Research Paper

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Opioid-induced constipation in patients with cancer: a "real-world," multicentre, observational study of diagnostic criteria and clinical features

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Abstract

The aim of this study was to investigate opioid-induced constipation (OIC) in a large cohort of "real-world" patients with cancer; the objectives were to determine the prevalence of OIC, the utility of a simple screening question, the accuracy of the Rome IV diagnostic criteria, the clinical features of OIC (physical and psychological), and the impact of OIC (quality of life). One thousand patients with cancer were enrolled in the study, which involved completion of the Rome IV diagnostic criteria for OIC, the Bowel Function Index, the Patient Assessment of Constipation Quality of Life questionnaire, and the Memorial Symptom Assessment Scale—Short Form. Participants also underwent a thorough clinical assessment by an experienced clinician (ie, "gold-standard" assessment of OIC). Fifty-nine percent of patients were clinically assessed as having OIC, 2.5% as having another cause of constipation, and 19% as not having constipation but were taking regular laxatives. The simple screening question produced a number of false-negative results (19% of patients), whereas the Rome IV diagnostic criteria had an accuracy of 81.9%. Patients with OIC had more symptoms overall, higher Memorial Symptom Assessment Scale—Short Form subscale scores (and total score), and higher Patient Assessment of Constipation Quality of Life questionnaire subscale scores (and the overall score). Opioid-induced constipation was not associated with demographic factors, cancer diagnosis, performance status, or opioid equivalent dosage: OIC was associated with opioid analgesic, with patients receiving tramadol and transdermal buprenorphine having less constipation. The study confirms that OIC is common among patients with cancer pain and is associated with a spectrum of physical symptoms, a range of psychological symptoms, and an overall deterioration in the quality of life.

Keywords: Analgesics, Opioid, Constipation, Cancer pain, Rome Foundation

1. Introduction

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."[4] Constipation is a common adverse effect of opioid analgesics, but the reported prevalence varies widely in published studies (40%-80%).[8] The reasons for the variance include the definition/diagnostic criteria adopted,[14] the methodology used (eg, impromptu reporting vs systematic assessment),[28] and the population investigated (eg, patients with cancer pain vs patients with nonmalignant pain).[17]

In 2016, the Rome Foundation published new diagnostic criteria for OIC (**Table 1**).[11] The diagnostic criteria for OIC are similar to those for functional constipation (with the exception of opioid usage and minimum symptom duration),[11] although the rationale for the adoption of similar diagnostic criteria is somewhat obscure. The diagnostic criteria for functional constipation have been tested against a clinical assessment by an experienced gastroenterologist and were reported to have a low sensitivity (33.9%), a high specificity (94.5%), and a "moderate" reliability.[29] However, the diagnostic criteria for OIC do not appear to have been similarly assessed, which ought to be a prerequisite to their adoption into clinical practice and clinical research.

The term "constipation" means different things to different people,[22] and there appears to be some ethnic/cultural differences relating to constipation. For example, a Swedish survey of the general population reported that 23.8% female respondents and 24.3% male respondents considered "straining in connection with bowel movement" was not suggestive of constipation.[38] Moreover, the clinical features of OIC vary from patient to patient and include symptoms directly related to constipation and/or symptoms resulting from complications of constipation.[9] Surprisingly, there is a paucity of good data on the frequency of these symptoms. Nevertheless, it is apparent that OIC has a significant negative effect on the quality of life for many patients, and that this relates to physical problems, psychological

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Table 1

Rome IV diagnostic criteria for functional constipation and opioid-induced constipation.[11]

Rome IV criteria for functional constipation	Rome IV criteria for opioid-induced constipation
1. Must include 2 or more of the following: a) Straining during more than one-fourth (25%) of defecations b) Lumpy or hard stools (BSFS 1-2) more than one-fourth (25%) of defecations c) Sensation of incomplete evacuation more than one-fourth (25%) of defecations d) Sensation of anorectal obstruction/blockage more than one-fourth (25%) of defecations e) Manual maneuvers to facilitate more than one-fourth (25%) of defecations (eg, digital evacuation and support of the pelvic floor) f) Fewer than 3 spontaneous bowel movements per week 2. Loose stools are rarely present without the use of laxatives 3. Insufficient criteria for irritable bowel syndrome Criteria fulfilled for the past 3 mo with symptom onset at least 6 mo before diagnosis.	1. New or worsening symptoms of constipation when initiating, changing, or increasing opioid therapy that must include 2 or more of the following: a) Straining during more than one-fourth (25%) of defecations b) Lumpy or hard stools (BSFS 1-2) more than one-fourth (25%) of defecations c) Sensation of incomplete evacuation more than one-fourth (25%) of defecations d) Sensation of anorectal obstruction/blockage more than one-fourth (25%) of defecations e) Manual maneuvers to facilitate more than one-fourth (25%) of defecations (eg, digital evacuation and support of the pelvic floor) f) Fewer than 3 spontaneous bowel movements per week 2. Loose stools are rarely present without the use of laxatives

BSFS, Bristol Stool Form Scale.

problems,[10] and social issues[13] (as well as a health economic impact).[16]

The aim of this study was to investigate OIC in a large cohort of "real-world" patients with cancer in the United Kingdom. The objectives were to determine the prevalence of OIC, the accuracy of a simple screening question, the accuracy of Rome IV diagnostic criteria, the clinical features of OIC (physical and psychological), the impact of OIC (quality of life), and the patterns of treatment for constipation within the United Kingdom.

