A group-based educational intervention to reduce opioid use for chronic pain: a randomized clinical trial

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Word count: 3097

Key Points

Question: Does a multi-component intervention that involves group meetings, education, individual support, and skill-based learning help people with chronic pain reduce use of opioids and improve pain interference with daily activities?

Findings: In this multi-centre randomized clinical trial including 608 participants from primary care settings in the UK with chronic pain due to non-malignant conditions, 29% of people in the intervention group, compared to 7% in the usual care group, discontinued opioids at 12-month follow-up, but there were no statistically significant differences in pain interference between the two groups at 12-months.

Meaning: A group-based educational intervention that included skill-based learning significantly reduced opioid use, but not perceived pain interference with daily life activities, compared to usual care.

Abstract

Background: Opioid use for chronic non-malignant pain can be harmful.

Objective: To test whether a multi-component group-based self-management intervention can reduce opioid use and improve pain-related disability, compared to usual care.

Design, Setting, and Participants: Randomized clinical trial of 608 adults who were using strong opioids (Buprenorphine, Dipipanone, Morphine, Diamorphine, Fentanyl, Hydromorphone, Methadone, Oxycodone, Papaveretum, Pentazocine, Pethidine, Tapentadol, Tramadol) to treat chronic non-malignant pain. The study was conducted in 191 primary care centers in England between 05/17/2017 and 01/30/2019. Final follow-up occurred 03/18/2020.

Intervention: Participants were randomized 1:1 to either usual care or a three-day group sessions that emphasized skill-based learning and education, supplemented by one-to-one support, delivered by a nurse and lay person for 12-months.

Main outcomes: Two primary outcomes were Patient-Reported Outcomes Measurement Information System Pain Interference Short Form (8A) (PROMIS-PI-SF-8A) (T-score range 40.7-77, 77 indicates worst pain interference) and the proportion of participants who discontinued opioids at 12-months, measured by self-report.

Results: Of 608 participants randomized (mean age 61; 362 (60%) female), median daily morphine equivalent dose: 46mg (IQR 25 to 79), 440 (72%) completed 12-month follow-up testing. There was no statistically significant difference in PROMIS-PI-SF-8A scores between the two groups at 12-month follow-up: -4.1 in the intervention group and -3.17 in usual care (between group difference: mean difference, -0.52 [95% CI -1.94 to 0.89], p=0.15). At 12 months, opioid discontinuation occurred in 65/225 (29%) of participants in the intervention group and 15/208 (7%) of those in the usual care group (odds ratio 5.55

[95% CI 2.80 to 10.99], absolute difference, 21.7% [95% CI, 14.8 to 28.6], p<0.001). Serious Adverse events occurred in 8% (25/305) and 5% (16/303) respectively of intervention and usual care participants. The most common serious adverse events were Gastrointestinal and Locomotor/ Musculoskeletal. Two people in the intervention group were hospitalised for possible/probable symptoms of opioid withdrawal (shortness of breath, hot flushes, fever and pain).

Conclusion and Relevance: A group-based educational intervention that included group and individual support and skill-based learning significantly reduced patient-reported use of opioids compared to usual care, but there was no effect on perceived pain interference with daily life activities.

Trial Registration: ISRCTN Number: 49470934
https://www.isrctn.com/

Introduction

Opioids are widely used to treat chronic non-malignant pain (CNMP).[1] In 2022, an Agency for Healthcare Research and Quality (AHQR) report concluded that opioids may have small beneficial effects but are not superior to non-opioid therapy and have increased risk of short- and long-term harms.[2] In 2020, more than 142 million opioid prescriptions were dispensed in the U.S.[3]

Optimal methods for reducing opioid use remain unclear. Tapering opioids quickly without providing alternatives for pain management have the potential to cause harm, including suicide, or mental health crisis.[4, 5] Evidence of effectiveness of opioid tapering interventions including pain self-management, complementary medicine, pharmacological and biomedical intervention and opioids replacement, remains unsatisfactory due to a combination of poor study methodology and lack of evidence of safety.[6]

Multimodal treatment approaches that include nonpharmacologic strategies may prevent harm from rapid tapering while still facilitating effective treatment of chronic pain.[7] The I-WOTCH randomized clinical trial (RCT) was conducted within the National Health Service to test whether a multimodal approach that facilitates opioid tapering in people with chronic non-malignant pain could reduce opioid use and improve pain control among people using opioids to treat chronic pain from non-malignant causes.

Methods

Trial design and oversight

The trial protocol is available in the supplement. The initial protocol was developed on 09/09/2016 and was finalized on 02/10/2021 before any data were evaluated. The initial

statistical analysis plan was completed on 05/08/2018 and was finalized on 01/29/2019 before any data were analyzed. The trial protocol was approved by the Yorkshire & The Humber - South Yorkshire Research Ethics Committee and was overseen by an Independent Trial Steering Committee, with an independent Data Monitoring and Ethics Committee. The clinical trial was designed as a pragmatic, multicentre, 1:1 RCT to test the superiority of an intervention, compared to usual care, for improving outcomes in people with chronic non-malignant pain. Enrolment began 5/17/2017 and ended 1/30/2019. Final follow-up occurred 03/18/2020.

Participants

Participants were aged ≥18 using strong opioids as defined by the British National Formulary (Buprenorphine, Dipipanone, Morphine, Diamorphine, Fentanyl, Hydromorphone, Methadone, Oxycodone, Papaveretum, Pentazocine, Pethidine, Tapentadol and Tramadol) for at least three months on most days in the preceding month for chronic non-malignant pain.[8] [eTable2 in Supplement 2] Ethnicity data were collected using self-report of UK Census categories to show the generalizability of our findings to the UK.

