
Laxative & related products (regular prescription)*	
None	333 (28%)
Bulk-forming laxatives	
- *ispaghula husk*	6 (0.5%)
Osmotic laxatives	
- *lactulose*	111 (9%)
- *macrogol*	545 (45.5%)
- *magnesium hydroxide*	52 (4.5%)
- *magnesium sulphate*	6 (0.5%)
- *sodium acid phosphate/sodium phosphate*	9 (0.5%)
Softening laxatives	
- *docusate sodium*	53 (4.5%)
- *liquid paraffin*	35 (3.0%)
- *liquid paraffin/magnesium hydroxide*	2 (0%)
Stimulant laxatives	
- *bisacodyl*	50 (4%)
- *senna*	129 (10.5%)
- *senna/ispaghula*	1 (0%)
- *senna/lemon balm*	1 (0%)
- *magnesium citrate/sodium picosulfate*	14 (1%)
- *sodium acid phosphate/sodium phosphate*	9 (0.5%)
- *sodium picosulfate*	88 (7.5%)
Peripherally acting mu opioid receptor antagonists	
- *naldemedine*	18 (1.5%)
- *naloxegol*	64 (5%)
- *naloxone*	4 (0.5%)
Lubiprostone	1 (0%)
Other miscellaneous oral preparations	3 (0%)
Suppositories / enemas	
- *arachis oil enema*	1 (0%)
- *docusate sodium suppository*	1 (0%)
- *glycerol suppository*	7 (0.5%)
- *lactulose enema*	1 (0%)
- *sodium acid phosphate/sodium phosphate enema*	4 (0.5%)
- *sodium citrate/sodium alkylsulphoacetate enema*	1 (0%)
- *water-based enema*	1 (0%)

*57 patients using two opioid analgesics

**289 patients using two or more laxatives

f) "I am leaving the house (and am concerned about access to toilet)" (10%).

In terms of satisfaction with the "effectiveness" of their prescribed laxatives, 335 (38.5%) participants were "very satisfied", 300 (34.5%) were "somewhat satisfied", 126 (14.5%) were "neither satisfied nor dissatisfied", 74 (8.5%) were "somewhat dissatisfied", and 24 (3%) were "very dissatisfied" (with missing data in eight cases). Similarly, in terms of satisfaction with the "tolerability ('side effects')" of their prescribed laxatives, 435 (50%) participants were "very satisfied", 251 (29%) were "somewhat satisfied", 111 (12.5%) were "neither satisfied nor dissatisfied", 47 (5.5%) were "somewhat dissatisfied", and 12 (1.5%) were "very dissatisfied" (with missing data in 11 cases).

Nevertheless, many participants had utilised other strategies / interventions to manage their OIC (Table 3). Furthermore, 27% participants had needed to use suppositories to manage their bowels, with 2% using them "almost constantly", 6% "frequently", 23% "occasionally", and 68% "rarely". Similarly, 26.5% participants had needed to use an enema to manage their bowels, with 2% using them "almost constantly", 8% "frequently", 23.5% "occasionally", and 66% "rarely". Ninety eight (8%) participants had had a manual evacuation: 2% reported this was done "almost constantly", 5% "frequently", 19.5% "occasionally", and 73.5% "rarely".

Six hundred and fifty three (54.5%) participants had a BFI score > 28.8, indicating inadequate management of OIC. The mean BFI score for Rome IV diagnostic criteria positive participants was 50.31 (SD ± 26.31), and 76% of these patients had a score of > 28.8. In contrast, the mean BFI score for Rome IV diagnostic criteria negative participants was 16.69 (SD ± 20.74), and only 23% of these patients had a score of > 28.8. The difference in the mean BFI scores was statistically significant (Student t test: $t = -23.63$; $p < 0.001$), as was the difference in the number of patients with a score of > 28.8 (Chi-squared test: $\chi^2 = 314.29$; $p < 0.001$). In terms of the PAQ-QOL data, the mean of the sub-scale scores,