2. Methods

The study was a prospective observational study conducted within 4 hospitals and 12 hospices in the United Kingdom (from August 2017 to August 2019). The study was sponsored by the Royal Surrey County Hospital and received ethical approval from the East Midlands—Leicester Central REC (reference number—17/EM/0212). The study was adopted by the UK NCRN portfolio (reference number—IRAS ID 222105) and registered on CancerTrials.gov registry (reference number—NCT04350112). The study was an investigator-initiated study, with unrestricted research funding received from Kyowa Kirin International.

Participants were recruited from inpatients and outpatients at the study sites. All patients who met the criteria for the study were eligible for entry into the study (convenience sampling and consecutive recruitment). The inclusion criteria were (1) age ≥ 18 years, (2) diagnosis of cancer, (3) diagnosis of cancer pain, and (4) receipt of regular opioids for at least the past 1 week (ie, opioid for mild-to-moderate pain/"weak" opioid or opioid for moderate-to-severe pain/"strong" opioid). The exclusion criteria were (1) inability to give informed consent and (2) inability to complete the questionnaire.

Informed consent was obtained from participants before entry into the study, which involved collection of demographic information, current opioid regimen (ie, specific opioid analgesic used and dosage/dosing frequency used), current laxative/related product regimen, assessment of Eastern Cooperative Oncology Group (ECOG) performance status (participant assessed),[26] completion of Rome IV diagnostic criteria for OIC (**Table 1**),[11] completion of the Bowel Function Index (BFI),[31] completion of the Patient Assessment of Constipation Quality of Life (PAC-QOL) questionnaire,[23] and completion of the Memorial Symptom Assessment Scale—Short Form (MSAS-SF).[6]

The Rome IV diagnostic criteria for OIC are not validated and consist of 6 statements relating to constipation-related symptoms and 1 "exclusion" statement relating to the coexistence of diarrhoea in the absence of laxatives (**Table 1**).[11] Patients were required to answer "yes" or "no" to each statement, and those who answer positively to ≥2 statements (and negatively to the exclusion statement) met 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 (in contrast to the Rome IV diagnostic criteria for functional constipation).

The BFI is a validated patient-reported outcome measure (PROM) and consists of 3 questions (and was used to assess the adequacy of treatment).[31] The BFI provides an overall score (range 1-100), and a score of >30 indicates inadequate treatment.[1,31] The PAC-QOL questionnaire is a validated PROM and consists of 28 questions (and was used to assess constipation-related quality of life).[23] The PAC-QOL questionnaire 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, and a satisfaction subscale score, and there is also an overall score.

The MSAS-SF is a validated 32-item PROM for assessing physical and psychological symptoms in patients with cancer.[6] Patients are asked about the presence of these symptoms and, for the physical symptoms, the distress caused by the symptom (options: symptom absent—scores 0; "not at all"—scores 0.8; "a little bit"—scores 1.6; "somewhat"—scores 2.4; "quite a bit"—scores 3.2, and "very much"—scores 4.0), and, for the psychological symptoms, the frequency of the symptom (options: symptom absent—scores 0; "rarely"—scores 1; "occasionally"—scores 2; "frequently"—scores 3; and "almost constantly"—scores 4). A series of subscale scores can be generated by calculating the mean of the scores for the relevant symptoms (range 0-4), ie, a physical subscale score, a psychological subscale score, a Global Distress Index score, and a total MSAS score: the higher the subscale score, the higher the burden of the relevant symptoms.

Participants were also asked the simple question: "Are you constipated?," with the answer options being "yes," "no," or "unsure." In addition, participants were asked about the applicability of an often-used palliative care "consensus" definition of constipation[18,34]: "The passage of small, hard faeces infrequently and with difficulty?," with the answer options again being "yes," "no," or "unsure."

Participants also underwent a thorough clinical assessment by an experienced palliative care clinician to determine whether they were constipated (or not), and if they were thought to be

constipated whether they had OIC (or another cause of constipation), and if they were thought to have OIC whether there were other risk factors for constipation (eg, poor diet, poor mobility, other drugs, and GI pathology). The assessments were mainly performed by physicians but were sometimes performed by experienced clinical nurse specialists; the assessments principally consisted of taking a specific history and performing a relevant examination.[9]

The sample size was somewhat 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 the European Association for Palliative Care,[7] then a sample size of 1000 would provide a 95% confidence interval of ±3.08% for the estimate of the prevalence percentage. It was decided in advance to replace patients who were recruited to the study but did not complete the study (for whatever reason).

For the purposes of the analysis, participants were characterised as either having OIC or not having OIC (ie, patients without constipation and patients with non-OIC constipation) on the basis of the thorough clinician assessment (the current "gold standard"): participants with missing data items were excluded from the specific analyses (but not excluded from the overall analysis).

Descriptive statistics were primarily used to explain the data derived from the various questions/assessment tools (numbers, percentages; median, range or interquartile ranges). The dose of opioid was converted into the morphine equivalent daily dose (MEDD) using "equianalgesic" tables in the British National Formulary[3] or the Palliative Care Formulary (if required).[36] Standard statistical methods were used in the analysis: χ^2 tests or Fisher exact tests were used to assess the association between the presence of OIC and categorical outcomes (eg, specific opioid analgesic used); independent samples *t* tests or Mann–Whitney *U* tests were used to assess the association between the presence of OIC and continuous outcomes; sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the Rome IV diagnostic criteria for OIC were calculated in the usual manner. An alpha 5% 2-sided cutoff was used to determine a significant association between the 2 groups of patients. However, a 1% cutoff was used to assess a significant association between the presence of OIC and the presence of individual MSAS-SF symptoms (ie, adjustment for multiple analyses).

