Opioid-induced constipation: a stepwise treatment algorithm feasibility study

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Received 20 October 2020
Accepted 8 July 2021

To cite: Davies AN, Leach C, Butler C, *et al*. *BMJ Supportive & Palliative Care* Epub ahead of print: [please include Day Month Year]. doi:10.1136/bmjspcare-2020-002754

ABSTRACT

Background Opioid-induced constipation (OIC) is frequently undertreated in patients with advanced cancer. Our hypothesis is that the use of a stepwise treatment algorithm, supported by regular patient-reported outcome measures, should improve the management of OIC. The aim of this feasibility study was to determine whether a definitive study could be successfully completed.

Methods Patients with OIC (Rome Foundation diagnostic criteria positive), and a Bowel Function Index (BFI) score of ≥30, were recruited to the study. The study involved weekly assessments, and decisions about management were based on the current BFI score (and the tolerability of the current treatment). Management was based on a four-step treatment algorithm, developed from recent international guidelines.

Results One hundred patients entered the study, and 79 patients completed the study. Fifty-seven (72%) participants responded to treatment, with 34 (43%) participants having a 'complete' response (ie, final BFI<30) and 23 (29%) participants having a 'partial' response (ie, change in BFI≥12). In participants with a complete response, 73.5% were prescribed conventional laxatives, 12% were prescribed a peripherally acting mu-opioid receptor antagonist (PAMORA) and 14.5% were prescribed a PAMORA and conventional laxative.

Discussion The feasibility study suggests that a definitive study can be successfully completed. However, we will amend the methodology to try to improve participant recruitment, participant retention and adherence to the treatment algorithm. The feasibility study also suggests that the use of the BFI to monitor OIC, and the use of a treatment algorithm to manage OIC, can result in clinically important improvements in OIC.

Trial registration number NCT04404933

Key messages

What was already known?
- Opioid-induced constipation (OIC) is a major problem, which is often under-recognised and often poorly managed.
- Multiple treatment guidelines exist, but there is no evidence that these improve management.

What are the new findings?
- This feasibility study confirms that a definitive study is doable.
- This feasibility study suggests that the regular assessment, and the use of a stepwise treatment algorithm, improve management of OIC.

What is their significance?
- Clinical: This feasibility study supports the use of regular assessment of OIC in clinical practice (using a validated patient reported outcome measure).
- Research: This feasibility study supports the undertaking of a definitive study, and provides insight into potentially positive changes to the study protocol.

INTRODUCTION

Opioid-induced constipation (OIC) has been defined as 'a change when initiating opioid therapy from baseline bowel habits that is characterised 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'.[1] Constipation is a common adverse effect of opioid analgesics, but the reported prevalence varies widely in published studies (40%–80%).[2] Moreover, OIC is associated with a variety of physical,[3] psychological[4] and social problems,[5] which negatively impacts on the patient's quality of life (and results in a significant health economic burden).[6]

OIC has a unique pathophysiology, which is mainly a peripherally (as opposed to centrally) initiated effect, and primarily a mu-opioid receptor mediated effect.[7] Thus, opioids decrease small bowel motility, decrease electrolyte and water secretion into the small bowel, increase ileocaecal valve tone, decrease large bowel motility, increase electrolyte and water absorption in the large bowel, increase anal sphincter tone and reduce anorectal sensitivity to distension. This unique pathophysiology explains the relative ineffectiveness of conventional laxatives in the prevention/treatment of OIC,[8] and the rationale for the development of the peripherally acting mu-opioid receptors antagonists (PAMORAs).

