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The effects of an evidence- and theory-informed feedback intervention on opioid prescribing for non-cancer pain in primary care: A controlled interrupted time series analysis

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Abstract

Background

The rise in opioid prescribing in primary care represents a significant international public health challenge, associated with increased psychosocial problems, hospitalisations, and mortality. We evaluated the effects of a comparative feedback intervention with persuasive messaging and action planning on opioid prescribing in primary care.

Methods and findings

A quasi-experimental controlled interrupted time series analysis used anonymised, aggregated practice data from electronic health records and prescribing data from publicly available sources. The study included 316 intervention and 130 control primary care practices in the Yorkshire and Humber region, UK, serving 2.2 million and 1 million residents, respectively. We observed the number of adult patients prescribed opioid medication by practice between July 2013 and December 2017. We excluded adults with coded cancer or drug dependency. The intervention, the Campaign to Reduce Opioid Prescribing (CROP), entailed bimonthly, comparative, and practice-individualised feedback reports to practices, with persuasive messaging and suggested actions over 1 year. Outcomes comprised the number of adults per 1,000 adults per month prescribed any opioid (main outcome), prescribed strong opioids, prescribed opioids in high-risk groups, prescribed other analgesics, and referred to musculoskeletal services. The number of adults prescribed any opioid rose pre-intervention in both intervention and control practices, by 0.18 (95% CI 0.11, 0.25) and 0.36 (95% CI 0.27, 0.46) per 1,000 adults per month, respectively. During the intervention period, prescribing per 1,000 adults fell in intervention practices (change −0.11; 95% CI −0.30, −0.08) and continued rising in control practices (change 0.54; 95% CI 0.29, 0.78),

with a difference of −0.65 per 1,000 patients (95% CI −0.96, −0.34), corresponding to 15,000 fewer patients prescribed opioids. These trends continued post-intervention, although at slower rates. Prescribing of strong opioids, total opioid prescriptions, and prescribing in high-risk patient groups also generally fell. Prescribing of other analgesics fell whilst musculoskeletal referrals did not rise. Effects were attenuated after feedback ceased. Study limitations include being limited to 1 region in the UK, possible coding errors in routine data, being unable to fully account for concurrent interventions, and uncertainties over how general practices actually used the feedback reports and whether reductions in prescribing were always clinically appropriate.

Conclusions

Repeated comparative feedback offers a promising and relatively efficient population-level approach to reduce opioid prescribing in primary care, including prescribing of strong opioids and prescribing in high-risk patient groups. Such feedback may also prompt clinicians to reconsider prescribing other medicines associated with chronic pain, without causing a rise in referrals to musculoskeletal clinics. Feedback may need to be sustained for maximum effect.

Author summary

Why was this study done?

- Opioid prescribing for non-cancer pain is rising despite limited knowledge on effectiveness and increasing evidence of harms, such as falls, fractures, overdose, and addiction.

- There are large differences in opioid prescribing between practices, suggesting prescribing is driven by clinician habits rather than patient need.

- We delivered evidence-based and theory-informed feedback reports to 316 general practices in Yorkshire, UK, every 2 months for 1 year, intended to reduce opioid prescribing by prompting physicians to think twice before starting patients on opioid medication and to review patients not currently benefiting from the medication.

What did the researchers do and find?

- We looked at trends in the number of patients prescribed opioids for non-cancer pain before, during, and after the intervention in 316 practices that received the feedback compared to 130 practices that did not.

- We also assessed changes in prescribing in patients at higher risk of longer or stronger opioid prescribing, and changes in the prescribing of other painkiller medications, to look at wider impacts on prescribing for pain.

- During the intervention period, the number of adults prescribed any opioid per 1,000 patients per month fell in intervention practices (change −0.11; 95% CI −0.30, −0.08) and rose in control practices (change 0.54; 95% CI 0.29, 0.78), with a difference of −0.65

(95% CI −0.96, −0.34), corresponding to 15,000 fewer patients prescribed opioids at the end of the intervention year.

- Prescribing of strong opioids, total opioid prescriptions, and prescribing in high-risk groups generally fell, although effects lessened after the feedback stopped.

- Prescribing of painkillers not specifically targeted by feedback also fell, without any increases in referrals to musculoskeletal services.

What do these findings mean?

- Repeated comparative feedback offers a promising and relatively efficient population-level approach to reduce opioid prescribing in primary care.

- Feedback may need to be sustained for maximum effect.

Introduction

Opioid prescribing is an internationally recognised threat to population health and a pressing challenge for healthcare services [1–5]. Prescription opioid use in the US has fallen little from 2010 peaks, despite increased awareness of risks and opioid abuse [6]. North America is experiencing an 'opioid crisis', with rapidly rising opioid-related mortality, initially due to prescription opioids and more recently due to illicit heroin and fentanyl use, reaching a peak in 2016 [7]. Other higher-income countries risk following similar trajectories [8]. These trends are largely attributed to prescribing for chronic non-cancer pain [9], where opioids are no more effective than non-opioid pain medications and are associated with increased falls, fractures, dependence, overdose, and mortality [10,11]. Despite increased awareness of the potential harms in opioid prescribing, prescription rates remain historically high in both North America and Europe [12–14].

Whilst a growing body of work has investigated problematic opioid prescribing [1,12,15–17], less attention has been paid to evaluating proposed solutions. A Cochrane review found inadequate evidence for interventions targeting opioid use in individuals with chronic pain [18]. However, more recent studies indicate the value of provider- and system-level interventions [19–21], including a multifaceted approach comprising nurse care management, an electronic registry, data-driven academic detailing, and electronic decision tools [20].

Observed large variations in opioid prescribing, up to 10-fold in a UK study of primary care practices, suggests that physician habits and norms are a major driver, rather than patient need and evidence of benefit [16]. An 'upstream' population approach would therefore aim to change physician behaviour around both initiating and continuing opioid prescribing. The audit and feedback approach involves giving healthcare providers a summary of their clinical performance over a specified period [22]. It generally has modest effects on healthcare practice, which can translate into substantial population impacts [22].

We devised and applied an evidence- and theory-informed feedback intervention, the Campaign to Reduce Opioid Prescribing (CROP), to reduce opioid prescribing in primary care by prompting physicians to initiate opioids with caution and review patients currently prescribed opioids with no clear individual benefit. We evaluated the effect of the feedback intervention

on prescribing of opioids and, anticipating the possibility of unintended consequences, prescribing of other analgesics and referrals to musculoskeletal services.

Methods

Study design and setting

In the UK, primary care is provided by general practices. Contracts for providing medical care relate to the practice rather than individual physicians. Patients are registered with a single practice rather than individual general practitioners, with an average practice list size of 9,000 patients and a single common electronic health record (EHR). The Yorkshire and Humber region covers an ethnically diverse population of 5.4 million residents with above average socioeconomic deprivation levels [23,24]. This study was conceived from our previous work that showed a rise in opioid prescribing in Leeds and Bradford, the 2 largest cities in West Yorkshire. Medicines optimisation leads, employed by clinical commissioning groups (CCGs), for West Yorkshire asked us to deliver an intervention to reduce opioid prescribing in this area. West Yorkshire (intervention group) has a population of 2.2 million residents served by 317 practices organised within 10 CCGs in 2016. One practice declined data sharing for this study. Five CCGs from the wider Yorkshire and Humber region (outside of West Yorkshire), with a population of 1 million residents and 130 practices, provided control data. We chose to use CCGs in the same region as our intervention sample for the control sample, as these would be subject to similar region-wide prescribing initiatives. Our main study population, and hence sample size, was therefore limited by the coverage of the data-sharing agreements. A further 3 CCGs in the region comprising 134 practices and approximately 650,000 residents were included as additional controls in an analysis using publicly available prescribing data.

We conducted a controlled interrupted time series (ITS) analysis. Controlled ITS is a quasi-experimental design used to evaluate the longitudinal effects of interventions, through regression modelling. The addition of a control group minimises potential confounding from concurrent interventions [25]. This design can detect whether an intervention effect is significantly greater than underlying trends and is appropriate in evaluating area-wide service improvement strategies when randomisation is not feasible [26,27].