3. Results

The study flowchart is shown in **Figure 1**, and the participants' characteristics are shown in **Table 2**. All patients were receiving regular opioid analgesics (**Table 2**), and 60 (6%) were taking more than 1 opioid analgesic. The median morphine equivalent daily

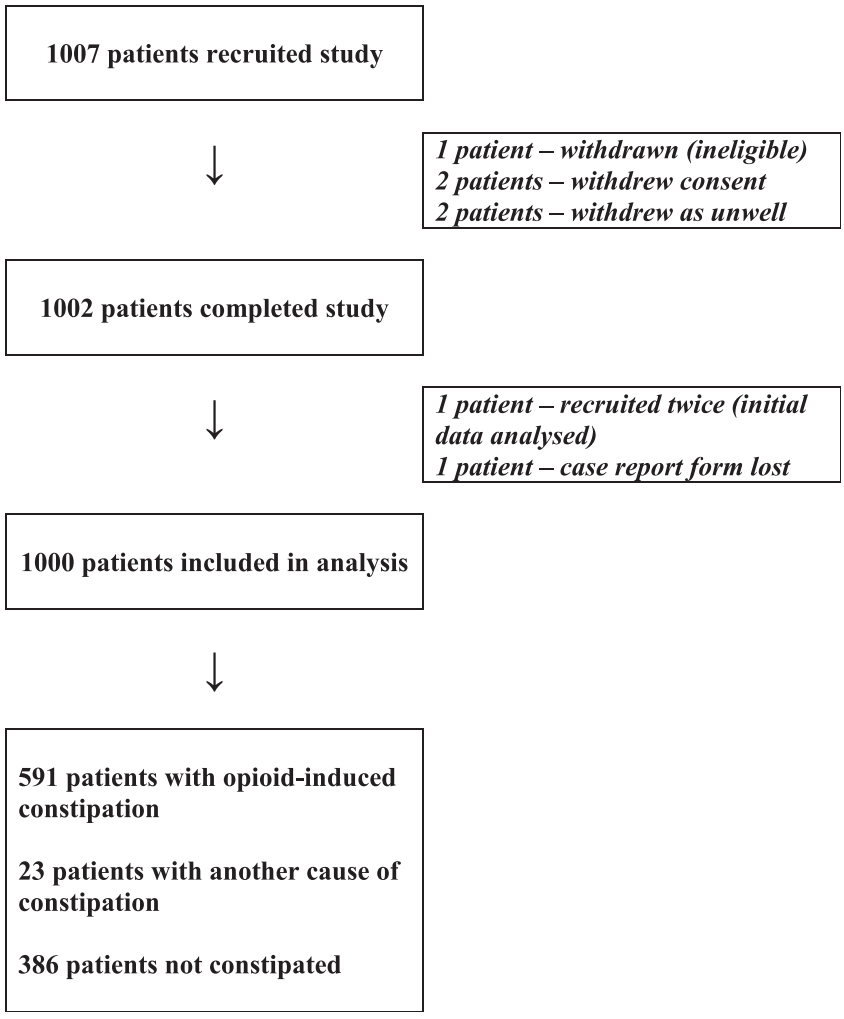

Figure 1. Study flowchart.

Table 2

Characteristics of study participants.

Characteristic	All participants (n = 1000)	Participants with OIC* (n = 591)	Participants without OIC* (n = 409)
Age			
Median (range)	65 y (29-93 y)	65 y (29-93 y)	67 y (32-93 y)
Gender			
Female	488 (49%)	288 (48.5%)	200 (49%)
Male	512 (51%)	303 (51.5%)	209 (51%)
Cancer primary location			
Breast	68 (6.5%)	36 (6%)	32 (8%)
Endocrine	11 (1%)	6 (1%)	5 (1%)
Gastrointestinal	610 (61%)	368 (62.5%)	242 (59%)
Gynaecological	34 (3.5%)	22 (3.5%)	12 (3%)
Haematological	31 (3%)	13 (2%)	18 (4.5%)
Head and neck	42 (4%)	24 (4%)	18 (4.5%)
Lung	79 (8%)	49 (8.5%)	30 (7.5%)
Neurological	3 (0.5%)	3 (0.5%)	0 (0%)
Skin	9 (1%)	4 (0.5%)	5 (1%)
Unknown primary	9 (1%)	5 (1%)	4 (1%)
Urological	94 (9.5%)	55 (9.5%)	39 (9.5%)
Other	10 (1%)	6 (1%)	4 (1%)
ECOG performance status			
0	63 (6%)	42 (7%)	21 (5%)
1	322 (32%)	196 (33%)	126 (30.5%)
2	313 (31.5%)	181 (30.5%)	132 (32.5%)
3	264 (26.5%)	152 (26%)	112 (27.5%)
4	38 (4%)	20 (3.5%)	18 (4.5%)
Opioid analgesic (regular prescription)†			
Alfentanil	4	3	1
Buprenorphine	82	38	44
Codeine	142	95	47
Dihydrocodeine	7	5	2
Fentanyl	90	52	38
Methadone	2	0	2
Morphine	515	319	196
Oxycodone	186	97	89
Tapentadol	4	2	2
Tramadol	30	16	14
Missing data	1	n/a	n/a
Laxative and related products (regular prescription)‡			
None	383	175	207
Bulk-forming laxatives	2	0	2
Ispaghula husk	1	0	1
Sterculia	1	0	1
Osmotic laxatives	377	238	139
Lactulose	35	24	11
Macrogol	342	214	128
Softening laxatives	210	151	59
Docusate sodium	210	151	59
Stimulant laxatives	262	180	82
Bisacodyl	24	19	5
Codanthramer	1	1	0
Senna	232	157	75
Sodium picosulfate	5	3	2
Suppositories/enemas	5	4	1
Bisacodyl suppository	1	1	0
Glycerol suppository	20	1	1
Sodium acid phosphate/sodium phosphate enema	1	1	0
Sodium alkylsulphoacetate/sodium citrate enema	1	1	0
Peripherally acting mu-opioid receptor antagonists	36	27	9
Methylnaltrexone	2	2	0
Naloxegol	33	25	8
Naloxone	1	0	1
Prucalopride	1	0	1
Missing data	1	n/a	n/a