International guidelines universally recommend that cancer patients commenced on opioid analgesics should be routinely coprescribed conventional laxatives[9 10] or possibly other treatments to manage constipation.[11] Surprisingly, there is little evidence to support this strategy or indeed to guide the choice of treatment.[11] Even more surprisingly, previous studies have reported frequent non-adherence to these clinical guidelines,[12] and equally lack of adoption/utilisation of new treatments (eg, PAMORAs).[13] The impact of these actions is that constipation/OIC is frequently undertreated in patients with advanced cancer.[14]

Our hypothesis is that the use of a stepwise treatment algorithm, which is supported by regular patient-reported outcome measures (PROMS), should improve the management of OIC (and so reduce the clinical impact of OIC). The aim of this non-randomised, feasibility study was to determine whether a definitive study (comparing a treatment algorithm and standard care) could be successfully completed: the criteria for success included recruitment of participants, retention of participants, adherence to study methods, adherence to the treatment algorithm and the effectiveness of the treatment algorithm.

METHODS

The study ('StOIC 2 study') was a prospective, non-randomised (single-arm), interventional study conducted at 4 hospitals and 12 hospices in the UK from August 2017 to August 2019. The study was an investigator-initiated study, with unrestricted research funding received from Kyowa Kirin International.

Participants recruited to this study were identified from suitable participants recruited to an observational study of diagnostic criteria and clinical features of OIC involving 1000 patients with cancer.[3] The inclusion criteria for the 'feeder' study were: (1) age ≥18 year; (2) diagnosis of cancer; (3) diagnosis of cancer pain and (4) receipt of regular opioids for at least the last 1 week (ie, opioid for mild-to-moderate pain/'weak' opioid or opioid for moderate-to-severe pain/'strong' opioid). The additional inclusion criteria for this study were: (1) diagnosis of OIC as defined by the Rome IV criteria for OIC (figure 1)[15] and (2) diagnosis of inadequately treated OIC as defined by a Bowel Function Index (BFI) score ≥30 (figure 2).[16 17] The exclusion criteria for the feeder study were: (1) inability to give informed consent and (2) inability to complete questionnaire. The additional exclusion criterion for this study was an estimated prognosis of <1 month (clinical assessment). Participants were recruited from inpatients and outpatients at the study sites (see the Acknowledgements section). All patients (in the feeder study) that met the criteria for the study were eligible for entry into the study (ie, convenience sampling with consecutive recruitment).

Informed consent was obtained from participants prior to entry into the study, which involved four face-to-face assessments and one telephone assessment. The first assessment for this study corresponded to the one and only assessment for the feeder study: it involved collection of demographic information, current opioid regimen, current laxative/related product regimen, assessment of Eastern Co-operative Oncology Group

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 (e.g. digital evacuation, support of 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

Figure 1 Rome IV diagnostic criteria for opioid-induced constipation.[15]

