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Reducing opioid use for chronic pain with a group-based intervention: a randomized clinical trial

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Key Points

Question: Among patients with chronic pain, does a multi-component intervention consisting of group meetings, education, individual support, and skill-based learning reduce opioid use and improve pain interference with daily activities, compared to usual care?

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

Meaning: Among patients with chronic pain due to non-malignant causes, a group-based educational intervention significantly reduced opioid use, but did not improve perceived pain,, 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 reduced opioid use and improved pain-related disability, compared to usual care.

Design, Setting, and Participants: Multicentered randomized clinical trial of 608 adults 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-long 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: The 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, MCID = 3.5) 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. 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 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 participants in usual care (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) of the intervention and 5% (16/303) of the usual care participants. The most common serious adverse events were Gastrointestinal (2% in intervention and 0% in usual care) and Locomotor/ Musculoskeletal (2% in intervention and 1% in usual care). Four people (1%) in the intervention group were hospitalised for possible or probable symptoms of opioid withdrawal (shortness of breath, hot flushes, fever and pain, small intestinal bleed, and an overdose suicide attempt). The most common adverse events (not requiring hospitalisation were) were psychological (2% in the intervention and 1% in the usual care group) and nervous system (2% in the intervention and <1% in the usual care group).

Conclusion and Relevance: In people with chronic pain due to non-malignant causes, compared to usual care, a group-based educational intervention that included group and individual support and skill-based learning significantly reduced patient-reported use of opioids, but had 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 for chronic non-malignant causes of pain, but are not superior to non-opioid therapy and are associated with 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 has potential to cause harm, including suicide, or mental health crisis.[4, 5] However, prior studies that used pain self-management, complementary medicine, pharmacological and biomedical intervention, and opioid replacement to reduce chronic opioid use were limited by poor study methodology or lack of evidence of safety.[6]

Multimodal treatment approaches that include nonpharmacologic strategies may prevent harm due to rapid tapering while 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 facilitated 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 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. Written informed consent was obtained by mail.

The trial protocol is available in the supplement (Supplement 1). The initial protocol was developed on 09/09/2016 and finalized on 02/10/2021 before any data were evaluated. The initial statistical analysis plan was completed on 05/08/2018 and finalized on 01/29/2019 before any data were analyzed.

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 and 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 3 months on most days in the preceding month for chronic non-malignant pain.[8] [eTable2 in Supplement 2] Race and ethnicity data were collected using self-report. Participants selected from fixed UK Census categories for race and ethnicity. Data on race and ethnicity were collected in order to evaluate the generalizability of results in the UK.

Potential participants with multiple prior prescriptions of strong opioids were identified from the electronic records of general (family) practices in the midlands and north-east geographic areas of EnglandPeople living in chronic care facilities (care homes) or unable to leave their home without assistance and those using methadone that was not prescribed for chronic pain

were excluded. Posters advertising the study were placed in clinics to identify potential volunteers. Eligibility was determined by telephone.

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

Randomization

Participants were randomized in a 1:1 ratio using a minimisation programme stratified by geographical locality (midlands/north-east of England), baseline score for pain intensity (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 performed by the WCTU programming team using Structured Query Language (SQL). Randomization was performed when at least 16 participants had completed baseline testing, since 16 participants was 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 a mutual 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 and led by a trained intervention nurse and by a lay person with chronic non-malignant pain and

experience with opioid tapering. Group topics for discussion included; education about opioids and withdrawal and skills-based learning for self-management of pain. Case studies illustrating successful opioid tapering and challenges were discussed. Participants also received an educational DVD, relaxation CD, mindfulness CD, and distraction techniques. 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 opioid tapering plan consisting of a reduction of 10% of the baseline dose each 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. Audio recordings of a 10% subset of intervention activities were analysed by the process evaluation team to assess intervention fidelity and the extent to which the intervention was delivered according to the manual of procedures.[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 measured at 12-month follow-up: 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, minimal clinically important difference (MCID) 3.5 [eTable 33 Supplement 2]) 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]. Results for both primary outcomes were from patient report, obtained by mailed questionnaire. Patients who did not return a mailed questionnaire

for the primary outcomes were telephoned. In addition, self-reported opioid use data were confirmed in a subsequent telephone call.