* Clinician assessment of OIC.

† Fifty-eight patients using 2 opioid analgesics; 2 patients using 3 opioid analgesics.

‡ Two hundred three patients using 2 products; 34 patients using 3 products; 2 patients using 4 products.

ECOG, Eastern Cooperative Oncology Group; OIC, opioid-induced constipation.

dose (MEDD) was 40 mg (range 1.6-1120 mg). Six hundred sixteen patients were receiving regular laxatives or related products (**Table 2**), and 239 (24%) were taking more than 1 laxative or related product.

Clinical assessment resulted in a diagnosis of constipation in 614 (61.5%) patients: 591 (59.0%) patients were assessed as having OIC and 23 (2.5%) patients as having another cause of constipation. However, 399 (67.5%) patients assessed as having OIC had other risk factors for constipation. Of note, 189 (19.0%) patients who were assessed as not having constipation were taking regular laxatives or related products to prevent/manage constipation.

By contrast, only 386 (38.5%) patients answered "yes" to the simple question: "Are you constipated?," with another 82 (8.0%) patients unsure about the answer to the question (with missing data for 2 patients). The clinicians deemed that the majority (94.5%) of the patients who answered "yes" were indeed constipated, but also that 250 (25.0%) patients who answered "no"/"unsure" were equally constipated (ie, 188 patients who answered "no" and 62 patients who answered "unsure").

Moreover, only 306 (30.5%) patients answered "yes" to the question relating to the palliative care "consensus" definition of constipation, with another 48 (5.0%) patients unsure about the answer to the question (with missing data for 8 patients). The clinicians deemed that the majority (89%) of the patients who answered "yes" were indeed constipated, but also that another 341 (34.0%) patients who answered "no"/"unsure" were equally constipated (ie, 306 patients who answered "no" and 35 patients who answered "unsure").

Data on the Rome IV diagnostic criteria (and the relationship to the clinical assessment) are shown in **Table 3** (and **Fig. 2**). In comparison with the gold standard of a thorough clinical assessment, the Rome IV diagnostic criteria for OIC had a sensitivity of 85.3% (95% CI: 82.2-88.0), a specificity of 77.0% (95% CI: 72.6-81.0), a positive predictive value of 84.3% (95% CI: 81.1-87.1), a negative predictive value of 78.4% (95% CI: 74.0-

Table 3

Comparison of Rome IV diagnostic criteria for OIC and clinician assessment of OIC.