Potential participants prescribed strong opioids on multiple occasions, were identified from the electronic records of general (family) practices in the midlands and north-east of England. People living in chronic care facilities (care homes) or unable to leave their home without assistance, and those using methadone not prescribed for chronic pain were excluded. People could also self-refer; posters were placed in clinics. Eligibility was determined by telephone.

Participants completed baseline questionnaires and written informed consent by mail. Medication use at baseline and informed consent were confirmed by telephone.

Randomization

Randomization Participants were randomized in a 1:1 ratio using a minimisation programme stratified by geographical locality (midlands/north-east of England), baseline pain intensity raw score (low intensity: ≤8/high intensity≥9) and baseline morphine equivalent dose of opioids (0-29, 30-59, 60-89, 90-119, 120-149 and 150+mg).

Randomization was managed and performed by the WCTU programming team using Structured Query Language (SQL), after all baseline data had been collected and when there was a sufficient number of participants (16 participants) to begin a group intervention group. Participants were not blinded to group assignment.

Intervention

The intervention was a group-based educational intervention designed to encourage opioid cessation (an agreed decision between the participant and nurse), increase participants' self-efficacy (confidence), implement self-management strategies for pain and improve wellbeing.[9]

The intervention included three day-long group meetings held once weekly led by a trained intervention nurse and by a lay person with chronic non-malignant pain and experience of opioid tapering. Topics for discussion in the groups included; education about opioids and withdrawal and skills-based learning for self-management of pain. Case studies illustrating successful opioid tapering and challenges were used. Additionally, participants had an

individual, one-hour consultation (based on Motivational Interviewing) with the nurse, two monitoring telephone calls (30 minutes each and a face to face consultation (one hour).[10] Nurses used a tapering application specifically designed for this trial that computed a standard tapering plan consisting of a reduction of 10% of the baseline dose per week until 30% of the baseline dose was reached, then a reduction of 10% of the remaining dose per week.[eTable 3 in Supplement 2] The tapering program was individualized according to opioid preparation and individual circumstances. Participants received an educational DVD relaxation, mindfulness, and distraction techniques. Audio recordings of 10% of intervention activities were analysed to assess intervention fidelity; the extent to which the intervention was delivered as conceived and planned.[11, 12] The total time required for each group and individual session was 17 hours over an 8-10 week period.

Primary Outcomes

There were two primary outcomes: the Patient-Reported Outcomes Measurement Information System (PROMIS) Pain Interference Short Form (8A) (PROMIS-PI-SF-8A) (T-score range 40.7-77, 77 indicates worst pain interference) and the proportion of participants reporting no opioid use over the previous four weeks at 12-month follow-up.[13][eTable 2 in Supplement 2]

Investigators originally planned to report opioid use as daily morphine equivalent dose (MED) during the four weeks prior to 12-month follow-up.[14] However, the final opioid use data did not satisfy the normality assumption of the linear regression, due to a large number of zero values and data were positively skewed.[eFigure 1-2 in Supplement 2] Therefore, the primary outcome for opioid use was changed to the proportion of participants reporting no opioid use. All primary outcomes were measured at baseline, 4, 8 and 12

months. Follow up questionnaires were mailed at four, eight, and 12-months. Self-reported opioid use data were checked in a subsequent telephone call.

Secondary Outcomes

Secondary outcomes were pain intensity (PROMIS Scale v1.0 – Pain Intensity Short-Form 3a) (T-score range: 36.3-81.8, 81.8 indicates worst pain intensity)[15, 16]; Severity of Opioid Withdrawal (Symptoms) Short Opiate Withdrawal Scale (ShOWS)(Score range: 0-30, 30 indicates worst symptoms)[17]; health related quality of life (SF-12 V2, and EQ-5D-5L) (SF-12 mental and physical component score range: 0-100, 100 indicates best functioning, EQ-5D-5L utility score range: <0-1, 1 indicates best quality of life, EQ-5D-5L VAS score range: 0-100, 100 indicates best health)[18, 19]; sleep quality (Pittsburgh Sleep Quality Index (PSQI))(Score range: 0-21, 21 indicates worst sleep quality)[20]; emotional wellbeing (Hospital Anxiety and Depression Scale (HADS)) (Score range: 0-21, 21 indicates worst anxiety or depression)[21]; Self-efficacy (Pain Self Efficacy Questionnaire) (Score range: 0-60, 60 indicates strongest self-belief) (PSEQ)[22] and the proportion of participants who reduced opioids by 50% from baseline. Secondary outcomes were measured at baseline, 4, 8 and 12 months. Follow up questionnaires were mailed at four, eight, and 12-months. When questionnaires were not returned by mail participants were telephoned to collect PROMIS-PI-SF-8A EQ-5D-5L.[19] Prescribed opioid medication from GP records and resource use was not reported. While the intent was to blind outcome assessors, some participants revealed treatment allocation during these calls; thus complete blinding was not achieved.

Adverse Events

Participants were asked if they experienced any adverse events (AE's) whilst tapering opioids in the induvial sessions by the nurse. The chief investigator and clinical members of the study

team assessed/confirmed each adverse event. All AE's and Serious Adverse Events (SAEs) were reported to the Trial Management Group for their review and oversight.