Validated MCID values specific to this intervention are not available for any outcome measures. MCID values are therefore based on existing literature [eTable 33-37 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.[eTable 30-32 and eFigure 1-2 in Supplement 2] Therefore, the primary outcome for opioid use was changed to the proportion of participants reporting no opioid use. This decision was made after looking at the blinded distribution of data.

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). MCID 3.5 [Supplement 2][15, 16]; Severity of Opioid Withdrawal (Symptoms) Short Opiate Withdrawal Scale (ShOWS)(Score range: 0-30, 30 indicates worst symptoms. MCID 3.0 [Supplement 2])[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, mental MCID 3.3, physical MCID 3.8 [eTable 34 Supplement 2],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, utility IMD 0.07, VAS MCID 7.0 [eTable 36 Supplement 2]) [18, 19]; sleep quality (Pittsburgh Sleep Quality Index (PSQI))(Score range: 0-21, 21 indicates worst sleep quality, MCID 3.0

[Supplement 2])[20]; emotional wellbeing (Hospital Anxiety and Depression Scale (HADS)) (Score range: 0-21, 21 indicates worst anxiety or depression, anxiety MCID 1.7, depression MCID 1.7 [eTable 35 Supplement 2])[21]; Self-efficacy (Pain Self Efficacy Questionnaire) (Score range: 0-60, 60 indicates strongest self-belief, MCID 7.0 [Supplement 2]]) (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. Additional secondary measures were the proportion of participants who reduced opioids by 50% from baseline, measured at four, eight and 12-months, and Pain Interference Short Form (8A) and the proportion of participants reporting no opioid use over the previous four weeks, measured at four and eight 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, opioid use and EQ-5D-5L.[19] Prescribed opioid medication from clinician records and use of healthcare resources were 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 (AEs) during their taper of opioids in each individual session by the nurse. The principal investigator and clinical members of the study team assessed/confirmed each adverse event. All AEs 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 attain a meaningful difference of 3.5 points difference on PROMIS-PI-SF-8A, equivalent to a standardise mean difference of 0.35, 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) and 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 analyses were according to treatment allocation at the time of randomisation. 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 statistical test.

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 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.

In 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 for this analysis, monotonicity was required. An inverse probability of missingness weighting (IPW) analysis was conducted as a sensitivity analysis to assess whether the missing data affected conclusions.[26]

A pre-specified subgroup analyses for the primary outcomes, testing for an 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 I 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 in 191 general practices, 2,220 potential participants expressed interest in study participation and 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 1] and [eTable7-9 in Supplement 2] mean age was 61 years (SD 12.9), 362 (60%) were female, and 588 (97%) gave their ethnicity as White British. At baseline, 34% (103/305) in the intervention group and 32% (98/303) in the usual care group were in the lowest opioid category (0-29.9 MED per day), with 12% (37/305) and 10% (29/303) in the highest opioid category (≥150 MED per day) in the intervention and usual care group respectively.[Table 1]

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 of attending at lease day one of the group sessions and a one-to-one session with the nurse., and 144 (47%) achieved full adherence to the programme. Median time from randomisation to the 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 the manual, was 83%, (range 25 to100 with a median of 88) and competence of 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 to manual mean of 91% (range 61 to 100) and competence mean of 93% (range 50 to 100%).[eTable 16-17 in Supplement 2]

Data for the PROMIS-PI-SF-8A were available from 439/608 (72%) participants and opioid use data were available from 433/608 (71%) participants at 12-month follow-up. PROMIS-PI-SF-8A scores improved in both groups over the 12-month trial: 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%) in usual care had discontinued opioids (absolute difference, 21.7% (95% CI, 14.8 to 28.6), p<0.001; odds ratio 5.55 (95% CI 2.80 to 10.99) [Table 2]).