Intervention

Evidence- and theory-informed feedback [28] to each practice reported the number of patients 18 years and older prescribed opioids in the preceding 8 weeks, excluding those with coded cancer, palliative care, or drug dependence, compared to other practices within their CCG and West Yorkshire, as well as changes over time. We did not define clinical categories, given highly variable diagnostic coding for painful conditions. Report content and formats followed a design previously demonstrated to reduce high-risk prescribing in primary care that addressed identified Theoretical Domains Framework determinants of adherence to quality indicators [28,29]. Reports emphasised 'thinking twice' before initiating opioids, rather than addressing the more complex patients prescribed multiple opioids (see S1 Text for the TIDieR summary and S2 Text for an illustrative report). Feedback highlighted patient groups at higher risk of long-term or stronger opioid prescribing: for example, individuals 75 years and older, individuals with coded mental health diagnoses, and individuals co-prescribed antidepressants [16]. The reports incorporated evidence-informed behaviour change techniques, such as specific recommendations for action and action plans, designed to enhance effectiveness [30]. Given the competing priorities and demands that primary care physicians face in routine practice, the reports used non-judgmental and encouraging language. We granted practices access to our EHR searches, allowing them to identify and review individual patients.

Practices received a total of 6 bimonthly reports. We posted 5 copies of each report to practice managers, and the local medicine optimisation leads emailed PDF copies to practice managers for 8 out of 10 CCGs.

The intervention did not involve any changes to existing musculoskeletal or pain services, which general practices and patients could access as usual throughout the study period.

Data sources and outcomes

Our primary outcome was the number of adults prescribed any opioid per 1,000 adults per month. Secondary outcomes included the number of adults prescribed any opioid per 1,000 adults per month in the high-risk groups highlighted in the feedback [16]. Co-prescription with antidepressants was used as a proxy for mental health illness to reflect our previous work that identified that mental health diagnoses are often poorly recorded in EHRs in the UK [31]. We collected retrospective aggregated, anonymised practice-level data for intervention and control CCGs through the centralised reporting of 2 EHR systems (The Phoenix Partnership SystmOne and EMIS Health), at monthly intervals for 3 periods: pre-intervention (1 July 2013 to 31 March 2016; 47 months), intervention (1 April 2016 to 31 March 2017; 12 months), and post-intervention (1 April 2017 to 31 December 2017; 9 months). We extracted data on numbers of adults prescribed opioids in the previous 8 weeks, excluding those ever coded with cancer, palliative care, or drug dependence. We categorised opioid strength according to World Health Organization reported potency [16]. 'Weaker' opioids (with or without acetaminophen or ibuprofen) comprised codeine, dihydrocodeine, tramadol, pethidine, meptazinol, and tapentadol. 'Strong' opioids comprised diamorphine, morphine, oxycodone, fentanyl, hydromorphone, buprenorphine (excluding preparations used for substance misuse), pentazocine, dipipanone, and papaveretum. We collected data to assess any potential wider impacts on prescribing for pain, specifically the number of adults prescribed non-steroidal anti-inflammatory drugs (NSAIDs) and gabapentinoids, and referrals to musculoskeletal services (see S3 Text for sample search). We converted the numbers of adults in a prescription category into monthly rates based on monthly numbers of relevant adults per practice. The denominator for all outcomes was the number of adults per practice per month, except for the number of adults aged over 75 years prescribed opioids, where the number of adults aged over 75 years per practice per month was used. No patient-level data were extracted to calculate morphine equivalent doses.

We collected monthly data on total opioid prescriptions from the publicly available OpenPrescribing database for the same time periods, to assess overall opioid prescribing trends for all intervention and control practices [32]. We converted the monthly prescribing data into opioid prescribing monthly rate per 1,000 patients based on the 2017–2018 practice list size. We collected data from the 2017–2018 Public Health England National General Practice Profiles [33] for practice-level variables, comprising practice list size; female-to-male patient ratio; percentage of patients with long-term conditions, as a proxy for disease burden; and percentage of patients reporting a positive experience of their practice, as a marker of satisfaction with care. We used the percentage of patients in employment and practice-level Index of Multiple Deprivation (IMD) score as markers of deprivation. The IMD measures area deprivation and is determined for each patient on the list, where available, and then averaged over the practice. We used overall achievement in the clinical domain of the Quality and Outcomes Framework —a performance management system whereby primary care practices are remunerated according to achievement of targets—as a measure of overall quality of care [34].

We estimated intervention costs based on known costs (e.g., postage and data extraction fees) and time spent by staff (full-time equivalent salaries). Potential opioid prescription

savings were calculated based on national opioid prescription costs and trends for the West Yorkshire population. A formal economic analysis was not conducted.

Data analysis

We used multilevel linear mixed-effects models (LMMs) for all outcomes. This was a 3-level model with a random intercept and random slope on month at the practice level, and a random intercept at the CCG level, with practice nested within CCG (S4 Text). The LMMs allowed the outcome to differ over time for each practice and accounted for correlations in outcomes over time within a practice and between practices within the same CCG area. A fixed-effect interaction term of intervention (control/intervention), the 3 intervention periods (pre-intervention/intervention/post-intervention), and month (July 2013 to December 2017) estimated the change in the outcomes over time across the 3 periods, and differences in change in outcomes between intervention and control practices, within a single model. We compared different structures of the covariance matrices (unstructured, independent, and identity) to assess which best accounted for autocorrelation. For all outcomes, the unstructured covariance (i.e., distinct variances and covariance) was the most appropriate, comparing both the Akaike information criterion (AIC) and Bayesian information criterion (BIC) values. Finally, each LMM included the predetermined practice characteristics as fixed effects, to assess whether any differences in the outcomes between the intervention and controls arms were due to practice differences. We checked that assumptions regarding autocorrelation—homoscedasticity of the residuals and normality of the residuals' distribution for LMMs—were not violated for all unadjusted and adjusted models. We confirmed that seasonality would not be an influence by reviewing changes in outcomes for each practice over time before developing models.

Sensitivity analysis (S5 Text) explored and confirmed the robustness of the modelling approaches, based on the main outcome adjusted LMM. We removed predicted values with residuals more than 2 or less than −2 to assess the impact of outliers; this made little difference to model estimates (S6 Text). Multicollinearity was not found for correlations between the practice characteristics ($\rho > 0.7$ and $p < 0.05$), and while some practice characteristics showed differences in rates of adults taking opioids at different levels of the practice characteristic (determined by including a 4-way interaction term with intervention, the 3 periods, and month), these differences did not change over time. Comparisons of AIC and BIC values for multilevel mixed-effects Poisson and negative binomial regression models and the adjusted LMM (all without CCG level due to convergence issues) for the main outcome indicated that the LMM was the most appropriate fit to the data (S6 Text).

We adhered to current reporting recommendations for ITS [35–37]. Our statistical analysis plan is provided (S7 Text).

Ethical approval

The University of Leeds School of Medicine Research Ethics Committee provided ethical approval for the evaluation (MREC 17–042).

Results

Intervention practices were similar to control practices but generally had larger list sizes, fewer patients with long-term conditions, and more deprived populations (Table 1). Before the intervention, the mean rate of adults prescribed opioids per 1,000 adults per month was 58.1 in intervention practices and 62.2 in control practices (Table 2). The number of patients at higher risk of long-term or stronger opioid prescribing who were prescribed opioids; the number of

Table 1. Summary of practice characteristics.

Dataset and group	Number of practices	Median list size (IQR)	Mean percent female (95% CI)	Median percent positive patient experience (IQR)[a]	Mean percent with LTC (95% CI)[b]	Median percent QOF score (IQR)[c]	Mean percent IMD (95% CI)[d]
CCG data							
Control practices	130	6,673 (4,102, 9,803)	49.4 (49.0, 51.6)	83.3 (76.5, 89.6)	55.4 (54.0, 58.1)	98.1 (96.1, 99.5)	28.9 (26.5, 32.1)
Intervention practices	313	7,550 (4,452, 10,540)	49.2 (48.8, 51.4)	83.8 (76.3, 89.7)	51.0 (50.0, 53.5)	98.1 (96.1, 99.4)	30.3 (28.9, 33.0)
OpenPrescribing data							
Control practices	264	7,131 (3,982, 9,878)	51.5 (48.0, 55.3)	86.4 (77.9, 91.6)	54.9 (53.9, 57.4)	98.6 (96.5, 99.8)	25.1 (23.3, 28.0)
Intervention practices	313	7,550 (4,452, 10,540)	49.2 (48.8, 51.4)	83.8 (76.3, 89.7)	51.0 (50.0, 53.5)	98.1 (96.1, 99.4)	30.3 (28.9, 33.0)

CCG, clinical commissioning group; GP, general practitioner; IMD, Index of Multiple Deprivation; LTC, long-term condition; QOF, Quality and Outcomes Framework.