Statistical Analysis

The original sample size calculation used the PROMIS-PI-SF-8A as the primary outcome.[13] To show a 3.5 points difference on PROMIS-PI-SF-8A, assuming a usual care arm mean of 50, a standard deviation of 10, at 5% significance with 90% power (ICC of 0.01, mean group size of 10 participants) allowing for 20% attrition required 468 randomised participants. Adjusting the significance level to 2.5% for two primary outcomes and adjusting the design effect for clustering to reflect actual group sizes gave a revised sample size of 542.

The original protocol, dated 09/09/2016, had a single primary outcome of pain interference. The target sample size of 468 was achieved on 24th October 2018 and on this date additional potential participants had provided informed consent and were available for randomization. Therefore, the protocol was revised on 12/19/2018 to increase the sample size to 542 and add the primary outcome of opioid use. The independent trial steering committee, data monitoring committee, funders, and ethics committee, all supported a decision to continue recruitment and include a secondary primary outcome. Independent Trial Steering Committee approval was given on October 12, 2018.[Supplement 2] Neither the study team nor the Independent Trial Steering Committee reviewed any data prior to this decision. The analysis plan and protocol were finalised before data collection was complete. No decisions on outcome selection were made after data were available.

The main analysis analysed participants as they were randomised. Primary outcomes used two-sided tests at the 2.5% significance level. All other statistical tests were two-sided at the

5% significance level. The estimate, 95% confidence interval (95% CI) and p-value were reported for each of the statistical tests.

Partially nested mixed effects regression (linear and logistic) models to estimate the treatment effects for both primary and secondary outcomes were used.[Table 2-3] Age, sex, site location, baseline pain intensity, baseline opioid band (for linear model only) and the baseline value of the dependent variable were co-variates in the fixed effects part of the model. The education support group was the cluster variable for the intervention group, with individual clusters of size 1 used for each participant in usual care, to account for the partial clustering.[23, 24] Model assumptions were assessed as appropriate.

As a sensitivity analysis, an instrumental variable (IV) analysis to adjust for non-adherence was performed on two levels of adherence (a) minimal adherence; attending day one of the intervention plus the first one-to-one session and (b) full adherence; attending three days, the first one-to-one session and one or more phone calls.[25] Additional to the usual assumptions of this analysis, monotonicity was also needed. An inverse probability of missingness weighting (IPW) analysis was carried out as a sensitivity analysis to assess whether the missing data affected conclusions.[26]

A pre-specified subgroup analyses for the primary outcomes, testing for interaction for baseline anxiety, depression, and opioid use, defined using their median values was completed. Pre-specified sensitivity analyses for the primary outcome, excluding participants included in process evaluation interviews, adjusting for the imbalance of death, and split by baseline pain disorders were also completed.[eTable 23-25] Because of the potential for type 1 error due to

multiple comparisons, findings for analyses of secondary end points should be interpreted as exploratory. Statistical analyses were conducted using STATA 16.1.[27]

Results

Recruitment

Of 20,900 people approached from 191 general practices, 2,220 potential participants expressed an interest in the study, nine people self-referred.[eTable 5-6 in Supplement 2] Of these,1,541 (69%) were reached by telephone and assessed for eligibility. Of these, 608 (39%) people were randomized [Figure 1, Table] and [eTable7-9 in Supplement 2] mean age was 61 years (SD 12.9), 362 (60%) were female, and 588 (3%) gave their ethnicity as White British.

35 group interventions were delivered at 25 community locations (median group size 9 (IQR 5 to 11)); 206/305 (68%) participants attended the first session, 161 (53%) achieved minimum adherence, and 144 (47%) achieved full adherence to the programme. Median time from randomisation to first group session was 12 days (IQR, 6 to 23).[eTable 15 in Supplement 2] Final follow-up was March 18, 2020 and the trial ended on November 11, 2021.

Mean adherence (fidelity) to the course manual, defined as intervention delivery and adhering to the steps outlined in manual, was 83%, (range 25 to100 with a median of 88) and competence of delivery; the skilfulness of the delivery as taught in the intervention training, had a mean of 79% (range 0-100% with a median of 86%). The nurse one-to-one consultation sample N=27 had an adherence mean of 91% (range 61 to 100) and competence mean of 93% (range 50 to 100%).[eTable 16-17 in Supplement 2]

Primary outcomes

We analysed all available PROMIS-PI-SF-8A data from 439/608 (72%) participants and opioid use data from 433/608 (71%) participants at 12-month follow-up. PROMIS-PI-SF-8A scores improved in both groups over 12-months; intervention -4.1 (95% CI -4.98 to -3.22), usual care -3.17 (95% CI -4.10 to -2.24).There was no statistically significant between group difference in PROMIS-PI-SF-8A scores; mean difference, -0.52 (95% CI -1.94 to 0.89), p=0.15.[Table 2] At 12 months 65/225 (29%) in the intervention group and 15/208 (7%) of those in usual care had discontinued opioids; odds ratio 5.55 (95% CI 2.80 to 10.99), absolute difference, 21.7% (95% CI, 14.8 to 28.6), p<0.001.[Table 2] At baseline, 34% (103/305) in the intervention group and 32% (98/303) in the usual care group were in the lowest opioid band (0-29.9 MED per day), with 12% (37/305) and 10% (29/303) in the highest opioid band (≥150 MED per day) in the intervention and usual care group respectively.[Table 1]