Secondary Outcomes

Of 10 secondary outcomes, collected over three timepoints (i.e. total of 30 secondary outcome measurements), five were statistically significant. At 12 month follow-up, the proportion of participants who reduced daily MED by ≥50% from baseline was 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. The proportion of participants who reduced daily MED by 50% or more at four and eight month follow-up was also statistically significant [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 differences 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 Instrumental Variable analysis were not meaningfully different from the primary analysis.[eTable 19-20 in Supplement 2] However, the analyses were limited by model assumptions, and the fact that the clinical trial was not blinded. 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 (arthritis flare up, which resulted in a hospital admission) was possibly study related. In this participant, pain temporarily worsened by opioid withdrawal required 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, one expected (hospitalisation from joint/back pain) and two unexpected (surges in pain and hot sensations 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]. The most common adverse events were psychological xxx (2% in the intervention and 1% in the usual care group) and nervous system (2% in the intervention and <1% in the usual care group).

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 10 secondary outcomes measures, collected over 3 timepoints (a total of 30 secondary outcome measurements), only 5 of the measurements were statistically significant and improved in the intervention group, compared to control. Tapering of opioids was achieved through health care professional and peer group support rather than prescribing additional medications. The intervention consisted of establishing a therapeutic alliance with the patient and gradual opioid tapering, to reduce adverse effects 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, but opioid tapering was not an explicit goal in these randomized clinical trials. None of these found a statistically significant between group difference in opioid use.

Another 2022 systematic review identified two RCTs (N=238) of pain management programmes not based in primary care 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 included specific aims to reduce reliance on opioid through behaviour change and incorporated a bio-psycho-social framework.

A subsequent randomized clinical trial of 250 participants published in 2022 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 and no adverse events related to the intervention were reported.[29]

Limitations

This study had several limitations. First, participant opioid use was measured using self-report on a mailed questionnaire, with participant-report 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 reduce use of opioid medications than people who did not participate. Fifth, only 47% of participants randomized to the intervention fully adhered 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 at baseline. 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.

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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.