[a]Results from GP patient survey question: 'Overall, how would you describe your experience of your GP practice'. The indicator value is the percentage of people who answered 'very good' or 'fairly good'.

[b]Results from GP patient survey question: 'Do you have any long-term physical or mental health conditions, disabilities or illnesses'. The indicator value is the percentage of people who answered 'Yes'.

[c]The percentage of all QOF points achieved across all domains as a proportion of all achievable points. (QOF is a financially incentivised quality improvement programme for all GP practices in England.)

[d]An overall measure of multiple deprivation experienced by people living in an area: the higher the score, the greater the deprivation.

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patients prescribed NSAIDs, gabapentin, or pregabalin; and the number of patients referred to musculoskeletal services were similar between intervention and control.

For the primary outcome, the rate of any opioid prescribing rose across all practices during the pre-intervention period, increasing more in control than in intervention practices, with an adjusted change in rate of 0.36 (95% CI 0.27, 0.46) and 0.18 (95% CI 0.11, 0.25) adults prescribed opioids per 1,000 per month, respectively (Table 3). During the intervention period, the opioid prescribing rate rose by 0.53 per 1,000 per month (95% CI 0.29, 0.77) in control practices but fell in intervention practices by 0.12 per 1,000 per month (95% CI −0.30, −0.07),

Table 2. Summary of opioid prescribing and other outcome-related characteristics at baseline for intervention and control practices.

Characteristic	Median (IQR) number of adults per 1,000 adults at baseline (2013 September)			
	CCG data		**OpenPrescribing data**	
	Control practices	**Intervention practices**	**Control practices**	**Intervention practices**
Opioid prescription	62.2 (49.7, 76.8)	58.1 (44.9, 71.9)	40.3 (30.6, 50.8)	34.5 (25.7, 44.7)
Strong opioid prescription	4.2 (2.8, 5.8)	4.9 (3.2, 7.0)		
Opioid prescription—patient >75 years	108.1 (83.9, 138.0)	119.5 (97.8, 143.7)		
Anti-depressant prescription	14.5 (10.0, 18.9)	12.8 (9.1, 17.0)		
Mental health diagnosis	23.9 (17.6, 32.3)	23.9 (17.7, 30.0)		
Benzodiazepine prescription	4.8 (3.3, 6.6)	3.9 (2.1, 5.9)		
Non-steroidal anti-inflammatory prescription	27.0 (20.2, 34.1)	27.9 (20.8, 40.5)		
Gabapentin prescription	8.0 (5.9, 10.8)	6.4 (4.5, 8.8)		
Pregabalin prescription	5.3 (3.5, 7.2)	5.2 (3.5, 7.2)		
Musculoskeletal referral	2.8 (1.9, 4.0)	3.5 (2.4, 4.6)		

CCG, clinical commissioning group.

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Table 3. Mean number of adults prescribed opioid per 1,000 adults and mean change per month: multilevel linear model—electronic health record data and denominator.

Outcome and time period	Month	Mean (95% CI) number of adults prescribed opioid per 1,000 adults			Mean (95% CI) change per month, over the time period		
		Control (n = 130)	Intervention (n = 213)	Difference	Control (n = 130)	Intervention (n = 213)	Difference
Adults prescribed opioid—unadjusted							
Pre-intervention	2013–09	57.3 (49.6, 64.9)	57.0 (50.0, 63.9)	−0.3 (−10.6, 10.0)	0.36 (0.27, 0.46)	0.18 (0.11, 0.25)	−0.18 (−0.30, −0.07)
	2016–03	68.2 (61.0, 75.4)	62.4 (55.7, 69.0)	−5.8 (−15.6, 3.9)			
Intervention	2016–04	63.9 (56.6, 71.1)	63.7 (57.0, 70.3)	−0.2 (−10.1, 9.6)	0.53 (0.29, 0.77)	−0.12 (−0.30, 0.07)	−0.65 (−0.95, −0.35)
	2017–03	69.7 (62.5, 77.0)	62.4 (55.7, 69.0)	−7.4 (−17.2, 2.5)			
Post-intervention	2017–04	66.3 (59.0, 73.5)	61.7 (55.0, 68.4)	−4.6 (−14.4, 5.3)	0.22 (−0.03, 0.46)	−0.04 (−0.24, 0.15)	−0.26 (−0.57, 0.05)
	2018–03	68.7 (61.3, 76.0)	61.2 (54.5, 68.0)	−7.4 (−17.4, 2.6)			
Adults prescribed opioid—adjusted[a]							
Pre-intervention	2013–09	55.0 (46.8, 63.2)	58.2 (50.6, 65.9)	3.2 (−8.0, 14.5)	0.36 (0.27, 0.46)	0.18 (0.11, 0.25)	−0.18 (−0.30, −0.07)
	2016–03	65.9 (58.2, 73.7)	63.6 (56.2, 71.0)	−2.3 (−13.1, 8.5)			
Intervention	2016–04	61.7 (53.8, 69.6)	64.9 (57.4, 72.4)	3.2 (−7.7, 14.0)	0.54 (0.29, 0.78)	−0.11 (−0.30, 0.08)	−0.65 (−0.96, −0.34)
	2017–03	67.6 (59.7, 75.5)	63.7 (56.2, 71.1)	−4.0 (−14.8, 6.9)			
Post-intervention	2017–04	64.2 (56.3, 72.1)	63.0 (55.5, 70.5)	−1.2 (−12.0, 9.7)	0.21 (−0.03, 0.46)	−0.05 (−0.24, 0.15)	−0.26 (−0.57, 0.05)
	2018–03	66.5 (58.6, 74.5)	62.5 (55.0, 70.0)	−4.0 (−15.0, 7.0)			
Adults prescribed strong opioid—adjusted[a]							
Pre-intervention	2013–09	3.9 (3.1, 4.7)	4.9 (4.2, 5.6)	1.0 (0.0, 2.1)	0.04 (0.03, 0.05)	0.04 (0.03, 0.05)	0.002 (−0.01, 0.01)
	2016–03	5.1 (4.4, 5.8)	6.2 (5.5, 6.8)	1.1 (0.1, 2.0)			
Intervention	2016–04	4.4 (3.7, 5.2)	6.2 (5.6, 6.8)	1.8 (0.8, 2.7)	0.01 (−0.01, 0.03)	−0.10 (−0.11, −0.08)	−0.11 (−0.13, −0.08)
	2017–03	4.6 (3.9, 5.3)	5.1 (4.5, 5.8)	0.6 (−0.4, 1.5)			
Post-intervention	2017–04	4.2 (3.5, 4.9)	5.1 (4.5, 5.7)	0.9 (−0.1, 1.8)	−0.03 (−0.05, −0.01)	−0.02 (−0.03, −0.003)	0.01 (−0.01, 0.04)
	2018–03	3.9 (3.2, 4.6)	4.9 (4.2, 5.5)	1.0 (0.1, 2.0)			
Adults aged >75 years prescribed opioid—adjusted[a]							
Pre-intervention	2013–09	81.9 (64.4, 99.3)	111.0 (95.8, 126.2)	29.1 (5.9, 52.3)	1.54 (1.33, 1.76)	0.77 (0.60, 0.94)	−0.78 (−1.05, −0.50)
	2016–03	128.2 (113.3, 143.1)	134.1 (120.6, 147.6)	5.9 (−14.3, 26.1)			
Intervention	2016–04	106.5 (91.5, 121.4)	137.4 (123.8, 151.0)	30.9 (10.7, 51.2)	1.82 (1.37, 2.27)	0.06 (−0.28, 0.41)	−1.76 (−2.33, −1.19)
	2017–03	126.5 (112.0, 141.0)	138.1 (124.8, 151.4)	11.6 (−8.2, 31.4)			

(Continued)

Table 3. (Continued)