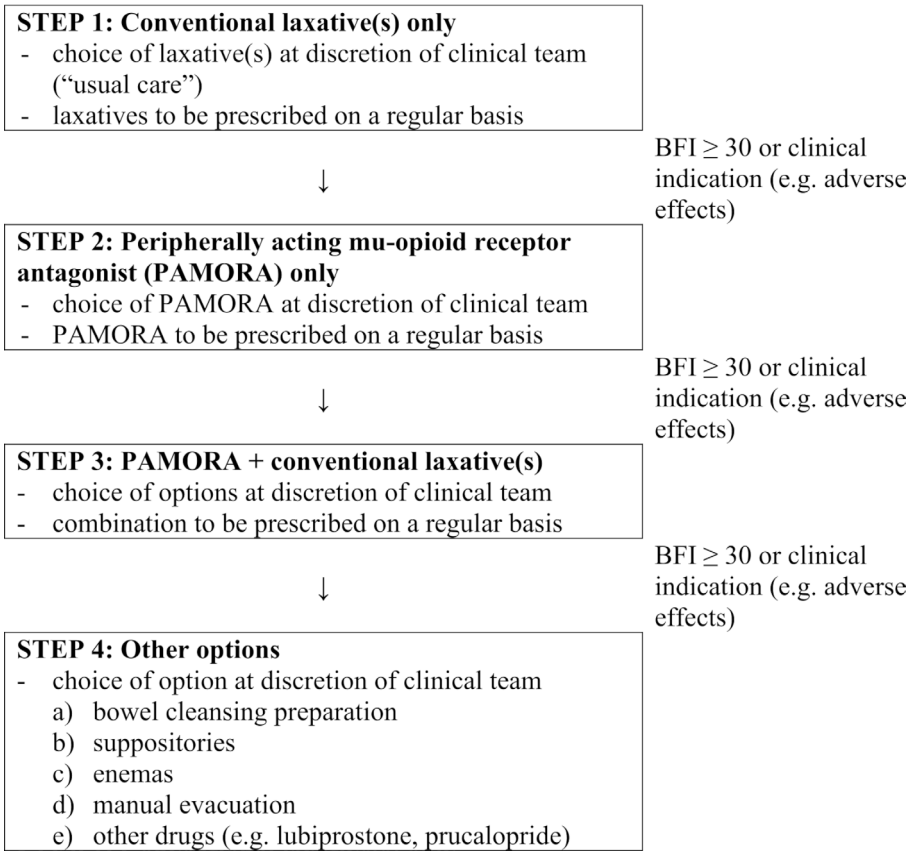

Figure 2 Opioid-induced constipation treatment algorithm. BFI, Bowel Function Index.

(ECOG) performance status[18] and completion of Rome IV diagnostic criteria for OIC,[15] the BFI,[16] the Patient Assessment of Constipation Quality of Life questionnaire (PAC-QOL)[19] and the Memorial Symptom Assessment Scale-short form (MSAS-SF).[20]

The second assessment (day 7; face to face), the third assessment (day 14; face to face) and the fourth assessment (day 21; telephone call), involved completion of the BFI, and if necessary amendment of the treatment regimen (figure 2). The fifth/final assessment (day 28; face to face) involved collection of current laxative regimen, and completion of the BFI, the PACQOL and the MSAS-SF. Participants were also required to maintain a bowel diary, which recorded the occurrence of evacuations, and the consistency of the stool (based on the Bristol Stool Form Scale).[21] The bowel diary was used to help monitor the effectiveness and tolerability of the laxative regimen.

The Rome IV diagnostic criteria for OIC were not formally validated (but generally accepted within gastroenterology),[7 11] and consists of six statements relating to constipation-related symptoms, and one 'exclusion' statement relating to the coexistence of diarrhoea in the absence of laxatives (figure 1).[15] Participants were required to answer 'yes' or 'no' to each statement, and those that answer positively to ≥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. There were no other validated diagnostic criteria for OIC at the time of the study.

The BFI is a validated PROM, and consists of three questions (and was used to assess the adequacy of treatment).[16] The BFI provides an overall score (range 1–100), and a score of ≥30 indicates inadequate treatment[16 17]: an improvement of ≥12 indicates a clinically meaningful improvement.[16] The BFI is easy to use and suitable for use in everyday clinical practice. The PAC-QOL is a validated PROM, and consists of 28 questions (and was used to assess constipation-related quality of life).[19] 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 MSAS-SF is a validated, 32 items PROM for assessing physical and psychological symptoms in patients with cancer.[20] Participants are asked about the presence of these symptoms, and for the physical ones the distress caused by the symptom ('not at all'; 'a little bit'; 'somewhat'; 'quite a bit'; 'very much') and for the psychological ones the frequency of the

During the last 7 days, how would you rate your ease of defecation on a scale from 0 to 100, where 0 = easy or no difficulty and 100 = severe difficulty?

During the last 7 days, how would you rate your feeling of incomplete bowel evacuation on a scale from 0 to 100, where 0 = no feeling of incomplete evacuation and 100 = a very strong feeling of incomplete evacuation?

During the last 7 days, how would you rate your constipation on a scale from 0 to 100, where 0 = not at all and 100 = very strong?