Secondary Outcomes

Of 11 secondary outcomes, collected over three timepoints, only six were statistically significant. At 12 month follow-up, the proportion of participants who reduced daily MED by ≥50% from baseline were 57% in the intervention and 27% in the control group, absolute difference 29.9% (95% CI 21.1 to 38.8), OR 3.76 (95% CI 2.47 to 5.71), p<0.001.[Table 2] At four month follow-up, participants randomized to the intervention had statistically significant improvement in mental health (SF-12 Mental Component Score and HADS depression subscale), pain self-efficacy (PSEQ), and health related quality of life (EQ-5D-5L utility and visual analogue scores) but not at any other time points.[Table 3] There were no statistically significant between group difference in pain intensity (Promis-3A), opioid withdrawal symptoms (ShOWS) or sleep quality measured by the PSQI at any time point.[Table 3]

Sensitivity analyses

The IV analysis were not materially different from the primary analysis.[eTable 19-20 in Supplement 2] However, the analysis is limited by the model assumptions, and the trial being an unblinded study. The findings from the IPW analysis showed no meaningful differences from the primary analysis.[eTable 4 in Supplement 2] The tests for interaction in pre-specified subgroup analyses were not statistically significant.[eTable 21-22 in Supplement 2] Additional pre-specified analyses also showed no change in conclusions.[eTable 23-25 in Supplement 2]

Adverse events

There were 52 Serious Adverse Events (32 intervention, 20 control), reported by 41 participants (25 intervention, 16 control), including five deaths (four intervention and one control), Metastatic Prostate Cancer, Aortic Dissection, Lymphoma Complication, Subdural empyema secondary to otitis media, and unknown cause of death. In the control group, one SAE (an arthritis flare up) was possibly study related, (pain temporarily worsened by opioid withdrawal requiring hospital admission for pain control). In the intervention group there was one probably related, and expected, SAE of moderate severity (hot flushes/shooting pains in limbs after tapering) and three possibly related SAEs, all severe; one expected (hospitalisation from joint/back pain) and two unexpected (surges after tapering & small intestinal bleed, and an overdose suicide attempt). Adverse events were reported respectively by 22/305 (7%) and 8/803(3%) intervention and control participants.[eTable 26-29 in Supplement 2]

Discussion

In this multi-centered randomized clinical trial, a group-based educational intervention that consisted of group and individual support as well as skill-based learning significantly reduced patient-reported use of opioids compared to usual care, but there was no effect on perceived pain interference with daily life activities at 12-month follow-up.

Of 11 secondary outcomes, collected over 3 timepoints, only six were statistically significant and improved in the intervention group, compared to control. Five of these six statistically significant secondary outcomes were only statistically different at 4-month follow-up. All significant outcomes showed benefit from the intervention. Tapering was achieved through health care professional and peer group support rather than prescribing additional medications. The intervention was unique in that it consisted of establishing a therapeutic alliance with the patient, gradual opioid tapering, to reduce adverse effects is successful including withdrawal symptoms.

A 2022 systematic review of opioid reduction interventions in primary care identified four RCTs (N=231) of patient centered interventions to reduce opioid use for chronic non-malignant pain.[28] The interventions included mindfulness oriented and meditation-cognitive behavioural approaches, opioid tapering was not an explicit goal. None of these found a statistically significant between group difference in opioid use. The review findings only apply to the heterogenous group of interventions tested. Our findings add to this by showing that there is a patient-centered intervention deliverable in primary care to effectively support opioid cessation.

Another 2022 systematic review identified two RCTs (N=238) of pain management programmes reporting on opioid cessation; 30% of those in the intervention group and 12% in usual care group stopped opioids (risk ratio 2.15 (95%CI 1.02 to 4.53).[6] Similar to the current trial the interventions had specific aims to reduce reliance on opioid through behaviour change and incorporating a bio-psycho-social framework.

A subsequent (2022) trial (N=250), reported that 16% of people receiving supportive group therapy, and 35% of people offered 'mindfulness orientated recovery enhancement' reduced opioid use by ≥50% (P=0.009) at nine months, no adverse events related to the intervention were reported.[29]

Limitations

This study has several limitations. First, participant opioid use was measured using self-report measures verified in a phone call from a member of the study team. Results for this primary outcome were not validated with blood or urine samples. Second participants were not blinded to group assignment. Third, study coordinators were regularly unblinded by study participants. Fourth, participants in this trial volunteered to participate in the trial and therefore were likely more committed to reducing use of opioid medications. Findings reported here may not be generalisable to people less inclined to stop use of opioid medications. Fifth, only 47% of participants randomized to the intervention had full adherence to the intervention, defined as attending Day 1-3 (group sessions), the first individual session with the nurse and at least one further follow-up session. Sixth , the 12-month follow-up rate was 72%. Seventh, 33% of participants used a morphine equivalent dose of < 30mg per day at baseline. Results may not be generalizable to people using higher doses of morphine. Eighth, participants were recruited from a community setting. Results

may not be applicable to other settings. Ninth, results may not be applicable to healthcare systems where opioid tapering requires a handover of prescribing between primary and secondary care. Tenth, the length of time needed to deliver the intervention and intensity may limit the scalability in clinical practice. Eleventh, some AEs may have been missed if participants did not recall or report these.

Conclusion

A group-based educational intervention that included group and individual support and skill-based learning significantly reduced patient-reported use of opioids compared to usual care, but there was no effect on perceived pain interference with daily life activities.