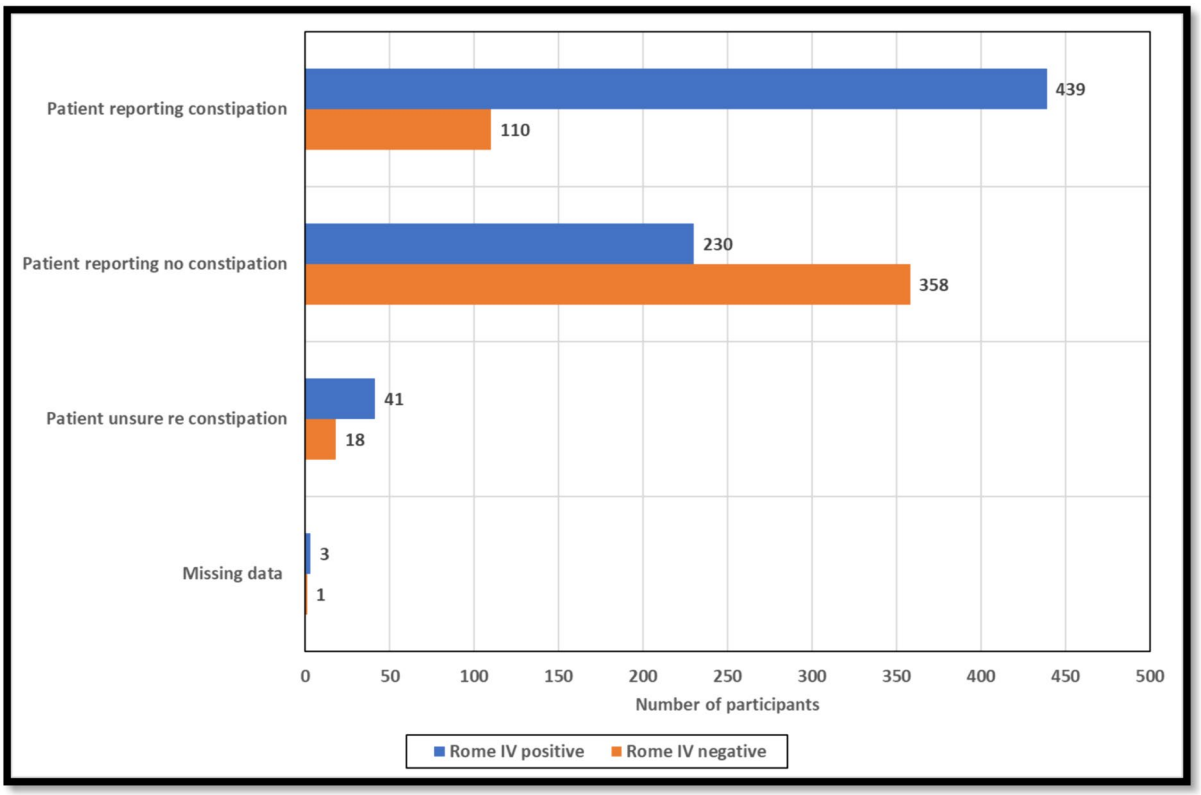

Fig. 1 Patient opinion re constipation versus Rome IV diagnostic criteria for opioid-induced constipation

and the mean overall score, were all worse for patients that were Rome IV diagnostic criteria positive (with the notable exception of the dissatisfaction subscale) (Student t test: all $p < 0.001$).

Discussion

This study confirms that OIC remains a significant problem amongst European cancer patients [26]. Thus, 59.5% participants fulfilled the Rome IV diagnostic criteria for OIC [6], The prevalence of OIC in this study was similar to that reported in the analogous StOIC I study (i.e. 59%) [7], although the latter study employed a thorough clinical assessment by an experienced palliative care clinician to determine whether subjects were constipated (or not). Importantly, the StOIC I study established that the Rome IV diagnostic criteria had an accuracy of 81.9% (95% CI: 79.4–84.2) when compared to a thorough clinical assessment by an experienced palliative care clinician [7]. Hence, the prevalence of OIC in this study may be an underestimate, which could explain why some participants self-reported constipation despite not fulfilling the Rome IV diagnostic criteria. Importantly, the above figure relates to the prevalence of "uncontrolled" OIC, with another 298 (25%) participants taking regular medication in order to prevent / manage OIC.