Figure 3 Bowel Function Index questions.[16]

symptom ('rarely'; 'occasionally'; 'frequently'; 'almost constantly'). A series of subscale scores can be generated by calculating the mean of the scores for the relevant symptoms, that is, physical subscale score, psychological subscale score, Global Distress Index Score and total MSAS score: the higher the subscale score, the higher the burden of the relevant symptoms.

At each assessment, the participant was reviewed by an experienced clinician (ie, physician, clinical nurse specialist) to determine whether there should be an amendment of the treatment regimen (figure 3): the decision to amend treatment was primarily based on the BFI score (ie, the effectiveness of the current treatment), but was influenced by the tolerability of the current treatment. The treatment algorithm consisted of four steps, and at each step participants were encouraged to maintain fluid intake and to exercise/maintain physical activity: step 1 involved conventional laxatives; step 2 involved PAMORAs; step 3 involved PAMORA and conventional laxatives and step 4 involved 'other options' (eg, rectal interventions, other oral medications). The treatment algorithm was based on a review of the literature, which was the basis of recent international guidelines.[11]

The original sample size was pragmatic (150 participants), which represented 15% of participants in the feeder study,[3] although we were unsure of the prevalence of OIC in the feeder study (as defined by the Rome IV criteria for OIC). It should be noted that the sample size of the feeder study was based on the prevalence of OIC suggested by an Expert Working Group of European Association of Palliative Care.[22] As participants to this study were only recruited from those involved in the feeder study, recruitment to this study was closed when recruitment to the feeder study was completed.

In terms of criteria for success, a figure of 67% (two-thirds) was employed for relevant criterion (ie, recruitment of participants, retention of participants, adherence to study methods, adherence to treatment algorithm, effectiveness of treatment algorithm). Participants were characterised as either having a complete response ('Group A': BFI score <30), a partial response ('Group B': BFI score ≥30, but an improvement in BFI of ≥12 from baseline assessment) or a non-response ('Group C': BFI score ≥30 and no improvement in BFI of ≥12 from baseline assessment).[16 17] For the purposes of the analysis, participants in Group A and Group B were designated as 'responders', and participants in Group C were designated as 'non-responders'.

Descriptive statistics were primarily used to explain the data derived from the various questions/assessment tools (numbers, percentages; mean, SD, median, range or IQR). Standard statistical methods were used in the analysis: χ^2 tests were used to assess the association between response and categorical outcomes; independent t-tests or Mann-Whitney U tests were used to assess the association between response and continuous outcomes. An alpha 5% two-sided cut-off was used to determine a significant association between the two groups of participants (ie, responders and non-responders).

RESULTS

The study flow chart is shown in figure 4, and the participants' characteristics are shown in table 1. One hundred and one patients consented to the study (ie, criterion for success achieved—67%), which represents 10% participants in the feeder study, and 17% participants with OIC in the feeder study (as defined by the Rome IV diagnostic criteria for OIC). Seventy-nine (79.0%) participants completed the study (ie, criterion for success achieved), with the main reason for withdrawal being deterioration in the underlying condition (12 participants), with another participant dying from the underlying condition during the study period.

The median BFI score at baseline was 69 (range: 30–100; IQR: 53–83). Of the participants that