Rome IV diagnostic criteria for OIC	Participants with OIC (clinician assessment), n = 591	Participants with no constipation or non-OIC (clinician assessment), n = 409	Sensitivity/specificity of Rome IV diagnostic criteria (vs clinician assessment)
Rome IV positive*	Yes—504 No—87	Yes—94 No—315	Sensitivity: 85.3% (95% CI: 82.2-88.0) Specificity: 77.0% (95% CI: 72.6-81.0) PPV: 84.3% (95% CI: 81.1-87.1) NPV: 78.4% (95% CI: 74.0-82.3) Accuracy: 81.9% (95% CI: 79.4-84.2)
Had to strain during more than one-fourth (25%) of defecations	Yes—411 (69.5%) No—178 (30.0%) Missing data—2 (0.5%)	Yes—79 (19.5%) No—330 (80.5%)	Sensitivity: 69.8% (95% CI: 65.9-73.5) Specificity: 80.7% (95% CI: 76.5-84.4) PPV: 83.9% (95% CI: 80.3-87.0) NPV: 65.0% (95% CI: 60.6-69.1) Accuracy: 74.2% (95% CI: 71.3-76.9)
Had lumpy or hard stools (BSFS type 1-2) with more than one-fourth (25%) of defecations	Yes—369 (62.5%) No—222 (37.5%)	Yes—60 (14.5%) No—349 (85.5%)	Sensitivity: 62.4% (95% CI: 58.4-66.4) Specificity: 85.3% (95% CI: 81.5-88.6) PPV: 86.0% (95% CI: 82.4-89.2) NPV: 61.1% (95% CI: 57.0-65.1) Accuracy: 71.8% (95% CI: 68.9-74.6)
Had the sensation of incomplete evacuation with more than one-fourth (25%) defecations	Yes—446 (75.5%) No—144 (24.5%) Missing data—1 (0.0%)	Yes—104 (25.5%) No—305 (74.5%)	Sensitivity: 75.6% (95% CI: 71.9-79.0) Specificity: 74.6% (95% CI: 70.1-78.7) PPV: 80.9% (95% CI: 77.4-84.1) NPV: 68.1% (95% CI: 63.5-72.4) Accuracy: 75.2% (95% CI: 72.4-77.8)
Had the sensation of anorectal obstruction/blockage with more than one-fourth (25%) defecations	Yes—309 (52.5%) No—277 (46.5%) Missing data—5 (1.0%)	Yes—48 (11.5%) No—359 (88.0%) Missing data—2 (0.5%)	Sensitivity: 52.7% (95% CI: 48.6-56.8) Specificity: 88.2% (95% CI: 84.7-91.2) PPV: 86.5% (95% CI: 82.4-89.9) NPV: 56.4% (95% CI: 52.5-60.3) Accuracy: 67.3% (95% CI: 64.3-70.2)
Had to use manual maneuvers to facilitate more than one-fourth (25%) defecations	Yes—165 (28.0%) No—423 (71.5%) Missing data—3 (0.5%)	Yes—22 (5.5%) No—387 (94.5%)	Sensitivity: 28.1% (95% CI: 24.5-31.9) Specificity: 95.1% (95% CI: 92.5-97.0) PPV: 88.2% (95% CI: 82.7-92.5) NPV: 47.8% (95% CI: 44.3-51.3) Accuracy: 55.4% (95% CI: 52.2-58.5)
Had fewer than 3 spontaneous bowel movements per wk	Yes—334 (56.5%) No—257 (43.5%)	Yes—71 (17.5%) No—338 (82.5%)	Sensitivity: 56.5% (95% CI: 52.4-60.6) Specificity: 82.6% (95% CI: 78.6-86.2) PPV: 82.5% (95% CI: 78.4-86.0) NPV: 56.8% (95% CI: 52.7-60.8) Accuracy: 67.2% (95% CI: 64.2-70.1)

* ≥2 positive responses to diagnostic criteria.

95% CI, 95% confidence interval; BSFS, Bristol Stool Form Scale; NPV, negative predictive value; OIC, opioid-induced constipation; PPV, positive predictive value.