Conflicts of Interest Disclosure

Competing interests SE is the Chair of the specialised pain CRG at NHS England, he is Chief investigator and principal investigator of a number of NIHR and Industry funded trials, he has received personal fees from Medtronic Ltd, Mainstay Medical, Boston Scientific Corp for consultancy work. His department has received research funding from the National Institute of Health and Care Research, Medtronic Ltd and Boston Scientific Corp. HS is director of Health Psychology Services Ltd, providing psychological services for a range of health-related conditions. AM has received fees from Pfizer for consultancy work. NKYT is chief investigator or coinvestigator of other chronic pain related projects funded by the NIHR, MRC, Warwick-Wellcome Translational Partnership. MU is chief investigator or coinvestigator on multiple previous and current research grants from the UK National Institute for Health and Care Research, Arthritis Research UK and is a coinvestigator on grants funded by the Australian NHMRC. He was an NIHR Senior Investigator until March

2021. He has received travel expenses for speaking at conferences from the professional organisations hosting the conferences. He is a director and shareholder of Clinvivo Ltd that provides electronic data collection for health services research. He is part of an academic partnership with Serco Ltd, funded by the European Social Fund, related to return to work initiatives. He receives some salary support from University Hospitals Coventry and Warwickshire. He is a coinvestigator on three NIHR funded studies receiving additional support from Stryker Ltd. He has accepted honoraria for teaching/lecturing from consortium for advanced research training in Africa. Until March 2020, he was an editor of the NIHR journal series, and a member of the NIHR Journal Editors Group, for which he received a fee. ADF is author of the My Opioid Manager book and App distributed in iTunes and Google Play. Both book and app are free of charge. She is author of the Opioid Manager App, a free app distributed only in iTunes for healthcare professionals. The app is owned by UHN, the hospital where ADF works. ADF has a monetized YouTube channel since January 2021 that contains some videos about opioids and opioid tapering. Since April 2021, ADF has an unrestricted educational grant to maintain an online self-assessment opioid course for healthcare professionals in Canada. The funding is provided by the Canadian Generics Pharmaceutical Association (CGPA). The funding organisation has no role in the preparation, approval, recruitment of participants, or data analysis of the course content. Responsibility for the course content is solely that of the authors. ST is chief investigator or coinvestigator on multiple previous and current research grants from the UK National Institute for Health and Care Research.

Acknowledgments

The Trial was funded by the National Institute for Health and Care Research. The funders had no role design and conduct of the study; collection, management, analysis, and interpretation

of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Access to data and data analysis

Prof. Lall and Miss Booth had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Disclaimer: The findings and conclusions in this article are those of the authors and do not necessarily reflect the views of The National Institute of Health and Care Research (NIHR).

Additional contributions: We would like to thank, all participants who took part in the study for their time and willingness to engage with the study. We would also like to thank the programming team; Mr Henry Adjei (MSc), Warwick Clinical Trials Unit, University of Warwick, UK, Mr Chockalingam Muthiah (BSc) Warwick Clinical Trials Unit, University of Warwick, Coventry, UK and Mr Adrian Willis (BA) Warwick Clinical Trials Unit, University of Warwick, Coventry, UK for their support in the development and running of the opioid tapering App. They did not receive compensation. We would also like to thank all administrative, academic and research staff for their contributions to the running of the study. We are grateful for the support and would like to thank the primary care practices and sites that helped set up and recruit to this study. We would like to thank, the venues who hosted the interventions across all regions. We would like to thank our Patient and Public volunteers who contributed their valuable time and input to the study. We would like to thank the North-East and North Cumbria Clinical Research Network for their Patient and Public volunteer sessions at the beginning of the study. Finally, we would like to thank all clinical and lay facilitators who delivered the intervention and the Clinical Research Networks who assisted

in recruitment for the study (North-East & North Cumbria, West Midlands, East Midlands, Thames Valley & South Midlands).

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Table 1: Summary Baseline demographic characteristics and outcome measures of all randomised participants by treatment group

	Education and support intervention N=305	**Usual care N=303**
Age (years); Mean (SD)	62.1 (11.9) [n=305]	60.4 (13.8) [n=303]
Gender		
N	304	301
Male	125 (41%)	117 (39%)
Female	178 (59%)	184 (61%)
Other	1 (<1%)	0 (0%)
Ethnicity[a]		
N	304	301
Black African	1 (<1%%)	0 (0%)
Black Caribbean	3 (1%)	3 (1%)
Black Other	1 (<1%%)	0 (0%)
Indian	2 (1%)	4 (1%)
Other	1 (<1%)	3 (1%)
Pakistani	1 (<1%)	0 (0%)
Prefer not to say	0 (0%)	1 (<1%)
White	295 (97%)	290 (96%)
Employment status		
N	304	301
Employed	67 (22%)	65 (22%)
Unable to work due to long term sickness	78 (26%)	76 (25%)
Retired from paid work	134 (44%)	136 (45%)
Other[b]	25 (8%)	24 (8%)
Age left full time education[c]		
N	304	301
Age 16 years or under	174 (57%)	172 (57%)
Age 17 years or over	125 (41%)	123 (41%)
Other	5 (2%)	6 (2%)
Length of time pain experienced		
N	304	301
5 years or less	52 (17%)	53 (18%)
More than 5 years	252 (83%)	248 (82%)
How long opioids taken		
N	304	301
5 years or less	115 (38%)	125 (42%)
More than 5 years	189 (62%)	176 (58%)
Type of pain disorder[d]		
N	299	300
Lower Back Pain	241 (81%)	249 (83%)
Chronic Widespread Pain	154 (52%)	137 (46%)
Multi-site pain	277 (93%)	264 (88%)