Outcome and time period	Month	Mean (95% CI) number of adults prescribed opioid per 1,000 adults			Mean (95% CI) change per month, over the time period		
		Control (n = 130)	Intervention (n = 213)	Difference	Control (n = 130)	Intervention (n = 213)	Difference
Post-intervention	2017–04	118.1 (103.6, 132.6)	133.1 (119.8, 146.4)	15.0 (−4.8, 34.7)	0.72 (0.28, 1.17)	0.09 (−0.26, 0.45)	−0.63 (−1.20, −0.06)
	2018–03	126.1 (111.7, 140.5)	134.1 (120.9, 147.3)	8.1 (−11.6, 27.7)			
Adults co-prescribed an antidepressant with opioid—adjusted[a]							
Pre-intervention	2013–09	11.7 (9.7, 13.8)	11.7 (9.9, 13.5)	−0.03 (−2.8, 2.7)	0.1 (0.07, 0.14)	0.12 (0.09, 0.14)	0.02 (−0.03, 0.06)
	2016–03	14.8 (13.0, 16.7)	15.3 (13.6, 17.0)	0.4 (−2.1, 3.0)			
Intervention	2016–04	14.2 (12.3, 16.2)	16.2 (14.5, 18.0)	2.0 (−0.6, 4.6)	0.18 (0.09, 0.27)	−0.003 (−0.08, 0.07)	−0.18 (−0.30, −0.06)
	2017–03	16.2 (14.3, 18.2)	16.2 (14.4, 17.9)	−0.04 (−2.7, 2.6)			
Post-intervention	2017–04	15.4 (13.5, 17.4)	16.1 (14.3, 17.8)	0.7 (−2.0, 3.3)	0.13 (0.04, 0.23)	0.04 (−0.03, 0.11)	−0.09 (−0.21, 0.03)
	2018–03	16.9 (14.9, 18.9)	16.5 (14.7, 18.3)	−0.4 (−3.1, 2.3)			
Adults with a mental health diagnosis prescribed opioid—adjusted[a]							
Pre-intervention	2013–09	20.3 (16.0, 24.6)	22.3 (18.2, 26.4)	2.0 (−4.0, 7.9)	0.2 (0.16, 0.23)	0.14 (0.11, 0.16)	−0.06 (−0.11, −0.02)
	2016–03	26.2 (22.0, 30.4)	26.3 (22.3, 30.4)	0.1 (−5.8, 5.9)			
Intervention	2016–04	24.6 (20.4, 28.8)	27.0 (22.9, 31.0)	2.4 (−3.5, 8.2)	0.27 (0.19, 0.35)	0.03 (−0.03, 0.09)	−0.24 (−0.35, −0.14)
	2017–03	27.6 (23.4, 31.8)	27.3 (23.2, 31.3)	−0.3 (−6.2, 5.6)			
Post-intervention	2017–04	26.2 (22.0, 30.4)	27.0 (22.9, 31.1)	0.8 (−5.1, 6.7)	0.18 (0.10, 0.26)	0.08 (0.02, 0.15)	−0.1 (−0.20, 0.004)
	2018–03	28.2 (23.9, 32.5)	27.9 (23.8, 32.0)	−0.3 (−6.2, 5.6)			
Adults co-prescribed a benzodiazepine with opioid—adjusted[a]							
Pre-intervention	2013–09	5.9 (5.0, 6.7)	4.6 (3.9, 5.2)	−1.3 (−2.4, −0.2)	−0.02 (−0.04, 0.01)	0.02 (0.0002, 0.04)	0.04 (0.006, 0.07)
	2016–03	5.3 (4.6, 6.1)	5.2 (4.6, 5.7)	−0.2 (−1.1, 0.7)			
Intervention	2016–04	5.2 (4.4, 6.0)	5.5 (4.8, 6.1)	0.2 (−0.8, 1.3)	0.05 (−0.02, 0.13)	−0.03 (−0.09, 0.03)	−0.09 (−0.19, 0.01)
	2017–03	5.8 (5.0, 6.7)	5.1 (4.4, 5.7)	−0.8 (−1.8, 0.3)			
Post-intervention	2017–04	5.3 (4.5, 6.2)	5.3 (4.7, 6.0)	0.0 (−1.1, 1.1)	0.02 (−0.06, 0.09)	−0.07 (−0.13, −0.01)	−0.09 (−0.19, 0.01)
	2018–03	5.5 (4.6, 6.4)	4.5 (3.8, 5.3)	−1.0 (−2.2, 0.2)			
Adults prescribed a non-steroidal anti-inflammatory—adjusted[a]							
Pre-intervention	2013–09	35.2 (29.9, 40.6)	40.8 (36.1, 45.4)	5.5 (−1.6, 12.7)	−0.15 (−0.20, −0.10)	−0.08 (−0.12, −0.05)	0.07 (0.005, 0.13)
	2016–03	30.8 (25.8, 35.8)	38.3 (33.8, 42.7)	7.5 (0.8, 14.2)			

(*Continued*)

Table 3. (Continued)

Outcome and time period	Month	Mean (95% CI) number of adults prescribed opioid per 1,000 adults			Mean (95% CI) change per month, over the time period		
		Control (n = 130)	Intervention (n = 213)	Difference	Control (n = 130)	Intervention (n = 213)	Difference
Intervention	2016–04	28.7 (23.6, 33.7)	36.6 (32.2, 41.1)	8.0 (1.2, 14.7)	−0.1 (−0.25, 0.05)	−0.35 (−0.47, −0.24)	−0.25 (−0.44, −0.06)
	2017–03	27.6 (22.6, 32.6)	32.8 (28.3, 37.2)	5.2 (−1.5, 11.9)			
Post-intervention	2017–04	26.3 (21.4, 31.3)	30.8 (26.4, 35.2)	4.5 (−2.2, 11.2)	−0.11 (−0.26, 0.03)	−0.16 (−0.28, −0.04)	−0.04 (−0.23, 0.15)
	2018–03	25.1 (20.2, 30.0)	29.1 (24.7, 33.5)	4.0 (−2.7, 10.6)			
Adults prescribed gabapentin—adjusted[a]							
Pre-intervention	2013–09	6.6 (4.4, 8.8)	6.1 (4.3, 8.0)	−0.5 (−3.4, 2.5)	0.07 (0.04, 0.11)	0.11 (0.09, 0.14)	0.04 (−0.005, 0.08)
	2016–03	8.8 (6.6, 11.0)	9.5 (7.6, 11.3)	0.7 (−2.2, 3.5)			
Intervention	2016–04	9.0 (6.7, 11.3)	10.5 (8.6, 12.5)	1.5 (−1.5, 4.5)	0.1 (−0.04, 0.24)	−0.15 (−0.26, −0.04)	−0.25 (−0.42, −0.07)
	2017–03	10.1 (7.8, 12.4)	8.9 (7.0, 10.8)	−1.2 (−4.2, 1.8)			
Post-intervention	2017–04	10.2 (7.9, 12.4)	9.0 (7.0, 10.9)	−1.2 (−4.2, 1.8)	0.03 (−0.11, 0.17)	−0.02 (−0.13, 0.09)	−0.05 (−0.23, 0.13)
	2018–03	10.5 (8.2, 12.7)	8.7 (6.8, 10.6)	−1.7 (−4.7, 1.2)			
Adults prescribed pregabalin—adjusted[a]							
Pre-intervention	2013–09	8.4 (7.0, 9.7)	5.0 (3.9, 6.1)	−3.4 (−5.1, −1.6)	−0.07 (−0.11, −0.04)	0.06 (0.04, 0.09)	0.14 (0.10, 0.18)
	2016–03	6.1 (4.8, 7.5)	6.8 (5.7, 7.9)	0.7 (−1.0, 2.5)			
Intervention	2016–04	5.6 (4.1, 7.1)	6.3 (5.1, 7.5)	0.7 (−1.2, 2.6)	−0.03 (−0.17, 0.10)	−0.02 (−0.13, 0.08)	0.01 (−0.16, 0.18)
	2017–03	5.3 (3.8, 6.8)	6.0 (4.8, 7.2)	0.8 (−1.2, 2.7)			
Post-intervention	2017–04	3.4 (1.9, 4.9)	5.2 (4.0, 6.4)	1.8 (−0.1, 3.8)	0.25 (0.11, 0.39)	0.24 (0.14, 0.35)	−0.01 (−0.18, 0.17)
	2018–03	6.1 (4.6, 7.6)	7.9 (6.7, 9.1)	1.8 (−0.2, 3.7)			
Adults referred to musculoskeletal services—adjusted[a]							
Pre-intervention	2013–09	2.7 (2.0, 3.3)	3.8 (3.2, 4.4)	1.1 (0.3, 2.0)	0.02 (0.009, 0.03)	0.004 (−0.005, 0.01)	−0.02 (−0.03, −0.002)
	2016–03	3.3 (2.8, 3.8)	3.9 (3.4, 4.4)	0.6 (−0.1, 1.3)			
Intervention	2016–04	3.4 (2.8, 3.9)	4.2 (3.7, 4.6)	0.8 (0.1, 1.5)	−0.02 (−0.04, 0.01)	0.003 (−0.01, 0.02)	0.02 (−0.008, 0.05)
	2017–03	3.2 (2.7, 3.7)	4.2 (3.7, 4.7)	1.0 (0.3, 1.7)			
Post-intervention	2017–04	3.3 (2.8, 3.9)	4.5 (4.0, 5.0)	1.1 (0.4, 1.9)	−0.05 (−0.07, −0.02)	−0.05 (−0.07, −0.04)	−0.01 (−0.04, 0.02)
	2018–03	2.8 (2.3, 3.4)	3.9 (3.4, 4.4)	1.1 (0.3, 1.8)			