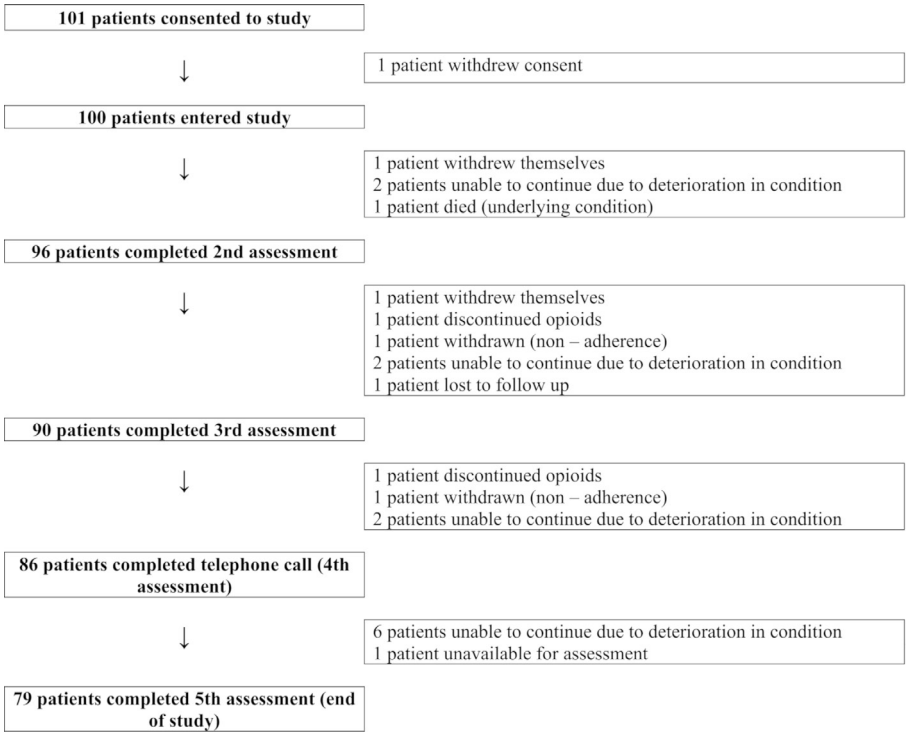

Figure 4 Study flow chart.

completed the whole study (n=79), 72% were 'responders' in that their BFI score was either <30 (43.0% participants: 'Group A'), or their BFI score had improved by ≥12 (29% participants: 'Group B'), at the end of the study (ie, criterion for success achieved). Of note, another 11 subjects had a BFI <30 on their penultimate assessment, and a further 9 subjects had a BFI <30 on an earlier assessment. The responders had a higher BFI at baseline than the non-responders (Mann-Whitney U test: p=0.040), but there was no difference between the groups in terms of age (Mann-Whitney U test: p=0.102), gender (χ^2 test: p=0.921) or ECOG performance status (χ^2 test: p=0.220).

Table 1 shows the laxative and related products prescribed at baseline, while table 2 shows the summary data for the end of study, and for the last visit (when≥2 assessments completed). In Group A, 25 (73.5%) were prescribed conventional laxatives, 4 (12%) were prescribed a PAMORA and 5 (14.5%) were prescribed a PAMORA and conventional laxatives, at the end of the study. Similarly, in Group B, eight (35%) were prescribed conventional laxatives, seven (30%) were prescribed a PAMORA and eight (35%) were prescribed a PAMORA and conventional laxatives, at the end of the study. No participants were prescribed a regular 'step 4' intervention.

Eight (35.0%) participants in Group B were not prescribed a PAMORA during the study, and in at least six cases this represented definite non-adherence with the treatment algorithm (based on sequential BFI scores). Similarly, nine (41.0%) participants in Group C were not prescribed a PAMORA during the study, and again in at least six cases this represented definite non-adherence with the treatment algorithm (ie, criterion for success achieved—79% overall). The rationale for the deviation was generally not recorded, although some participants were noted to be reluctant to change treatment.

Table 3 shows the summary data for MSAS-SF and PAC-QOL (change from baseline to final assessment). No statistically significant difference was found in the number of symptoms or subscale scores on the MSAS-SF between the responders and the non-responders. However, unsurprisingly, there were statistically significant differences in certain subscale scores on the PAC-QOL between the responders and non-responders (ie, physical subscale, worries/concerns subscale, satisfaction subscale). No serious adverse effects were reported, and no patients withdrew/were withdrawn due to adverse effects.