In this study, the presence of OIC was associated with lower age, specific cancer subtypes, and higher MEDD. Other studies have not reported similar findings in respect of age or cancer subtype [7], although the raw data from one study suggests OIC was more common in patients with breast cancer [27]. If our results are correct, then the explanation for the association with specific cancer subtypes is somewhat obscure. In terms of MEDD, previous studies have generally reported no association [7, 28, 29], although certain studies have reported a "weak" positive association [27], and also a "hyperbolic" relationship [30]. Transdermal buprenorphine was associated with a lower frequency of OIC in this cohort of patients. The StOIC I study reported a similar finding [7], and a recent systematic review of transdermal opioids supports this finding [31]. Other opioids were associated with neither a higher nor lower frequency of OIC, including the oxycodone / naloxone formulation.

The high prevalence of OIC suggests inadequate assessment, and/or suboptimal treatment, and/or inadequate re-assessment (in the setting of a class of drugs that has multiple negative impacts on the gastrointestinal tract) [4]. In terms of assessment, the study confirms that the single question ("Are you constipated"?) is inadequate [7, 32], and

Table 3 Other strategies / interventions utilised to manage opioid-induced constipation

Interventions to manage constipation	Number of participants ($n = 1200$)
"Since starting your opioid painkiller, have you changed your diet to help to manage your constipation (e.g. increased amount of fibre, increased amount of fruit)?"	Yes – 373 (31%) No – 813 (68%) Unsure – 13 (1%) Missing data – 1 (0%)
"Since starting your opioid painkiller, have you increased the amount of fluid you drink to help to manage your constipation?"	Yes – 510 (42.5%) No – 663 (55.5%) Unsure – 26 (2%) Missing data – 1 (0%)
"Since starting your opioid painkiller, have you increased the amount of exercise you take to help to manage your constipation?"	Yes – 109 (9%) No – 1075 (89.5%) Unsure – 15 (1.5%) Missing data – 1 (0%)
"Since starting your opioid painkiller, have you used any 'over the counter' (purchased) laxatives to help to manage your constipation?"	Yes – 277 (23%) No – 915 (76.5%) Unsure – 8 (0.5%)
"Since starting your opioid painkiller, have you used any complementary therapies / alternative treatments to help to manage your constipation?"	Yes – 90 (7.5%) No – 1102 (92%) Unsure – 6 (0.5%) Missing data – 2 (0%)
"Since starting your opioid painkiller, have you ever reduced the dose of the painkiller to help to manage your constipation?"	Yes – 72 (6%) No – 1121 (93.5%) Unsure – 5 (0.5%) Missing data – 2 (0%)
"Since starting your opioid painkiller, have you ever stopped the painkiller to help to manage your constipation?"	Yes – 45 (4%) No – 1149 (96%) Unsure – 2 (0%) Missing data – 4 (0%)
"Since starting opioid painkillers, has your doctor / nurse advised you to reduce the dose to help to manage your constipation?"	Yes – 26 (2%) No – 1168 (97.5%) Unsure – 6 (0.5%)
"Since starting opioid painkillers, has your doctor / nurse changed the painkiller to help to manage your constipation?"	Yes – 52 (4.5%) No – 1133 (94.5%) Unsure – 15 (1%)

that a more thorough assessment is required [4]. Moreover, the results confirm that people's opinions on what symptoms constitute (or not) constipation are somewhat variable. For example, 15.5% of participants that self-reported no constipation did admit to "straining during more than ¼ (25%) of defecations". In terms of re-assessment, the study demonstrates that asking patients about the effectiveness of interventions is equally inadequate. However, it confirms that the BFI score is a suitable outcome measure. Thus, there was a statistically significant association between the BFI scores (i.e. mean score, and score > 28.8) and the Rome IV diagnostic criteria.