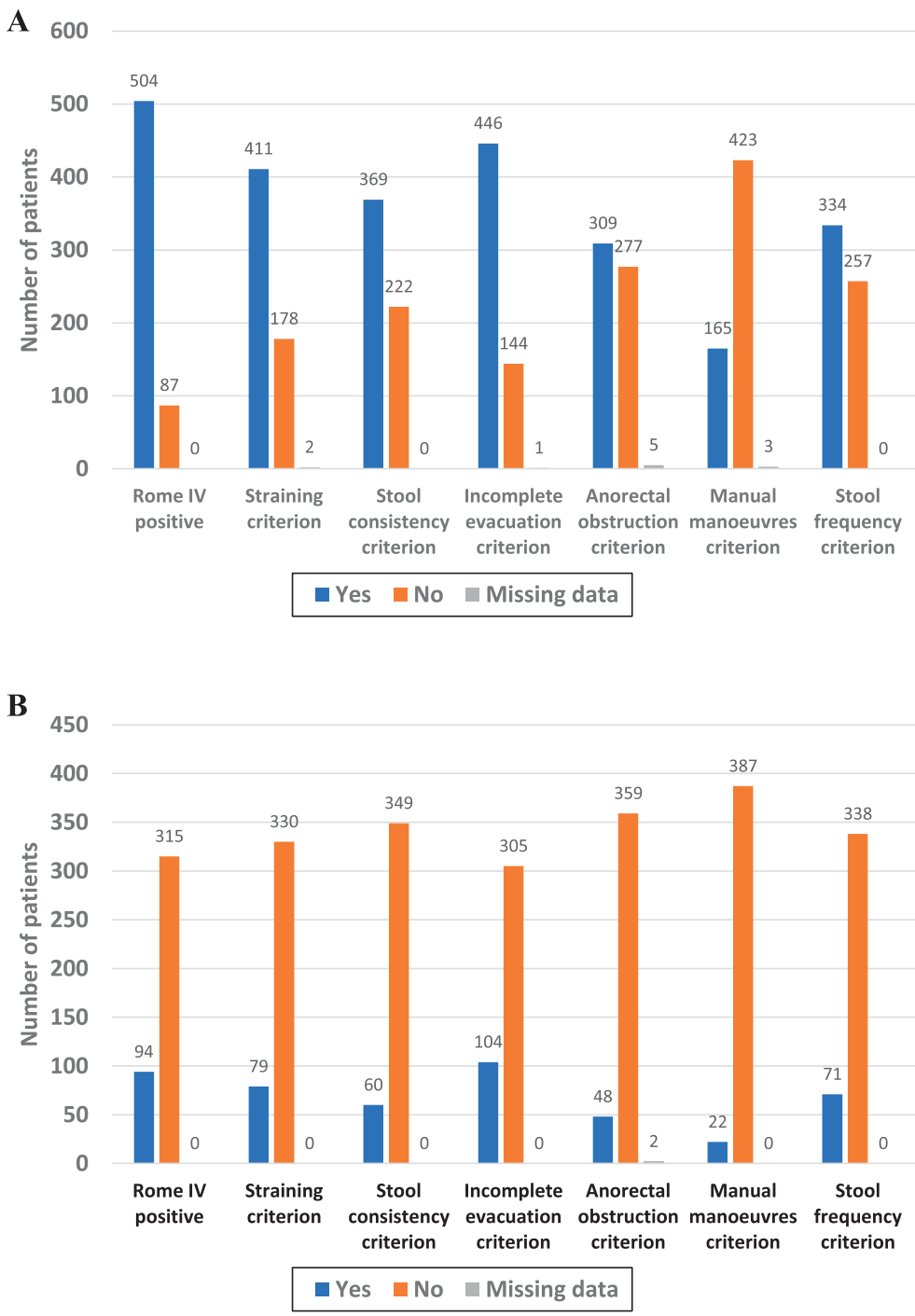

Figure 2. (A) Data on Rome IV diagnostic criteria for patients deemed to have OIC on clinical assessment (n = 591). (B) Data on Rome IV diagnostic criteria for patients deemed not to have OIC on clinical assessment (n = 409). OIC, opioid-induced constipation.

82.3), and an accuracy of 81.9% (95% CI: 79.4-84.2). Of note, 446 (75.5%) patients with clinician-determined OIC met the criterion of sensation of incomplete evacuation (accuracy of 75.2%; 95% CI: 72.4-77.8), whereas only 334 (56.5%) patients with clinician-determined OIC met the criterion of fewer than 3 spontaneous bowel movements per week (accuracy of 67.2%; 95% CI: 64.2-70.1).

Clinician-determined OIC was not associated with the participant's age (Mann–Whitney *U* test: $P = 0.077$), gender (χ^2 test: $P = 0.958$), cancer diagnosis (χ^2 test: $P = 0.617$), ECOG performance status (χ^2 test: $P = 0.553$), or opioid dosage (ie, MEDD) (Mann–Whitney *U* test: $P = 0.977$). Thus, the median MEDD for the patients with OIC was 48 (range 24-160), whereas the median MEDD for the patients without OIC was also 48 (range

Table 4

Memorial Symptom Assessment Scale—Short Form and Patient Assessment of Constipation Quality of Life summary data.

	Participants with OIC (clinician assessment), n = 591	Participants with no constipation or non-OIC (clinician assessment), n = 409	Statistical analysis
MSAS-SF data			
No. of symptoms	17 (IQR: 13-21)	14 (IQR: 9-18)	Mann–Whitney *U* test, $P < 0.001$
Physical subscale score	Mean score 2.63 (SD: 0.61)	Mean score 2.34 (SD: 0.63)	Independent samples *t* test, $P < 0.001$
Psychological subscale score	Mean score 2.40 (SD: 0.69)	Mean score 2.21 (SD: 0.60)	Independent samples *t* test, $P < 0.001$
Global Distress Index score	Mean score 2.63 (SD: 0.60)	Mean score 2.31 (SD: 0.62)	Independent samples *t* test, $P < 0.001$
Total MSAS score	Mean score 2.49 (SD: 0.55)	Mean score 2.25 (SD: 0.52)	Independent samples *t* test, $P < 0.001$
PAC-QOL data			
Physical subscale score	Mean score 1.74 (SD = 1.03)	Mean score 0.74 (SD = 0.88)	Independent samples *t* test, $P < 0.001$
Psychosocial subscale score	Mean score 0.83 (SD = 0.70)	Mean score 0.4 (SD = 0.52)	Independent samples *t* test, $P < 0.001$
Worries/concerns subscale score	Mean score 1.59 (SD = 0.90)	Mean score 0.87 (SD = 0.74)	Independent samples *t* test, $P < 0.001$
Satisfaction subscale score	Mean score 1.50 (SD = 0.62)	Mean score 2.10 (SD = 0.84)	Independent samples *t* test, $P < 0.001$
Overall score	Mean score 1.50 (SD = 0.69)	Mean score 0.99 (SD = 0.55)	Independent samples *t* test, $P < 0.001$

IQR, interquartile range; MSAS-SF, Memorial Symptom Assessment Scale—Short Form; OIC, opioid-induced constipation; PAC-QOL, Patient Assessment of Constipation Quality of Life.

20-200). However, clinician-determined OIC was associated with the specific opioid analgesic used (χ^2 test: $P = 0.007$), with patients prescribed (transdermal) buprenorphine and tramadol having less constipation than patients prescribed (transdermal) fentanyl, morphine, and oxycodone.

Data from the MSAS-SF are shown in **Tables 4 and 5**. Patients with clinician-determined OIC had more symptoms and greater distress due to these symptoms (greater frequency for psychological symptoms). The physical symptoms more commonly reported included a number of gastrointestinal symptoms (eg, feeling bloated, lack of appetite, nausea, and vomiting) and equally a variety of nongastrointestinal symptoms (eg, lack of energy, difficulty concentrating, problems with urination, and problems with sexual interest or activity). Data from the PAC-QOL questionnaire are also shown in **Table 4**. Unsurprisingly, patients with clinician-determined OIC generally had worse scores (and so worse constipation-related quality of life).