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References

1. Jones, M., et al., *A Brief History of the Opioid Epidemic and Strategies for Pain Medicine.* Pain and Therapy, 2018. **7**.
2. *Systematic Review: Opioid Treatments for Chronic Pain. Content last reviewed June 2022. Effective Health Care Program, Agency for Healthcare Research and Quality, Rockville, MD.* Accessed January 8, 2023. Available from: https://effectivehealthcare.ahrq.gov/products/opioids-chronic-pain/research.
3. Prevention, C.f.D.C.a. *Centers for Disease Control and Prevention; U.S. Opioid Dispensing Rate Maps*. 2021. Accessed January 8, 2023. Available from: https://www.cdc.gov/drugoverdose/rxrate-maps/index.html.
4. Agnoli, A., et al., *Association of Dose Tapering With Overdose or Mental Health Crisis Among Patients Prescribed Long-term Opioids.* Jama, 2021. **326**(5): p. 411-419.
5. Larochelle, M.R., et al., *Comparative Effectiveness of Opioid Tapering or Abrupt Discontinuation vs No Dosage Change for Opioid Overdose or Suicide for Patients Receiving Stable Long-term Opioid Therapy.* JAMA Netw Open, 2022. **5**(8): p. e2226523.
6. Avery, N., et al., *Efficacy of interventions to reduce long term opioid treatment for chronic non-cancer pain: systematic review and meta-analysis.* Bmj, 2022. **377**: p. e066375.
7. Eucker, S.A., M.R. Knisely, and C. Simon, *Nonopioid Treatments for Chronic Pain—Integrating Multimodal Biopsychosocial Approaches to Pain Management.* JAMA Network Open, 2022. **5**(6): p. e2216482-e2216482.
8. Committee, J.F., *British National Formulary (BNF) 75 March-September 2018*. 75th Revised edition ed. 2018: Pharmaceutical Press. 1600.
9. Sandhu, H.K., et al., *Development and testing of an opioid tapering self-management intervention for chronic pain: I-WOTCH.* BMJ Open, 2022. **12**(3): p. e053725.
10. Crawley, A., et al., *Tapering opioids using motivational interviewing.* Canadian Family Physician, 2018. **64**(8): p. 584-587.
11. Nichols, V.P., et al., *Process evaluation protocol for the I-WOTCH study: an opioid tapering support programme for people with chronic non-malignant pain.* BMJ open, 2019. **9**(10): p. e028998-e028998.
12. Song, M.K., M.B. Happ, and M. Sandelowski, *Development of a tool to assess fidelity to a psycho-educational intervention.* J Adv Nurs, 2010. **66**(3): p. 673-82.
13. Amtmann, D., et al., *Development of a PROMIS item bank to measure pain interference.* Pain, 2010. **150**(1): p. 173-182.
14. Sandhu, H.K., et al., *Testing a support programme for opioid reduction for people with chronic non-malignant pain: the I-WOTCH randomised controlled trial protocol.* BMJ Open, 2019. **9**(8): p. e028937.
15. Askew, R.L., et al., *Development of a crosswalk for pain interference measured by the BPI and PROMIS pain interference short form.* Qual Life Res, 2013. **22**(10): p. 2769-76.
16. Cook, K.F., et al., *Establishing a common metric for self-reported pain: linking BPI Pain Interference and SF-36 Bodily Pain Subscale scores to the PROMIS Pain Interference metric.* Qual Life Res, 2015. **24**(10): p. 2305-18.
17. Gossop, M., *The development of a Short Opiate Withdrawal Scale (SOWS).* Addict Behav, 1990. **15**(5): p. 487-90.
18. Gandek, B., et al., *Cross-validation of item selection and scoring for the SF-12 Health Survey in nine countries: results from the IQOLA Project. International Quality of Life Assessment.* J Clin Epidemiol, 1998. **51**(11): p. 1171-8.
19. Herdman, M., et al., *Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L).* Qual Life Res, 2011. **20**(10): p. 1727-36.
20. Buysse, D.J., et al., *The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research.* Psychiatry Res, 1989. **28**(2): p. 193-213.

21. Zigmond, A.S. and R.P. Snaith, *The hospital anxiety and depression scale.* Acta Psychiatr Scand, 1983. **67**(6): p. 361-70.
22. Nicholas, M.K., *The pain self-efficacy questionnaire: Taking pain into account.* Eur J Pain, 2007. **11**(2): p. 153-63.
23. Baldwin, S.A., et al., *Evaluating models for partially clustered designs.* Psychol Methods, 2011. **16**(2): p. 149-65.
24. Candlish, J., et al., *Appropriate statistical methods for analysing partially nested randomised controlled trials with continuous outcomes: a simulation study.* BMC Med Res Methodol, 2018. **18**(1): p. 105.
25. Gruber, J.S., et al., *Estimation of treatment efficacy with complier average causal effects (CACE) in a randomized stepped wedge trial.* Am J Epidemiol, 2014. **179**(9): p. 1134-42.
26. Seaman, S.R. and I.R. White, *Review of inverse probability weighting for dealing with missing data.* Stat Methods Med Res, 2013. **22**(3): p. 278-95.
27. STATA. Accessed July 15, 2021. Available from: https://www.stata.com.
28. de Kleijn, L., et al., *Opioid reduction for patients with chronic pain in primary care: systematic review.* Br J Gen Pract, 2022. **72**(717): p. e293-e300.
29. Garland, E.L., et al., *Mindfulness-Oriented Recovery Enhancement vs Supportive Group Therapy for Co-occurring Opioid Misuse and Chronic Pain in Primary Care: A Randomized Clinical Trial.* JAMA Internal Medicine, 2022. **182**(4): p. 407-417.
30. Cella, D., Gershon, R, Bass, M, Rothrock, N. *Assessment Centre*. 2013. Accessed January 11, 2023. Available from: https://www.assessmentcenter.net.