DISCUSSION

Multiple guidelines exist on the management of OIC, although we are not aware of any previous research studies that have tested the effectiveness of such guidelines in routine clinical practice (within this population). This study was a feasibility study, and the results suggest that a definitive study could be successfully undertaken Moreover, the results of the feeder study suggest that a definitive study should be undertaken, since the management of OIC appears to be suboptimal in a significant number of patients within this population.[3]

Table 1 Characteristics of study participants

Characteristic	No of participants (n = 100)
Age	
Median (range)	63 years (35–86 years)
Gender	
Female	47
Male	53
Cancer primary location	
Breast	12
Endocrine	4
Gastrointestinal	24
Gynaecological	5
Haematological	7
Head and neck	8
Lung	16
Neurological	1
Sarcoma	3
Skin	1
Urological	17
Other	2
ECOG performance status	
0	3
1	41
2	33
3	22
4	1
Opioid analgesic at baseline (regular prescription)*	
Alfentanil	1
Buprenorphine	8
Codeine	19
Fentanyl	15
Morphine	50
Oxycodone	15
Tramadol	2
Laxative and related products at baseline (regular prescription)†	
None	28
Osmotic laxatives	36
Lactulose	4
Macrogol	32
Softening laxatives	30
Docusate sodium	30
Stimulant laxatives	42
Bisacodyl	7
Senna	35
Peripherally acting mu-opioid receptor antagonists	5
Naloxegol	5

*Ten patients using two opioid analgesics.

†Twenty-six patients using two products; eight patients using three products.

ECOG, Eastern Co-operative Oncology Group.

The criteria for success included satisfactory recruitment of study participants. The study recruited 101 participants (from a group of 1000), although the planned sample size was 150 participants. However, recruitment was deemed to be more than adequate. Thus, 10% of the original group, and 17% of the eligible patients within the original group, were recruited.[3] The definitive study will include more research sites (with more potential participants).

The Rome IV diagnostic criteria for OIC were not formally validated (but generally accepted within gastroenterology),[7 11] and there were no other validated diagnostic criteria for OIC, at the time of the study. However, the linked study assessed the sensitivity, specificity and accuracy of the Rome IV diagnostic criteria (vs the 'gold standard' of a thorough clinical assessment by an experienced clinician).[3] Hence, we plan to use the Rome IV diagnostic criteria for OIC in the definitive study. It should be noted that there are still no other validated diagnostic criteria for OIC.

Equally relevant to success is the retention of study participants. Most participants completed the study, with the main reason for withdrawal being a deterioration in the underlying condition. This is a recurring problem within palliative care research,[23] and may be limited by changing the inclusion criterion to an estimated prognosis of >3 months (as opposed to an estimated prognosis of >1 month). Moreover, in the definitive study, we will account for withdrawals in the sample size calculation and allow substitution of withdrawn participants.

Another criterion for success was adherence to the study methods. Completion of the bowel diary was sporadic, and, as these data were not integral to the treatment algorithm, we have decided to exclude the use of the bowel diary in the definitive study. No other problems were identified with the study methods, and so no other changes are planned for the definitive study. A further criterion for success was adherence to the treatment algorithm. It appears that a number of participants were not managed as per the treatment algorithm, and especially were not escalated from step 1 (ie, conventional laxatives) to step 2 (ie, PAMORA). We plan to redraft the instructions to investigators to reiterate that patients reporting a 'high' BFI should be moved up the treatment algorithm at that visit.

Importantly, this study suggests that the use of a treatment algorithm, together with the use of a validated PROM (ie, the BFI), results in significant improvements in OIC. Moreover, the improvements in BFI scores were associated with improvements in OIC-related quality of life (as measured by the PAC-QOL). However, these improvements need to be confirmed in an adequately powered definitive study (ie, a randomised controlled trial with the control arm being 'usual care' for OIC). It should be noted that the interventions employed were standard treatments for OIC, with established efficacy and tolerability in this condition.[11] Indeed, no participants were withdrawn