[a]Adjusted for percent female, Quality and Outcomes Framework score, percentage of patients reporting a positive experience of their practice, percentage of patients with long-term conditions, and Index of Multiple Deprivation.

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Fig 1. Mean number of adults prescribed opioid per 1,000 adults: multilevel linear model estimates: Electronic health record data and denominator.
Adjusted for percent female, Quality and Outcomes Framework score, percentage of patients reporting a positive experience of their practice, percentage of patients with 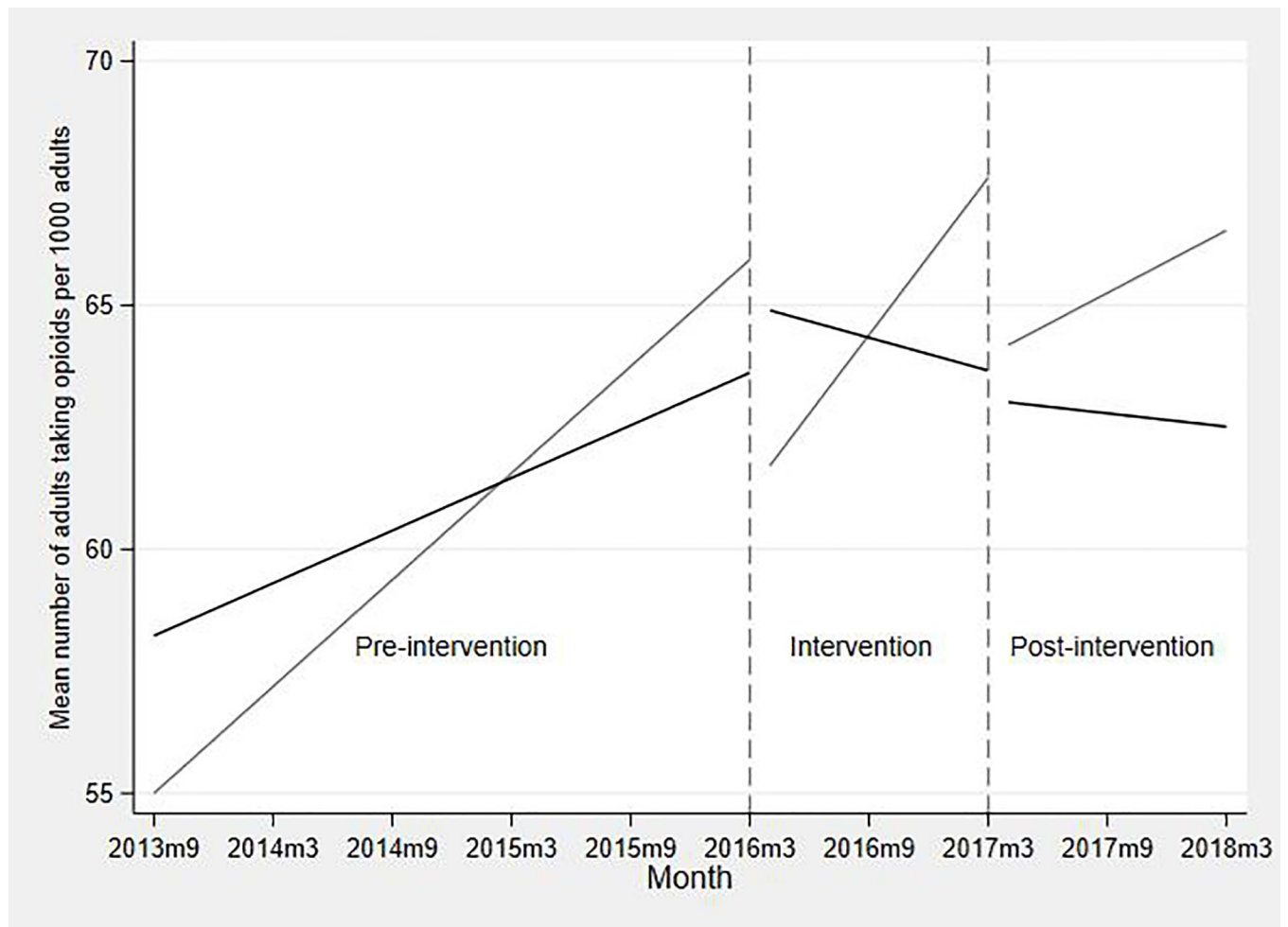long-term conditions, and Index of Multiple Deprivation. Black line = intervention practices; grey line = control practices.

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a difference of 0.65 (95% CI −0.95, −0.35; Fig 1). Post-intervention, the opioid prescribing rates decreased in both groups, with a smaller difference in mean change per month between the control and intervention practices of 0.26 (95% CI −0.57, 0.05). By the final month of follow-up, there was a mean difference of 7.4 (95% CI −17.4, 2.6) per 1,000 adults prescribed opioids between control and intervention practices. We estimate that this corresponds to around 15,000 fewer adults prescribed opioids during the intervention year in our total intervention population of 1.9 million. Estimated intervention effects changed little after adjustment for practice characteristics, and therefore adjusted estimates are shown.

We observed trends generally favouring the intervention for groups at higher risk of long-term or stronger opioid prescribing. During the intervention, the rate of strong opioid prescribing decreased more in intervention than control practices (−0.11; 95% CI −0.13, −0.08), although rates in both groups similarly declined post-intervention. The rate of opioid prescribing in those aged 75 years and over decreased more in intervention practices than in control practices during the intervention period (−1.76; 95% CI −2.33, −1.19), with a sustained, if reduced, post-intervention difference (−0.63; 95% CI −1.20, −0.06). During the intervention

Table 4. Mean number of prescriptions for opioids per 1,000 adults: Multilevel linear model—OpenPrescribing data, Public Health England National General Practice Profiles denominator.

Time period	Month	Mean (95% CI) number of prescriptions for opioids per 1,000 adults			Mean (95% CI) change per month, over the time period		
		Control (*n* = 264)	Intervention (*n* = 313)	Difference	Control (*n* = 264)	Intervention (*n* = 313)	Difference
Pre-intervention	2013–09	38.7 (33.2, 44.2)	33.5 (29.3, 37.6)	−5.3 (−12.1, 1.6)	0.11 (0.06, 0.15)	0.11 (0.09, 0.14)	0.01 (−0.04, 0.06)
	2016–03	41.9 (36.6, 47.2)	36.9 (32.9, 40.9)	−5.0 (−11.7, 1.7)			
Intervention	2016–04	43.3 (38.0, 48.6)	37.9 (33.9, 41.9)	−5.4 (−12.1, 1.3)	0.02 (−0.05, 0.10)	−0.08 (−0.13, −0.03)	−0.10 (−0.19, −0.01)
	2017–03	43.5 (38.2, 48.8)	37.0 (33.0, 41.1)	−6.5 (−13.2, 0.2)			
Post-intervention	2017–04	43.7 (38.4, 49.0)	37.1 (33.0, 41.1)	−6.7 (−13.4, 0.0)	−0.03 (−0.10, 0.05)	−0.05 (−0.10, 0.001)	−0.02 (−0.11, 0.07)
	2018–03	43.4 (38.1, 48.8)	36.5 (32.5, 40.6)	−6.9 (−13.6, −0.2)			

CCG and practice levels, adjusted for percent female, Quality and Outcomes Framework score, percentage of patients reporting a positive experience of their practice, percentage of patients with long-term conditions, and Index of Multiple Deprivation.