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]
Sex		
N	304	301
Male	125 (41%)	117 (39%)
Female	178 (59%)	184 (61%)
Other	1 (<1%)	0 (0%)
Race and ethnicity/ancestry[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, MED/d[e]		
0-29.9	103 (34%)	98 (32%)
30-59.9	95 (31%)	103 (34%)
60-89.9	42 (14%)	44 (15%)
90-119.9	18 (6%)	17 (6%)
120-149.9	10 (3%)	12 (4%)
≥150	37 (12%)	29 (10%)
Daily Morphine equivalence dose (mg); Median (IQR)	49 (25-81) [n=305]	44 (25-75) [n=303]
Baseline scale scores, mean (SD)		
Pain interference (PROMIS-8A)[f]	68.5 (6.0) [n=304]	68.2 (6.2) [n=301]
Pain intensity (PROMIS-3A)[g]	69.3 (6.8) [n=305]	68.8 (7.1) [n=303]
SF-12 Mental[h]	41 (10.8) [n=304]	41 (11.4) [n=301]
SF-12 Physical[h]	32 (8.1) [n=304]	32 (8.1) [n=301]
Pittsburgh SQI[i]	12 (4.3) [n=278]	12 (4.1) [n=285]
HADS Anxiety[j]	9 (5.1) [n=303]	9 (5.1) [n=298]
HADS Depression[j]	9 (4.6) [n=304]	9 (4.6) [n=298]
Pain self-efficacy[k]	24 (12.7) [n=301]	25 (13.6) [n=300]
EQ-5D-5L utility[l])	0.3 (0.3) [n=304]	0.4 (0.3) [n=301]
EQ-5D-5L VAS[l]	47 (21.4) [n=304]	49 (21.3) [n=301]
ShOWS[m]	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 minimal clinically important difference (MCID) 3.5 [eTable 33 Supplement 2]

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] MCID 3.5 [Supplement 2]

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 MCID 3.3, Physical MCID 3.8 [eTable 34 Supplement 2]

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. MCID 3.0 [Supplement 2]

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 MCID 1.7, depression MCID 1.7 [eTable 35 Supplement 2]

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. MCID 7.0 [Supplement 2]

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 MCID 0.07, VAS MCID 7.0 [eTable 36 Supplement 2]

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. MCID 3 [Supplement 2]

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. Indicative minimal clinically important difference (MCID) 3.5 [eTable 33 Supplement 2]

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.