Table 2 Laxative and related product usage in different response groups

Response group	Final visit (≥2 assessments) (n=96)	End of study (n=79)
Group A (complete response)—BFI <30	41 (43%) ► 29 conventional laxative(s) ► 4 PAMORA ► 8 PAMORA +conventional laxative(s)	34 (43%) ► 25 conventional laxative(s) ► 4 PAMORA ► 5 PAMORA + conventional laxative(s)
Group B (partial response)— BFI≥30 but improvement of ≥12 from baseline	27 (28%) ► 10 conventional laxative(s) ► 8 PAMORA ► 9 PAMORA + conventional laxative(s)	23 (29%) ► 8 conventional laxative(s) ► 7 PAMORA ► 8 PAMORA + conventional laxative(s) ► (8 patients not treated with PAMORA during study)
Group A and B (all responders)	68 (71%) ► 39 conventional laxative(s) ► 12 PAMORA ► 17 PAMORA + conventional laxative(s)	57 (72.0%) ► 33 conventional laxative(s) ► 11 PAMORA ► 13 PAMORA + conventional laxative(s)
Group C (non-response)— BFI≥30 and no improvement of <12 from baseline	28 (29%) ► 12 conventional laxative(s) ► 7 PAMORA ► 9 PAMORA + conventional laxative(s)	22 (28%) ► 9 conventional laxative(s) ► 6 PAMORA ► 7 PAMORA + conventional laxative(s) ► (9 patients not treated with PAMORA during study)

BFI, Bowel Function Index; PAMORA, peripherally acting mu-opioid receptor antagonist.

due to adverse effects, and there were no reports of unanticipated adverse effects. Other researchers have reported similar results in analogous studies of other symptoms in this population (eg, pain).[24]

In conclusion, the feasibility study suggests that a definitive study can be successfully completed. However, we will amend the methodology to try to improve participant retention, and to improve adherence to the treatment algorithm (details given above). The feasibility study also suggests that the use of the BFI to monitor OIC, and the use of a treatment algorithm to manage OIC, can result in clinically important improvements in OIC and OIC-related quality of life.

Table 3 MSAS-SF and PAC-QOL summary data

	Responders ('Group A' and 'Group B') (n=57)	Non-responders ('Group C') (n=21)	Statistical analysis
MSAS-SF data			
No of symptoms	Median change number 0 (IQR: −4 to 6)	Median change number - 2 (IQR: −5 to 3)	Mann-Whitney U test p=0.149
Physical subscale score	Mean change score 0.17 (SD=0.77)	Mean change score −0.01 (SD=0.48)	Independent t-test p=0.320
Psychological subscale score	Mean change score 0.01 (SD=0.58)	Mean change score −0.15 (SD=0.68)	Independent t-test p=0.309
Global Distress Index score	Mean change score 0.15 (SD=0.68)	Mean change score −0.01 (SD=0.48)	Independent t-test p=0.325
Total MSAS score	Mean change score 0.08 (SD=0.62)	Mean change score −0.03 (SD=0.45)	Independent t-test p=0.459
PAC-QOL data			
Physical subscale	Mean change score 0.94 (SD=1.02)	Mean change score 0.17 (SD=0.88)	Independent t-test p=0.003
Psychosocial subscale	Mean change score 0.21 (SD=0.58)	Mean change score −0.01 (SD=0.41)	Independent t-test p=0.115
Worries/concerns subscale	Mean change score 0.52 (SD=0.85)	Mean change score −0.06 (SD=0.55)	Independent t-test p=0.005
Satisfaction subscale	Mean change score −0.77 (SD=0.93)	Mean change score 0.03 (SD=0.55)	Independent t-test p<0.001
Overall score	Mean change score 0.29 (SD=0.58)	Mean change score 0.002 (SD=0.45)	Independent t-test p=0.43

MSAS-SF, Memorial Symptom Assessment Scale – short form; PAC-QOL, Patient Assessment of Constipation Quality of Life.

Contributors AND conceived the study, and was the chief investigator. KB was the study statistician. All other authors were principal investigators, and everyone contributed to the writing of the paper.

Competing interests AND 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.

Patient consent for publication Not required.

Ethics approval 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).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data will be made available to other researchers on request.

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