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period, rates of opioid prescribing fell more per month in intervention practices than in control practices in adults co-prescribed an antidepressant (−0.18; 95% CI −0.30, −0.06) and in adults with a mental health diagnosis (−0.24; 95% CI −0.35, −0.14), although post-intervention differences were not sustained. Rates of co-prescribed benzodiazepines did not differ significantly between intervention and control practices.

Regarding other analgesics, we observed declining pre-intervention trends for NSAID prescribing, with a larger decrease in intervention practices than control practices during the intervention (−0.35; 95% CI −0.47, −0.24) and both groups having similar post-intervention decreases. Rates of gabapentin prescribing decreased more in intervention practices than control practices during the intervention period (−0.25; 95% CI −0.42, −0.07), but this was not the case for pregabalin prescribing (0.01; 95% CI −0.16, 0.18). We observed no differences in rates of musculoskeletal referrals between intervention and control practices during the intervention period (0.02; 95% CI −0.008, 0.05) or after (0.01; 95% CI −0.04, 0.02).

Using publicly available data for total opioid prescriptions, we observed rising pre-intervention trends for both groups, a small decline during the intervention in intervention practices (−0.1; 95% CI −0.19, −0.01), and fairly static post-intervention rates in both groups (Table 4).

The results of a simple (uncontrolled) ITS of intervention practices mirrored those of the controlled ITS (Table 5). This provides greater confidence that any association between the intervention and the effect is likely to be causal, and provides evidence that the control practices did not experience some other event [35].

We estimated that the feedback intervention cost approximately US$66,000 to deliver, including US$52,000 in staff costs, US$3,200 in data extraction fees, and US$5,200 in stationary costs. Nationally, opioid prescription costs rose by approximately US$26,000 per 100,000 population during the intervention year. The reduction in opioid prescribing equated to around US$1,155,000 savings across intervention CCGs. The intervention gave overall cost savings of US$1,000,000 once all costs were accounted for.

Discussion

We observed that repeated evidence- and theory-informed comparative feedback reversed a rising trend of opioid prescribing in primary care, with sustained, if attenuated, effects. We have therefore demonstrated a successful, scalable strategy to reduce population-level opioid prescribing. The feedback intervention had a modest effect, with a difference of 0.65 fewer adults prescribed any opioid per 1,000 per month in intervention practices compared to

Table 5. Mean number of adults prescribed opioid per 1,000 adults: Multilevel linear model—electronic health record data and denominator, intervention only model (*n* = 313).

Time period	Month	Mean (95% CI) number of adults prescribed opioid per 1,000 adults—adjusted	Mean (95% CI) change per month, over the timeframe
Pre-intervention	2013–09	57.1 (54.3, 70.6)	0.18 (0.10, 0.25)
	2016–03	62.4 (55.6, 72.1)	
Intervention	2016–04	63.7 (55.5, 71.9)	−0.12 (−0.32, 0.08)
	2017–03	62.4 (54.3, 70.6)	
Post-intervention	2017–04	61.8 (53.6, 70.0)	−0.04 (−0.25, 0.16)
	2018–03	61.3 (53.1, 69.6)	

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control practices. However, at a population level, there were substantially fewer patients taking prescribed opioid medications.

The number of patients prescribed strong opioids fell during the intervention, although at a slower rate than the number of patients prescribed any opioid, possibly reflecting a longer de-prescribing process than for weaker opioids, given the need for gradual reductions to limit withdrawal symptoms. The intervention also had sustained effects for patients in targeted high-risk groups, including adults with coded mental health diagnoses and those co-prescribed antidepressants. The greatest effect was in adults aged 75 years and older, with a greater reduction in intervention practices than control practices of almost 1.8 adults aged 75 years and older prescribed opioids per 1,000 per month. This is important given the heightened risks of premature mortality, associated falls, and unplanned hospital admissions in this population [38,39].

Contrary to expectations, we observed reductions in wider analgesic prescribing not specifically targeted by feedback, specifically of NSAIDs and gabapentin, and no increases in referrals to musculoskeletal services. This provides some reassurance that the intervention had few rebound effects on wider service utilisation and costs. Indeed, it may have prompted primary care physicians to think differently about the value of prescribing analgesics in chronic non-cancer pain, and to prefer self-management options.

Prescribing data from publicly available sources [32] confirm that the intervention changed the underlying trend of rising opioid prescriptions, although it levelled off rather than fell. The smaller effect in this dataset is likely due to additional 'noise' in these data, which include prescriptions for cancer pain and drug dependency, especially as primary care physicians are encouraged to prescribe stronger opioids earlier and longer for palliative care [40].

There is a growing evidence base on the value of provider- and system-level interventions to reduce opioid use in adults with chronic non-cancer pain [19–21,41,42]. We provide evidence for a relatively efficient and scalable population strategy to address prescribing of both weaker and stronger opioids. The widespread use of EHR systems means that primary care prescribing data can be used to both drive and monitor change at a relatively low cost [43–45]. Our estimated costs suggest this intervention is relatively efficient given potential savings in projected opioid prescription costs.

Our intervention incorporated a range of evidence- and expert-informed suggestions to improve the effectiveness of feedback, such as providing repeated feedback with comparators to reinforce desired behaviour, recommending specific actions, and ensuring credibility of information [30]. However, the success of our strategy may also have depended upon

contextual factors, specifically the timing and nature of the targeted clinical behaviour [46]. The intervention occurred during a period when primary care physicians were becoming increasingly aware of an opioid prescription problem and recognised a need for action. Feedback, used alone or with other interventions, may not be effective in changing all types of clinical behaviour [29]; opioid prescribing represents a relatively discrete behaviour that is reasonably within physician control [30].

We highlight 5 limitations. First, our study took place in a single region, potentially limiting generalisability to the rest of the UK and other healthcare systems. However, primary care physicians internationally report similar types of challenges in managing opioid prescribing [47], and performance feedback has been shown to work in many settings [22]. As only 1 out of 317 practices declined participation, selection bias is unlikely. We also demonstrated effects in a population with relatively high levels of socioeconomic deprivation, a factor that is associated with higher levels of opioid prescribing [48].

Second, routinely collected data are prone to coding errors. Such errors are less likely for prescribing data, but our use of 'ever coded' diagnoses may have overestimated current diagnoses, especially cancer and drug dependence. Some practices may have responded to feedback by re-categorising patients as drug dependent, thereby taking them out of the denominator and inflating intervention effects. However, we observed similar patterns of reductions in OpenPrescribing data. Sensitivity analysis showed that 'extreme' values, possibly due to coding errors, did not affect model estimates. Furthermore, the modelling approaches accounted for missing data within practices.

Third, the quasi-experimental design cannot fully account for concurrent interventions. Our previous publication showing the rise in prescribing in this area may have alerted practices to rising opioid prescribing [16]. Media attention to the North American 'opioid crisis' during the intervention period may also have influenced prescribing behaviour. Media coverage of the scale of UK opioid prescribing began towards the end of the intervention period and is unlikely to significantly account for observed changes in opioid prescribing [49,50]. Use of control practices [26] and a simple ITS analysis provides greater confidence that any association between intervention and effect is likely to be causal.

Fourth, this study did not specifically examine the acceptability of the feedback reports and whether or how they were used by general practices. This will be addressed in a separate process evaluation.

Fifth, we cannot be certain whether reductions in opioid prescribing were always clinically appropriate as we did not assess individual patient clinical indications and outcomes. The absence of any increases in prescribing of other potentially harmful analgesics and in referrals suggests that the intervention did not generate increased demand.

Patients have strong expectations for prescription pain relief, making reductions in prescribing challenging if they are perceived as undermining therapeutic relationships and patient satisfaction. Strategies to bring about significant improvements in healthcare delivery are unlikely to succeed if they fail to address multiple barriers and enablers. Addressing the rise of opioid prescribing and its legacy is likely to require sustained, coordinated efforts across all levels of healthcare systems that target organisational, clinical, and patient behaviours [51]. Performance feedback offers one approach that can be coupled with complementary educational campaigns and decision support to change physician prescribing habits and patient expectations [22]. We welcome further research to determine whether our findings can be replicated in other healthcare systems. There are further opportunities to evaluate and enhance feedback effectiveness, ideally involving head-to-head comparisons of different ways of delivering feedback within randomised designs [52].