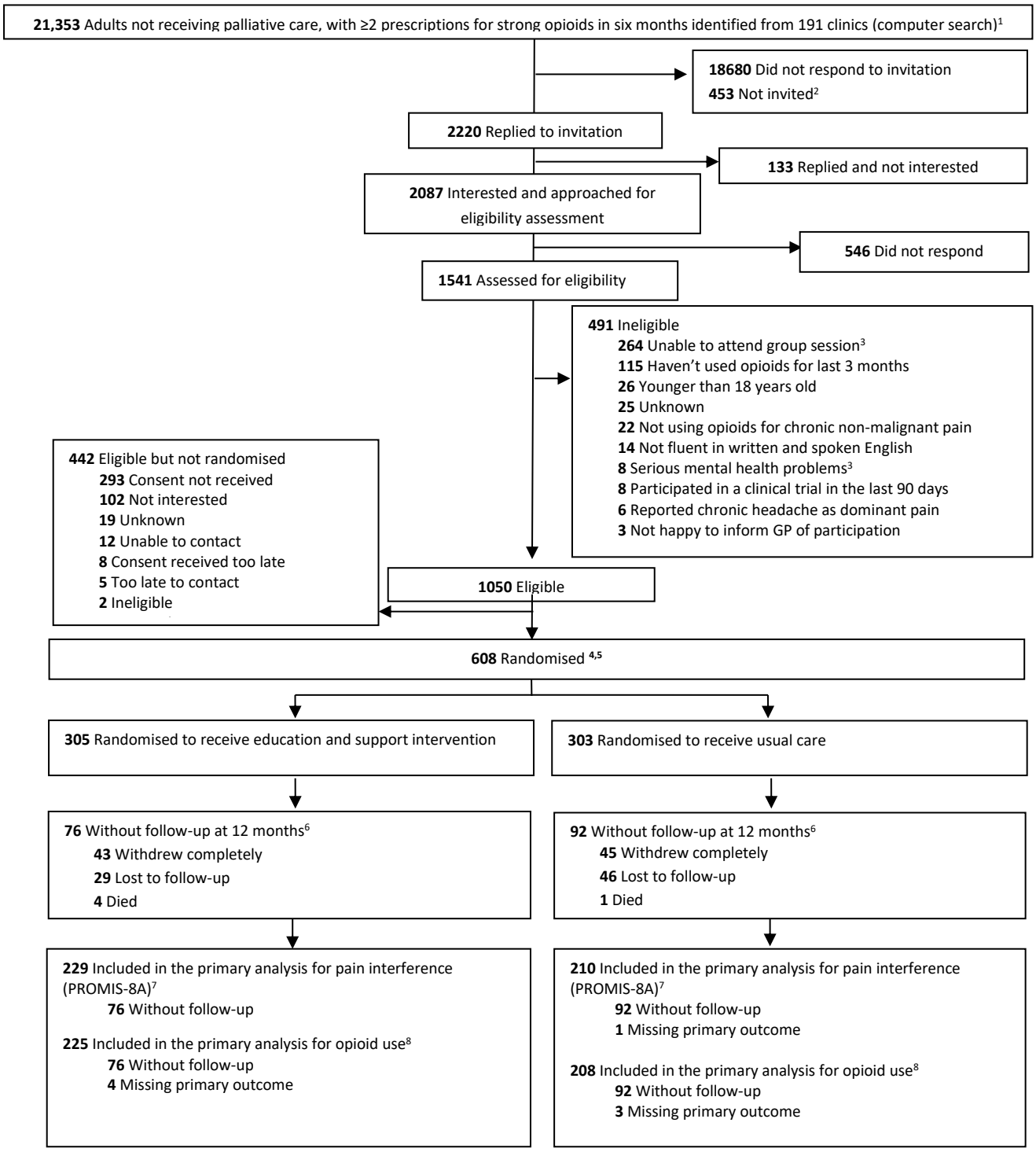
Table 3: Secondary outcomes

	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, MCID and calculations of each secondary outcome

Figure 1: Participant selection, randomisation, and follow-up



1: 9 Self-referrals, 5 Secondary care referrals.

2: GP practice felt it inappropriate to approach. Reasons including malignant pain, short life expectancy, care home resident/housebound, severe mental illness, active cancer causing pain.

3: One person listed both reasons

4: 2 Self-referrals, 2 Secondary care referrals.