	Education and support intervention N=305	Usual care N=303
Daily morphine equivalent dose opioid use[e]		
0-29.9 MED per day	103 (34%)	98 (32%)
30-59.9 MED per day	95 (31%)	103 (34%)
60-89.9 MED per day	42 (14%)	44 (15%)
90-119.9 MED per day	18 (6%)	17 (6%)
120-149.9 MED per day	10 (3%)	12 (4%)
≥150 MED per day	37 (12%)	29 (10%)
Daily Morphine equivalence dose (mg); Median (IQR)	49 (25-81) [n=305]	44 (25-75) [n=303]
Pain interference (PROMIS-8A)[f]; Mean (SD)	68.5 (6.0) [n=304]	68.2 (6.2) [n=301]
Pain intensity (PROMIS-3A)[g]; Mean (SD)	69.3 (6.8) [n=305]	68.8 (7.1) [n=303]
SF-12 Mental[h]; Mean (SD)	41 (10.8) [n=304]	41 (11.4) [n=301]
SF-12 Physical[h]; Mean (SD)	32 (8.1) [n=304]	32 (8.1) [n=301]
Pittsburgh SQI[i]; Mean (SD)	12 (4.3) [n=278]	12 (4.1) [n=285]
HADS Anxiety[j]; Mean (SD)	9 (5.1) [n=303]	9 (5.1) [n=298]
HADS Depression[j]; Mean (SD)	9 (4.6) [n=304]	9 (4.6) [n=298]
Pain self-efficacy[k]; Mean (SD)	24 (12.7) [n=301]	25 (13.6) [n=300]
EQ-5D-5L utility[l]; Mean (SD)	0.3 (0.3) [n=304]	0.4 (0.3) [n=301]
EQ-5D-5L VAS[l]; Mean (SD)	47 (21.4) [n=304]	49 (21.3) [n=301]
ShOWS[m]; Mean (SD)	11 (5.5) [n=303]	11 (5.0) [n=301]

a Ethnicity was self-reported using the listed options, with participants only able to select one option. There were no participants who reported Chinese or Bangladeshi ethnicity.

b Other employment status includes participants who are still in education part/full time, look after home/family, unemployed or other

c Leaving education at age 17 years or over includes participants who left education between age 17-19 years, age 20 or over, or participants still in education. Other most often referred to those who returned to education later in life.

d Participants self-reported sources of pain and were able to report more than one.

e Opioid band by region, See eTable 2in Supplement 2

f Patient-reported Outcomes Measurement Information System (PROMIS) Pain interference Short Form (8A) uses 8 self-reported items from the prior 7 days to determine how much pain interferes with daily life. Reported as standardised T scores, calculated using the recommended HealthMeasures Scoring Service, higher scores indicate greater interference. Scores 40.7-60 are considered average while 60-77 indicates high interference. [30] Indicative meaningful difference (IMD) 3.5 [eTable 5 Supplement 3]

g Patient-reported Outcomes Measurement Information System (PROMIS) Pain intensity Short Form (3A) uses 3 self-reported items from the prior 7 days to determine how much pain interferes with daily life. Reported as standardised T scores, calculated using the recommended HealthMeasures Scoring Service, higher scores indicate greater pain intensity. Scores 36.3-60 are considered average while 60-81.7 indicates high pain intensity. [30] IMD 3.5 [eTable 5 Supplement 3]

h The 12-item Short Form Health Survey complies 8 domains of daily living to assess quality of life. Scores range from 0 to 100 with higher scores reflecting better physical and mental functioning. Mental IMD 3.3, Physical IMD 3.8 [eTable 5 Supplement 3

i Pittsburgh Sleep Quality Index (PSQI) scores range from 0-21, with higher scores indicating worse sleep quality. The 19 self-reported questions are combined to create seven component scores. The score is calculated by summing the seven component scores (range 0-3) to create a global score ranging from 0-21. This global score has been reported. IMD 3.0 [eTable 5 Supplement 3]

j Hospital Anxiety and Depression Scale (HADS) anxiety and depression scores range from 0-21, with higher scores indicating worse anxiety/depression. Each of the seven questions measuring anxiety have a score ranging from 0-3. These seven scores are summated to create the reported anxiety score. The same method applies to depression score. Anxiety IMD 1.7, depression IMD 1.7 [eTable 5 Supplement 3]

k Pain self-efficacy questionnaire (PSEQ) scores range from 0-60 with higher scores indicating stronger self-efficacy beliefs. The PSEQ consists of 10 questions, each having a score ranging from 0-6. The PSEQ score is calculated by summing these 10 scores to create the reported score. IMD 7.0 [eTable 5 Supplement 3]

l EuroQol-5 Dimension (EQ-5D-5L) utility score ranges from <0-1, with higher scores indicating better quality of life. EQ-5D-5L Visual Analogue Scale (VAS) score ranges from 0-100, with scores of 100 indicating 'best health you can imagine' and 0 indicating 'worst health you can imagine'. These scores ranging from 0-100 were self-reported by participants and that self-reported score is reported. Utility IMD 0.07, VAS IMD 7.0 [eTable 5 Supplement 3]

m Short Opioid Withdrawal Scale (ShOWS) score ranges from 0-30 where a higher score indicates more severe symptoms. The ShOWS consists of 10 questions, each with a score of 0-3, which are summed together to give the reported score. IMD 3 [eTable 5 Supplement 3]

Table 2 Daily Opioid use and PROMIS-8A at 12 months (primary outcome), 4 months, and 8 months (secondary outcomes)