The median BFI score for patients with clinician-determined OIC was 60 (interquartile range: 43%-80%; 90% of patients had BFI > 30), whereas the median BFI score for those patients with clinician-determined non-OIC or no constipation was 13 (interquartile range: 3%-30%; 25.5% of patients had BFI > 30).

4. Discussion

This study confirms that (clinician-determined) OIC is a common problem in patients with cancer pain. Thus, 59.1% of patients were assessed as having OIC on clinical assessment, whereas a further 18.9% of patients were assessed as not being constipated but were taking regular laxatives or related products to manage constipation. This study also confirms that OIC is associated with significant morbidity in patients with cancer. Thus, patients with cancer pain (and those with noncancer pain) on opioid analgesics should be regularly and thoroughly assessed for constipation. Similarly, patients with cancer pain on opioid analgesics should be routinely prescribed "prophylactic" laxatives (or related products to manage constipation).[5,33]

This study appears to be the first to examine the utility of the Rome IV diagnostic criteria for OIC, and additional studies are needed to confirm/refute our findings (and to validate the complete diagnostic criteria and the individual questions). The Rome IV diagnostic criteria for OIC are analogous to the Rome IV diagnostic criteria for functional constipation,[11] which have been found to have a low sensitivity (33.9%) but have a high specificity (94.5%).[29] Our data suggest that the Rome IV diagnostic criteria for OIC have a relatively higher sensitivity (85.3%) but have a relatively lower specificity (77.0%). Indeed, the Rome IV diagnostic criteria for OIC failed to identify a significant number of patients with OIC (as determined by a thorough clinical assessment by an experienced palliative care clinician). However, the simple question ("Are you constipated") failed to identify an even larger number of patients with OIC. Thus, the gold standard for diagnosing OIC remains a thorough clinical assessment, ie, focussed history, focussed examination, and (if appropriate) targeted investigations.[9]

Opioid-induced constipation was not associated with any demographic features (age or gender), disease-related factors (cancer diagnosis or ECOG performance status), or opioid dosage. Laugsand et al.[21] reported similar findings, with the exception that they found an association between the intensity of constipation and Karnofsky Performance Status. Bennett et al.[2] also reported some similar findings, but they found no association between constipation and physical functioning. The data on opioid dosage are consistent across studies[2,12,21] and support the guidance that OIC should not be treated by reduction of opioid dosage.[18] Opioid-induced constipation was associated with opioid type, with patients prescribed (transdermal) buprenorphine and tramadol having less constipation than patients prescribed (transdermal) fentanyl, morphine, and oxycodone. Certain systematic reviews suggest that transdermal buprenorphine may cause less constipation than morphine (but not transdermal fentanyl).[35,39]

Unsurprisingly, "constipation-related" symptoms were common, although some symptoms were more prevalent than others. For example, 75.5% of patients with OIC complained of a sensation of incomplete evacuation, whereas only 52.0% of patients with OIC complained of a sensation of anorectal obstruction. Importantly, only 56.5% of patients with OIC reported fewer than 3 spontaneous bowel movements per week. Of note, the frequency of spontaneous bowel movements is often used as an indicator of constipation (or lack of constipation) in clinical practice[18] and also within clinical research.[15] Moreover, the figure of 3 spontaneous bowel movements is often used as a cutoff for diagnosing constipation.[15,18] These results confirm the assertion that change in frequency is much more important than

Table 5

Memorial Symptom Assessment Scale—Short Form data.

MSAS-SF symptom	Participants with relevant symptom, n = 988*	Participants with OIC with relevant symptom, n = 585	Participants with no constipation/non-OIC constipation with relevant symptom, n = 403	Statistical analysis (χ^2 tests with continuity correction)
Lack of energy	883 (89.5%)	541 (92.5%)	342 (85.0%)	**$P < 0.001$**
Pain	863 (87.5%)	525 (89.5%)	338 (84.0%)	**$P = 0.009$**
Feeling drowsy	788 (80.0%)	488 (83.5%)	300 (74.5%)	**$P = 0.001$**
Dry mouth	738 (74.5%)	454 (77.5%)	284 (70.5%)	$P = 0.014$
Worrying	697 (70.5%)	435 (74.5%)	262 (65.0%)	**$P = 0.002$**
Feeling sad	685 (69.5%)	423 (72.5%)	262 (65.0%)	$P = 0.018$
Difficulty concentrating	654 (66.0%)	416 (71.0%)	238 (59.0%)	**$P < 0.001$**
Constipation	653 (66.0%)	516 (88.0%)	137 (34.0%)	**$P < 0.001$**
Lack of appetite	630 (64.0%)	419 (71.5%)	211 (52.5%)	**$P < 0.001$**
Change in the way food tastes	582 (59.0%)	365 (62.5%)	217 (54.0%)	**$P = 0.009$**
Feeling irritable	569 (57.5%)	362 (62.0%)	207 (51.5%)	**$P = 0.001$**
Difficulty sleeping	530 (53.5%)	346 (59.0%)	184 (45.5%)	**$P < 0.001$**
Feeling bloated	518 (52.5%)	361 (61.5%)	157 (39.0%)	**$P < 0.001$**
Shortness of breath	501 (50.5%)	309 (53.0%)	192 (47.5%)	$P = 0.125$
Nausea	489 (49.5%)	322 (55.0%)	167 (41.5%)	**$P < 0.001$**
Feeling nervous	471 (47.5%)	294 (50.5%)	177 (44.0%)	$P = 0.055$
Weight loss	468 (47.5%)	301 (51.5%)	167 (41.5%)	**$P = 0.002$**
Numbness/tingling in hands and feet	449 (45.5%)	281 (48.0%)	168 (41.5%)	$P = 0.059$
Sweats	438 (44.5%)	303 (52.0%)	135 (33.5%)	**$P < 0.001$**
"I don't look like myself"	406 (41.0%)	266 (45.5%)	140 (34.5%)	**$P = 0.001$**
Changes in skin	397 (40.0%)	248 (42.5%)	149 (37.0%)	$P = 0.101$
Dizziness	371 (37.5%)	227 (39.0%)	144 (35.5%)	$P = 0.361$
Cough	364 (37.0%)	226 (38.5%)	138 (34.0%)	$P = 0.181$
Swelling of arms or legs	313 (31.5%)	183 (31.5%)	130 (32.5%)	$P = 0.799$
Diarrhoea	309 (31.5%)	190 (32.5%)	119 (29.5%)	$P = 0.361$
Difficulty swallowing	308 (31.0%)	208 (35.5%)	100 (25.0%)	**$P < 0.001$**
Itching	303 (30.5%)	187 (32.0%)	116 (29.0%)	$P = 0.319$
Problems with urination	295 (30.0%)	205 (35.0%)	90 (22.5%)	**$P < 0.001$**
Mouth sores	267 (27.0%)	170 (29.0%)	97 (24.0%)	$P = 0.096$
Vomiting	263 (26.5%)	180 (31.0%)	83 (20.5%)	**$P < 0.001$**
Hair loss	208 (21.0%)	134 (23.0%)	74 (18.5%)	$P = 0.101$
Problems with sexual interest or activity	202 (20.5%)	142 (24.5%)	60 (15.0%)	**$P < 0.001$**