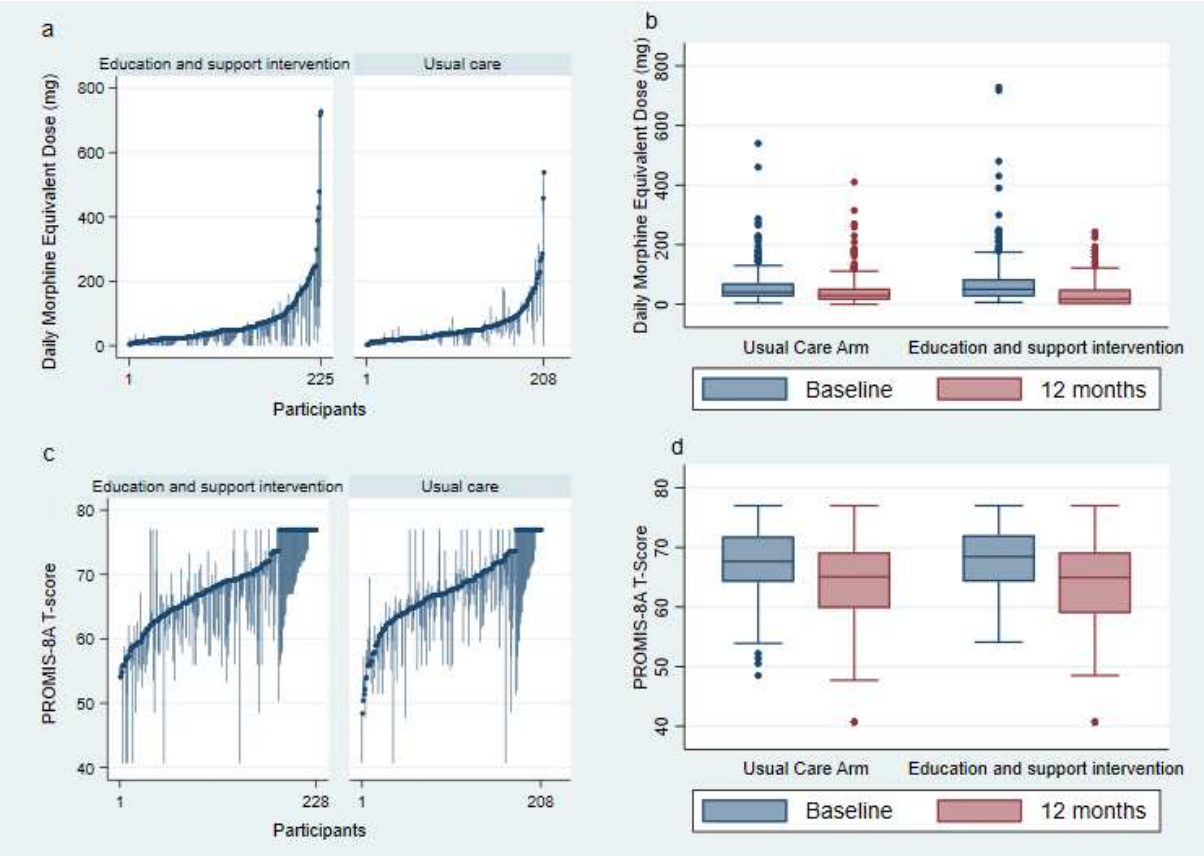
5: Randomisation stratified by geographical locality, baseline pain severity (low/high) and baseline morphine equivalent dose of opioids.

6: *See eTable 11 in Supplement 2 for follow-up rates and availability for secondary outcomes at 4 and 8 months. See eTable 10, 12-14 in Supplement 2 for information on withdrawals.*

7: Patient-reported Outcomes Measurement Information System (PROMIS) Pain interference Short Form (8A)

8: Opioid use calculated as morphine equivalent dose (MED) per day in the four weeks prior to 12-month follow-up.

Figure 2: Pain interference and morphine equivalent dose opioid use baseline and 12-month scores



The parallel line plots (a & c) contain a line for each participant in the study with baseline and 12-month data available. Each line starts at the baseline value (circle) and extends along the line to the 12-month value. The lower plot (c) shows the PROMIS-8A standardised T score, with higher scores signifying higher pain interference in daily life (See Table 1 footnote f for information on PROMIS-8A scoring and ranges). The higher plot (a) shows the daily morphine equivalent dose (continuous value) used in the previous 4 weeks from the timepoint. To the right are the corresponding box and whisker plots (b & d) with line and box indicating median and first and third quartile ranges, whiskers indicating 1.5x the interquartile range, and dots representing more extreme data.