	Education and support intervention	Usual care	Absolute difference (95% CI)	Adjusted effect estimate (95% CI)	P-value
Primary outcome[a]					
Fully tapered off opioids at 12 months (MED=0)[b]	65/225 (29%)	15/208 (7%)	AD 21.7% (14.8 to 28.6)	OR 5.55 (2.80, 10.99) [c]	p<0.001
PROMIS-8A[d] at 12 months; Mean (sd)	64.2 (7.7) [n=229]	64.7 (7.3) [n=210]	MD -0.52 (-1.94 to 0.89)	-0.89 (-2.12 to 0.33) [e]	p=0.15
Secondary outcomes					
Fully tapered off opioids at 4 months (MED=0)[b]	58/224 (26%)	7/201 (3%)	AD 22.4% (16.1 to 28.7)	OR 11.61 (5.06, 26.63) [c]	p<0.001
Fully tapered off opioids at 8 months (MED=0)[b]	57/193 (30%)	11/163 (7%)	AD 22.8% (15.3 to 30.3)	OR 7.25 (3.46, 15.18) [c]	p<0.001
≥50% MED reduction from baseline at 4 months	112/224 (50%)	31/201 (15%)	AD 34.6% (26.3 to 42.8)	OR 6.12 (3.77, 9.92) [f]	p<0.001
≥50% MED reduction from baseline at 8 months	110/193 (57%)	38/163 (23%)	AD 33.7% (24.1 to 43.2)	OR 4.94 (3.04, 8.03) [f]	p<0.001
≥50% MED reduction from baseline at 12 months	129/225 (57%)	57/208 (27%)	AD 29.9% (21.1 to 38.8)	OR 3.76 (2.47, 5.71) [f]	p<0.001
PROMIS-8A [d] at 4 months; Mean (sd)	64.5 (7.5) [n=227]	64.6 (7.2) [n=202]	MD -0.09 (-1.48 to 1.31)	-0.73 (-1.93 to 0.48) [e]	p=0.24
PROMIS-8A [d] at 8 months; Mean (sd)	64.5 (7.3) [n=199]	64.9 (7.5) [n=166]	MD -0.39 (-1.93 to 1.14)	-0.75 (-2.10 to 0.59)[e]	p=0.27

Abbreviations: OR, Odds ratio; MD, Mean difference; AD, Absolute difference; MED, Morphine equivalent dose; PROMIS-8A, Patient-reported Outcomes Measurement Information System (PROMIS) Pain interference Short Form (8A)

a 433 (71.2%) of the 608 randomised participants have opioid use primary outcome data reported. 439 (72.2%) of the 608 randomised participants have pain interference (PROMIS-8A) primary outcome data reported.

b Daily morphine equivalent dose (MED) over previous four weeks. Reported are those who fully tapered off opioids (MED=0mg). See eTable 1 in Supplement 2 for equivalences used. See eTable18 in Supplement 2 for breakdown of opioid tapering by baseline MED band.

c Based on partially nested mixed-effect logistic model adjusted for age, gender, baseline pain intensity, geographical location and baseline MED. The education support group was used as the cluster variable for the intervention arm, with individual clusters of size 1 used for each participant in usual care. Odds ratio and 95% confidence interval reported.

d PROMIS-8A T-score reported. Refer to Table 1 footnote a on PROMIS-8A scoring and calculation

e Based on a heteroscedastic partially nested mixed-effect model with corrected degrees of freedom, adjusted for age, gender, baseline pain intensity, geographical location, baseline opioid band and baseline PROMIS-8A T-score. The education support group was used as the cluster variable for the intervention arm, with individual clusters of size 1 used for each participant in usual care.

f Based on partially nested mixed-effect logistic model adjusted for age, gender, baseline pain intensity, geographical location and baseline opioid band. The education support group was used as the cluster variable for the intervention arm, with individual clusters of size 1 used for each participant in usual care. Odds ratio and 95% confidence interval reported.