* Incomplete data in 12 participants. P values in bold are significant.

MSAS-SF, Memorial Symptom Assessment Scale—Short Form; OIC, opioid-induced constipation.

absolute frequency in diagnosing OIC (and indeed other types of constipation).[4]

Patients with OIC had more physical symptoms and greater distress related to these physical symptoms (as measured by the MSAS-SF). In addition to gastrointestinal symptoms, OIC was associated with a number of other systemic symptoms. For example, constipation was associated with a number of central effects, including "feeling drowsy" and "difficulty concentrating." The latter was not unexpected because constipation is a well-recognised precipitant of delirium.[27,30] Opioid-induced constipation was also associated with a number of psychological symptoms, particularly "worrying", and patients also complained of feeling irritable and having problems with sleep and sexual interest/function. Indeed, OIC was associated with impaired quality of life (evidenced by the subscales of the PAC-QOL questionnaire and the Global Distress Index of the MSAS-SF).

Some of the reported symptoms represent complications of the constipation, whereas others may represent concomitant opioid-related adverse effects (to which this group of patients may have increased susceptibility). For example, constipation can result in nausea and vomiting, but these symptoms are common adverse effects of opioid analgesics (mediated through central and/or peripheral mechanisms).[7,37] Researchers have

previously reported that a single-nucleotide polymorphism in the cholinergic receptor muscarinic 3 was associated with the intensity of constipation and also with the intensity of nausea and vomiting in patients with cancer receiving opioid analgesics.[19,21]

The study data suggest that the management of OIC was suboptimal in this cohort of patients. Thus, 30% of patients assessed as having OIC on clinical assessment were not receiving regular laxatives or related products to manage constipation (despite international recommendations).[5,33] Furthermore, 63.5% of patients had a BFI of >30, which indicates inadequate treatment.[1,31] Many (20.5%) patients were receiving multiple formulations, although surprisingly few (3.5%) patients were receiving a peripherally acting mu-opioid receptor antagonist. Peripherally acting mu-opioid receptor antagonists have marketing authorisations for opioid-induced constipation, and studies suggest that they are somewhat effective and well tolerated.[24] Previous studies have also reported suboptimal management of constipation in this cohort of patients,[20] which is in part related to nonadherence to clinical guidelines[25] and also to nonadoption of innovative treatments.[32]

A limitation of the study is that it was conducted in a single country because it is known that the term "constipation" means different things to different people (and there may be relevant ethnic/cultural differences).[22] Another limitation of the study is that the clinical assessment was not formalised (and so not standardised). Nevertheless, constipation/OIC is a common clinical problem in palliative care and so something that all palliative care clinicians would have experience in undertaking.

Despite the limitations, the results of the study are probably generalisable to day-to-day clinical practice because the study was multicentre (with centres distributed throughout England), the sample size was large (1000 participants), and the sample population were "real-world" patients (heterogenous participants; maximal inclusion criteria and minimal exclusion criteria).

In summary, the study confirms that OIC is common among patients with cancer pain and is associated with a spectrum of physical symptoms, a range of psychological symptoms, and an overall deterioration in quality of life. Importantly, the study found that a simple question ("Are you constipated?") is inadequate, and that the Rome IV diagnostic criteria for OIC have an accuracy of ~82%. Thus, a thorough clinical assessment by an experienced clinician remains the gold standard for diagnosing/excluding OIC (and other types of constipation).

Conflict of interest statement

A. Davies and C. Leach have both received personal fees for consultancy/educational activities from Kyowa Kirin International. The remaining authors have no conflicts of interest to declare.

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