In this study, 54.5% participants had a BFI score > 28.8 (indicating inadequate management of OIC) [22], which is slightly lower than reported in the analogous StOIC I study (i.e. 63.5%) [7]. Cancer pain guidelines universally recommend the co-prescription of "laxatives" with opioid analgesics [13, 14], although previous research suggests that this practice is not universal [15, 26]. In this study, 333 (28%) participants were not prescribed a regular conventional laxative / PAMORA, including 144 participants that met the Rome IV diagnostic criteria. Moreover, many participants that were prescribed regular conventional laxatives were receiving suboptimal regimens, e.g. softening laxative alone, stimulant laxative alone. Equally concerning is that many (33%) participants that were prescribed a regular conventional laxative / PAMORA were not taking these medications on a daily basis.

Numerous treatment guidelines are available to guide management [4, 33]. Furthermore, there are now a number of alternative pharmacological interventions that have been shown in randomised controlled trials (and/or systematic reviews) to be very effective in the management of OIC, e.g. PAMORAs [34, 35], linaclotide [36], lubiprostone [37], prucalopride [38]. Importantly, there is limited evidence that lifestyle changes are effective in preventing / managing OIC (e.g. higher fibre intake, higher fluid intake, increased exercise), and such interventions can be difficult for patients with

advanced cancer [4]. Moreover, there is limited evidence that conventional laxatives are effective in preventing / managing OIC [4], although they remain the recommended first line option (e.g. macrogol, combination softener laxative / stimulant laxative) [4, 33].

Disappointingly, few of the patients in this study were receiving a PAMORA (or an alternative pharmacological intervention). It is difficult to explain the latter, since PAMORAs have been demonstrated to be effective, well tolerated, and notably cost effective [39, 40]. Even more disappointing is the frequency of use of rectal interventions (i.e. suppositories, enemas, manual evacuation), the need for patients to seek alternative treatments (i.e. over the counter laxatives, complementary therapies), and the perceived need for opioid dose reduction or discontinuation.

Recently, Davies et al. demonstrated that clinically important improvements in OIC could be achieved by managing patients with a step-wise treatment algorithm (i.e. conventional laxatives, then PAMORA, then PAMORA/conventional laxatives, then alternative intervention), with the decision to change / escalate treatment based upon weekly BFI scores (and the tolerability of interventions) [41]. Importantly, many patients with OIC also have other causes of constipation [7, 42], and this explains the need for some patients to take both a PAMORA and conventional laxatives: thus, the PAMORA manages the OIC, whilst the conventional laxative manages the other causes of constipation. It should be noted that some of the alternative pharmacological interventions are effective in managing both OIC and other types of constipation (e.g. linaclotide, lubiprostone, prucalopride) [4].

The major limitation of this study is the use of the Rome IV diagnostic criteria. As discussed, these have an accuracy of ~ 82% when compared to a thorough clinical assessment by an experienced palliative care clinician [7]. However, given the focus of this study, we feel that these criteria were accurate enough (and reduced the burden for the relevant clinical services). The major strengths of this study are the relatively large sample size, the fact that participants were "real-world" patients (non-restrictive inclusion / exclusion criteria), and the fact that participants were recruited from 24 research sites in 10 different European countries. Thus, the results are likely to be a reasonable representation of clinical practice within these specific countries (and probably elsewhere in Europe).

Conclusion

OIC is a major problem in cancer pain patients, leading to a number of physical, psychological, and social problems (and poorer quality-of-life). This study suggests that management in Europe is often inadequate, and this undoubtedly relates to a combination of inadequate assessment, inappropriate treatment, and inadequate reassessment. However, a number of evidence-based strategies / interventions are already available to improve this important clinical problem.

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Author contribution AD conceived the study, wrote the protocol, and wrote the first draft of the paper. NF was the lead research nurse for the study, and coordinated setting up the study in the various countries. All the other authors (JG-B, CC, GE, FE, CL, RM, WO, CR, MV, MW) were involved in setting up the study in their relevant countries. All the authors contributed to the final manuscript.

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Data availability Requests for access to study data should be directed to corresponding author.

Declarations

Conflict of interest AD, GE, and CL have both received personal fees for consultancy / educational activities from Kyowa Kirin International. None of the other authors have relevant conflicts of interest.

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