Conclusions

We observed that an evidence- and theory-informed feedback intervention reversed rising opioid prescribing trends in a primary care setting. Effects decreased following cessation of the feedback, which may need to be sustained for maximum long-term impact. We observed no concurrent increases in prescribing of other analgesics or demand for musculoskeletal services. Feedback therefore offers a scalable approach to reduce population-level opioid prescribing.

Supporting information

S1 Text. TIDieR checklist for the Campaign to Reduce Opioid Prescribing intervention, incorporating the reporting and design elements of audit and feedback intervention recommendations.
(PDF)

S2 Text. Sample practice report. The baselayer of the map used in this file is from https://commons.wikimedia.org/wiki/File:England_Clinical_Commissioning_Group_(CCG)_Map_(Labelled).svg.
(PDF)

S3 Text. Primary outcome search terms for The Phoenix Partnership SystmOne electronic health record system.
(PDF)

S4 Text. Multilevel linear mixed-effects model.
(PDF)

S5 Text. Sensitivity analysis.
(PDF)

S6 Text. Mean number of adults prescribed opioid per 1,000 adults: Multilevel linear model—electronic health record data and denominator, residuals ±2 removed.
(PDF)

S7 Text. Statistical analysis plan.
(PDF)

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References

1. Kiang MV, Humphreys K, Cullen MR, Basu S. Opioid prescribing patterns among medical providers in the United States, 2003–17: retrospective, observational study. BMJ. 2020; 368:l6968. https://doi.org/10.1136/bmj.l6968 PMID: 31996352

2. Kalkman GA, Kramers C, van Dongen RT, van den Brink W, Schellekens A. Trends in use and misuse of opioids in the Netherlands: a retrospective, multi-source database study. Lancet Public Health. 2019; 4(10):E498–505. https://doi.org/10.1016/S2468-2667(19)30128-8 PMID: 31444001

3. Fredheim OMS, Mahic M, Skurtveit S, Dale O, Romundstad P, Borchgrevink PC. Chronic pain and use of opioids: a population-based pharmacoepidemiological study from the Norwegian Prescription Database and the Nord-Trøndelag Health Study. Pain. 2014; 155(7):1213–21. https://doi.org/10.1016/j.pain.2014.03.009 PMID: 24637039

4. Lalic S, Gisev N, Bell JS, Korhonen MJ, Ilomäki J. Predictors of persistent prescription opioid analgesic use among people without cancer in Australia. Br J Clin Pharmacol. 2018; 84(6):1267–78. https://doi.org/10.1111/bcp.13556 PMID: 29451672

5. Rosner B, Neicun J, Yang JC, Roman-Urrestarazu A. Opioid prescription patterns in Germany and the global opioid epidemic: systematic review of available evidence. PLoS ONE. 2019; 14(8):e0221153. https://doi.org/10.1371/journal.pone.0221153 PMID: 31461466

6. Jeffery MM, Hooten WM, Henk HJ, Bellolio MF, Hess EP, Meara E, et al. Trends in opioid use in commercially insured and Medicare Advantage populations in 2007–16: retrospective cohort study. BMJ. 2018; 362:k2833. https://doi.org/10.1136/bmj.k2833 PMID: 30068513

7. Ballantyne JC, Mao J. Opioid therapy for chronic pain. N Engl J Med. 2003; 349(20):1943–53. https://doi.org/10.1056/NEJMra025411 PMID: 14614170

8. Berterame S, Erthal J, Thomas J, Fellner S, Vosse B, Clare P, et al. Use of and barriers to access to opioid analgesics: a worldwide, regional, and national study. Lancet. 2016; 387(10028):1644–56. https://doi.org/10.1016/S0140-6736(16)00161-6 PMID: 26852264

9. Ray WA, Chung CP, Murray KT, Hall K, Stein C. Prescription of long-acting opioids and mortality in patients with chronic noncancer pain. JAMA. 2016; 315(22):2415–23. https://doi.org/10.1001/jama.2016.7789 PMID: 27299617

10. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. JAMA. 2016; 315(15):1624–45. https://doi.org/10.1001/jama.2016.1464 PMID: 26977696

11. Krebs EE, Gravely A, Nugent S, Jensen AC, DeRonne B, Goldsmith ES, et al. Effect of opioid vs nonopioid medications on pain-related function in patients with chronic back pain or hip or knee osteoarthritis pain: the space randomized clinical trial. JAMA. 2018; 319(9):872–82. https://doi.org/10.1001/jama.2018.0899 PMID: 29509867

12. Jani M, Birlie Yimer B, Sheppard T, Lunt M, Dixon WG. Time trends and prescribing patterns of opioid drugs in UK primary care patients with non-cancer pain: a retrospective cohort study. PLoS Med. 2020; 17(10):e1003270. https://doi.org/10.1371/journal.pmed.1003270 PMID: 33057368

13. Schieber LZ, Guy GP Jr, Seth P, Young R, Mattson CL, Mikosz CA, et al. Trends and patterns of geographic variation in opioid prescribing practices by state, United States, 2006–2017. JAMA Netw Open. 2019; 2(3):e190665. https://doi.org/10.1001/jamanetworkopen.2019.0665 PMID: 30874783

14. Verhamme KMC, Bohnen AM. Are we facing an opioid crisis in Europe? Lancet Public Health. 2019; 4 (10):e483–4. https://doi.org/10.1016/S2468-2667(19)30156-2 PMID: 31444002

15. Curtis HJ, Croker R, Walker AJ, Richards GC, Quinlan J, Goldacre B. Opioid prescribing trends and geographical variation in England, 1998–2018: a retrospective database study. Lancet Psychiatry. 2019; 6(2):140–50. https://doi.org/10.1016/S2215-0366(18)30471-1 PMID: 30580987

16. Foy R, Leaman B, McCrorie C, Petty D, House A, Bennett M, et al. Prescribed opioids in primary care: cross-sectional and longitudinal analyses of influence of patient and practice characteristics. BMJ Open. 2016; 6(5):e010276. https://doi.org/10.1136/bmjopen-2015-010276 PMID: 27178970

17. Zin CS, Chen L-C, Knaggs RD. Changes in trends and pattern of strong opioid prescribing in primary care. Eur J Pain. 2014; 18(9):1343–51. https://doi.org/10.1002/j.1532-2149.2014.496.x PMID: 24756859

18. Eccleston C, Fisher E, Thomas KH, Hearn L, Derry S, Stannard C, et al. Interventions for the reduction of prescribed opioid use in chronic non-cancer pain. Cochrane Database Syst Rev. 2017; 11(11): CD010323. https://doi.org/10.1002/14651858.CD010323.pub3 PMID: 29130474

19. Katzman JG, Qualls CR, Satterfield WA, Kistin M, Hofmann K, Greenberg N, et al. Army and navy ECHO pain telementoring improves clinician opioid prescribing for military patients: an observational cohort study. J Gen Intern Med. 2019; 34(3):387–95. https://doi.org/10.1007/s11606-018-4710-5 PMID: 30382471

20. Liebschutz JM, Xuan Z, Shanahan CW, LaRochelle M, Keosaian J, Beers D, et al. Improving adherence to long-term opioid therapy guidelines to reduce opioid misuse in primary care: a cluster-randomized clinical trial. JAMA Intern Med. 2017; 177(9):1265–72. https://doi.org/10.1001/jamainternmed.2017.2468 PMID: 28715535

21. Samet JH, Tsui JI, Cheng DM, Liebschutz JM, Lira MC, Walley AY, et al. Improving the delivery of chronic opioid therapy among people living with human immunodeficiency virus: a cluster randomized clinical trial. Clin Infect Dis. 2020 Jul 22. https://doi.org/10.1093/cid/ciaa1025 PMID: 32697847

22. Ivers N, Jamtvedt G, Flottorp S, Young JM, Odgaard-Jensen J, French SD, et al. Audit and feedback: effects on professional practice and healthcare outcomes. Cochrane Database Syst Rev. 2012; 6: CD000259. https://doi.org/10.1002/14651858.CD000259.pub3 PMID: 22696318

23. Race Disparity Unit. Regional ethnic diversity. GOV.UK; 2020 [cited 2021 Sep 16]. Available from: https://www.ethnicity-facts-figures.service.gov.uk/uk-population-by-ethnicity/national-and-regional-populations/regional-ethnic-diversity/latest.