Table 3: Secondary outcomes

	Education and support intervention	Usual care	Mean difference (95% CI)	Adjusted effect estimate (95% CI)[a]	P-value[a]
Pain intensity (PROMIS-3A)[a]					
4 months; Mean (SD)	65.0 (8.1) [n=189]	65.9 (7.7) [n=151]	-0.96 (-2.66, 0.75)	-1.42 (-3.08 to 0.23)	p=0.09
8 months; Mean (SD)	65.0 (8.7) [n=182]	65.9 (7.3) [n=147]	-0.92 (-2.69, 0.85)	-1.47 (-3.03 to 0.09)	p=0.06
12 months; Mean (SD)	64.7 (8.6) [n=187]	65.6 (7.7) [n=159]	-0.91 (-2.64, 0.83)	-1.31 (-2.88 to 0.26)	p=0.10
SF-12 Mental[b]					
4 months; Mean (SD)	45.8 (11.6) [n=189]	44.4 (12.1) [n=151]	1.38 (-1.16, 3.92)	2.29 (0.30 to 4.27)	p=0.02
8 months; Mean (SD)	43.9 (11.7) [n=181]	44.3 (12.0) [n=146]	-0.39 (-2.98, 2.20)	0.28 (-1.79 to 2.35)	p=0.79
12 months; Mean (SD)	43.4 (11.8) [n=185]	44.1 (11.2) [n=160]	-0.67 (-3.12, 1.77)	0.41 (-1.59 to 2.42)	p=0.68
SF-12 Physical[b]					
4 months; Mean (SD)	33.9 (10.0) [n=189]	33.2 (9.3) [n=151]	0.67 (-1.41, 2.75)	0.87 (-0.62 to 2.36)	p=0.25
8 months; Mean (SD)	34.2 (9.2) [n=181]	33.2 (9.4) [n=146]	0.97 (-1.07, 3.01)	1.06 (-0.52 to 2.65)	p=0.19
12 months; Mean (SD)	33.6 (8.8) [n=185]	33.8 (9.3) [n=160]	-0.24 (-2.15, 1.66)	-0.02 (-1.49, 1.44)	p=0.98
Pittsburgh SQI[b]					
4 months; Mean (SD)	11.2 (4.4) [n=177]	12.1 (4.2) [n=141]	-0.94 (-1.90, 0.01)	-0.65 (-1.38 to 0.08)	p=0.08
8 months; Mean (SD)	10.8 (4.5) [n=170]	11.8 (4.2) [n=140]	-0.97 (-1.96, 0.02)	-0.72 (-1.46 to 0.02)	p=0.06
12 months; Mean (SD)	11.3 (4.3) [n=175]	11.6 (4.4) [n=150]	-0.33 (-1.29, 0.62)	-0.10 (-0.82, 0.63)	p=0.80
HADS Anxiety[b]					
4 months; Mean (SD)	8.1 (4.8) [n=187]	8.3 (5.3) [n=149]	-0.16 (-1.25, 0.93)	-0.59 (-1.30 to 0.12)	p=0.10
8 months; Mean (SD)	8.3 (5.0) [n=176]	7.7 (5.0) [n=146]	0.59 (-0.51, 1.69)	0.27 (-0.44 to 0.99)	p=0.44
12 months; Mean (SD)	8.3 (5.0) [n=182]	7.8 (5.3) [n=157]	0.49 (-0.61, 1.59)	0.11 (-0.67 to 0.89)	p=0.78
HADS Depression[b]					
4 months; Mean (SD)	7.6 (4.4) [n=190]	8.1 (4.6) [n=150]	-0.55 (-1.53, 0.42)	-0.94 (-1.63 to -0.25)	p=0.01
8 months; Mean (SD)	7.9 (4.7) [n=181]	8.1 (4.5) [n=147]	-0.17 (-1.18, 0.83)	-0.35 (-1.04 to 0.34)	p=0.31
12 months; Mean (SD)	8.3 (4.8) [n=182]	7.7 (4.7) [n=156]	0.58 (-0.45, 1.60)	-0.02 (-0.77, 0.73)	p=0.95
Pain self-efficacy[b]					
4 months; Mean (SD)	31.2 (14.6) [n=189]	28.8 (14.7) [n=147]	2.39 (-0.78, 5.56)	4.19 (1.97 to 6.41)	p<0.001
8 months; Mean (SD)	30.4 (14.8) [n=180]	29.0 (14.4) [n=146]	1.37 (-1.84, 4.59)	2.05 (-0.18 to 4.28)	p=0.07
12 months; Mean (SD)	29.1 (15.2) [n=185]	29.1 (13.5) [n=159]	-0.01 (-3.08, 3.06)	1.43 (-0.87, 3.73)	p=0.22
EQ-5D-5L utility[b]					
4 months; Mean (SD)	0.43 (0.28) [n=228]	0.40 (0.30) [n=199]	0.03 (-0.03, 0.08)	0.57 (0.01 to 0.10)	p=0.02
8 months; Mean (SD)	0.39 (0.28) [n=197]	0.41 (0.29) [n=166]	-0.02 (-0.08, 0.04)	-0.001 (-0.05 to 0.05)	p=0.96
12 months; Mean (SD)	0.42 (0.28) [n=227]	0.41 (0.29) [n=209]	0.01 (-0.05, 0.06)	0.02 (-0.02 to 0.06)	p=0.32
EQ-5D-5L VAS[b]					
4 months; Mean (SD)	53.3 (22.6) [n=227]	51.6 (23.3) [n=199]	1.66 (-2.72, 6.04)	4.43 (0.70 to 8.16)	p=0.02
8 months; Mean (SD)	53.1 (23.2) [n=197]	51.5 (23.7) [n=165]	1.58 (-3.28, 6.44)	3.88 (-0.24 to 7.99)	p=0.06
12 months; Mean (SD)	52.0 (24.0) [n=228]	51.3 (23.7) [n=209]	0.68 (-3.81, 5.17)	2.35 (-1.62 to 6.32)	p=0.24
ShOWS[b]					
4 months; Mean (SD)	9.2 (5.1) [n=190]	9.6 (6.0) [n=150]	-0.4 (-1.59, 0.79)	-0.65 (-1.61 to 0.31)	p=0.18
8 months; Mean (SD)	9.3 (5.4) [n=181]	9.5 (5.2) [n=146]	-0.20 (-1.36, 0.97)	-0.29 (-1.20 to 0.61)	p=0.52
12 months; Mean (SD)	9.3 (5.4) [n=183]	9.4 (5.5) [n=156]	-0.11 (-1.27, 1.06)	-0.35 (-1.34, 0.65)	p=0.49

a Based on a heteroscedastic partially nested mixed-effect model with corrected degrees of freedom, adjusted for age, gender, baseline pain intensity, geographical location, baseline opioid band and baseline outcome score. The education support group was used as the cluster variable for the intervention arm, with clusters of size 1 used for each participant in usual care.

b See Table 1 footnotes f-m for information on scoring and calculations of each secondary outcome