24. Department for Communities and Local Government. The English indices of deprivation 2010: statistical release. London: Department for Communities and Local Government; 2011.

25. Shadish WR, Cook TD, Campbell DT. Experimental and quasi-experimental designs for generalized causal inference. Boston: Houghton Mifflin; 2002. https://doi.org/10.1037/1082-989x.7.1.3 PMID: 11928889

26. Fretheim A, Zhang F, Ross-Degnan D, Oxman AD, Cheyne H, Foy R, et al. A reanalysis of cluster randomized trials showed interrupted time-series studies were valuable in health system evaluation. J Clin Epidemiol. 2015; 68(3):324. https://doi.org/10.1016/j.jclinepi.2014.10.003 PMID: 25499983

27. Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. J Clin Pharm Ther. 2002; 27(4):299–309. https://doi.org/10.1046/j.1365-2710.2002.00430.x PMID: 12174032

28. Glidewell L, Willis TA, Petty D, Lawton R, McEachan RRC, Ingleson E, et al. To what extent can behaviour change techniques be identified within an adaptable implementation package for primary care? A prospective directed content analysis. Implement Sci. 2018; 13(1):32. https://doi.org/10.1186/s13012-017-0704-7 PMID: 29452582

29. Willis TA, Collinson M, Glidewell L, Farrin AJ, Holland M, Meads D, et al. An adaptable implementation package targeting evidence-based indicators in primary care: a pragmatic cluster-randomised evaluation. PLoS Med. 2020; 17(2):e1003045. https://doi.org/10.1371/journal.pmed.1003045 PMID: 32109257

30. Brehaut JC, Colquhoun HL, Eva KW, Carroll K, Sales A, Michie S, et al. Practice feedback interventions: 15 suggestions for optimizing effectiveness. Ann Intern Med. 2016; 164(6):435–41. https://doi.org/10.7326/M15-2248 PMID: 26903136

31. McLintock K, Russell AM, Alderson SL, West R, House A, Westerman K, et al. The effects of financial incentives for case finding for depression in patients with diabetes and coronary heart disease: interrupted time series analysis. BMJ Open. 2014; 4(8):e005178. https://doi.org/10.1136/bmjopen-2014-005178 PMID: 25142262

32. EBM DataLab. OpenPrescribing. Oxford: University of Oxford; 2017.

33. Public Health England. National general practice profiles. London: Public Health England; 2021 [cited 2021 Sep 16]. Available from: https://fingertips.phe.org.uk/profile/general-practice.

34. Doran T, Fullwood C, Gravelle H, Reeves D, Kontopantelis E, Hiroeh U, et al. Pay-for-performance programs in family practices in the United Kingdom. N Engl J Med. 2006; 355(4):375–84. https://doi.org/10.1056/NEJMsa055505 PMID: 16870916

35. Lopez Bernal J, Cummins S, Gasparrini A. The use of controls in interrupted time series studies of public health interventions. Int J Epidemiol. 2018; 47(6):2082–93. https://doi.org/10.1093/ije/dyy135 PMID: 29982445

36. Hudson J, Fielding S, Ramsay CR. Methodology and reporting characteristics of studies using interrupted time series design in healthcare. BMC Med Res Methodol. 2019; 19(1):137. https://doi.org/10.1186/s12874-019-0777-x PMID: 31272382

37. Turner SL, Karahalios A, Forbes AB, Taljaard M, Grimshaw JM, Korevaar E, et al. Creating effective interrupted time series graphs: review and recommendations. Res Synth Methods. 2021; 12(1):106–17. https://doi.org/10.1002/jrsm.1435 PMID: 32657532

38. Reid MC, Henderson CR, Papaleontiou M, Amanfo L, Olkhovskaya Y, Moore AA, et al. Characteristics of older adults receiving opioids in primary care: treatment duration and outcomes. Pain Med. 2010; 11 (7):1063–71. https://doi.org/10.1111/j.1526-4637.2010.00883.x PMID: 20642732

39. Daoust R, Paquet J, Moore L, Émond M, Gosselin S, Lavigne G, et al. Recent opioid use and fall-related injury among older patients with trauma. CMAJ. 2018; 190(16):E500–6. https://doi.org/10.1503/cmaj.171286 PMID: 29685910

40. Chapman EJ, Edwards Z, Boland JW, Maddocks M, Fettes L, Malia C, et al. Practice review: evidence-based and effective management of pain in patients with advanced cancer. Palliat Med. 2020; 34 (4):444–53. https://doi.org/10.1177/0269216319896955 PMID: 31980005

41. Tadrous M, Greaves S, Martins D, Nadeem K, Singh S, Mamdani MM, et al. Evaluation of the fentanyl patch-for-patch program in Ontario, Canada. Int J Drug Policy. 2019; 66:82–6. https://doi.org/10.1016/j.drugpo.2019.01.025 PMID: 30743092

42. Chen T-C, Chen L-C, Knaggs RD. A 15-year overview of increasing tramadol utilisation and associated mortality and the impact of tramadol classification in the United Kingdom. Pharmacoepidemiol Drug Saf. 2018; 27:487–94. https://doi.org/10.1002/pds.4320 PMID: 28944519

43. Curtis HJ, Goldacre B. OpenPrescribing: normalised data and software tool to research trends in English NHS primary care prescribing 1998–2016. BMJ Open. 2018; 8(2):e019921. https://doi.org/10.1136/bmjopen-2017-019921 PMID: 29476029

44. Hallsworth M, Chadborn T, Sallis A, Sanders M, Berry D, Greaves F, et al. Provision of social norm feedback to high prescribers of antibiotics in general practice: a pragmatic national randomised controlled trial. Lancet. 2016; 387(10029):P1743–52. https://doi.org/10.1016/S0140-6736(16)00215-4 PMID: 26898856

45. Guthrie B, Kavanagh K, Robertson C, Barnett K, Treweek S, Petrie D, et al. Data feedback and behavioural change intervention to improve primary care prescribing safety (EFIPPS): multicentre, three arm, cluster randomised controlled trial. BMJ. 2016; 354:i4079. https://doi.org/10.1136/bmj.i4079 PMID: 27540041

46. Brown B, Gude WT, Blakeman T, van der Veer SN, Ivers N, Francis JJ, et al. Clinical Performance Feedback Intervention Theory (CP-FIT): a new theory for designing, implementing, and evaluating feedback in health care based on a systematic review and meta-synthesis of qualitative research. Implement Sci. 2019; 14(1):40. https://doi.org/10.1186/s13012-019-0883-5 PMID: 31027495

47. Desveaux L, Saragosa M, Kithulegoda N, Ivers NM. Understanding the behavioural determinants of opioid prescribing among family physicians: a qualitative study. BMC Fam Pract. 2019; 20(1):59. https://doi.org/10.1186/s12875-019-0947-2 PMID: 31077137

48. Mordecai L, Reynolds C, Donaldson LJ, de C Williams AC. Patterns of regional variation of opioid prescribing in primary care in England: a retrospective observational study. Br J Gen Pract. 2018; 68(668): e225–33. https://doi.org/10.3399/bjgp18X695057 PMID: 29440012

49. Gornall J. Exposed: national disgrace as a quarter of a million patients are turned into drug addicts by their doctors. The Daily Mail. 2017 Mar 28.

50. Rhodes D. NHS accused of fuelling rise in opioid addiction. BBC News. 2018 Mar 15 [cited 2021 Sep 20]. Available from: https://www.bbc.co.uk/news/uk-england-43304375.

51. Ferlie EB, Shortell SM. Improving the quality of health care in the United Kingdom and the United States: a framework for change. Milbank Q. 2001; 79(2):281–315. https://doi.org/10.1111/1468-0009.00206 PMID: 11439467

52. Grimshaw J, Ivers N, Linklater S, Foy R, Francis JJ, Gude WT, et al. Reinvigorating stagnant science: implementation laboratories and a meta-laboratory to efficiently advance the science of audit and feedback. BMJ Qual Saf. 2019; 28(5):416–23. https://doi.org/10.1136/bmjqs-2018-008355 PMID: 30852557