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Pain

Association of opioid prescribing practices with chronic pain and benzodiazepine co-prescription: a primary care data linkage study

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Abstract

Background: Opioid prescribing is increasing worldwide with associated increases in misuse and other harms. We studied variations in national opioid prescription rates, indicators of prescribing quality, co-prescribing of benzodiazepines and relationship with pain severity in Scotland.

Methods: Electronic linkages of opioid prescribing in Scotland were determined from: (i) national data from Information Services Division, NHS Scotland (2003–2012); and (ii) individual data from Generation Scotland: Scottish Family Health Study. Descriptive analyses were conducted on national data, multilevel modelling to examine factors associated with variations in prescribing rates. χ^2 tests examined associations between individual pain severity and opioid prescriptions.

Results: The number of strong opioid prescriptions more than doubled from 474 385 in 2003 to 1 036 446 in 2012, and weak opioid prescribing increased from 3 261 547 to 4 852 583. In Scotland, 938 674 individuals were prescribed an opioid in 2012 (18% of the population). Patients in the most deprived areas were 3.5 times more likely to receive a strong opioid than patients in the least deprived. There was significant variation in prescribing rates between geographical areas, with much of this explained by deprivation. Of women aged 25–40 yr prescribed a strong opioid, 40% were also prescribed a

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benzodiazepine. There was significant association between pain severity and receipt of opioid prescription. Over 50% of people reporting severe pain were not prescribed an opioid analgesic.
Conclusions: We found opioid prescribing in primary care to be common and increasing in Scotland, particularly for severe pain. Co-prescribing of opioids and benzodiazepines was common.

Keywords: benzodiazepines; chronic pain; data linkage; general practice; opioids

Editor's key points

- Opioid prescribing has been increasing with an alarming increase in misuse and negative outcomes.
- National data from Scotland were analysed to determine overall opioid prescribing patterns and associations with sociodemographics, pain, and benzodiazepine use.
- From 2003 to 2012, strong opioid prescriptions doubled, with 18% of the population prescribed an opioid in 2012.
- There were significant associations between opioid prescribing with pain and regional and sociodemographic factors, although many patients with severe pain did not receive opioid prescriptions.
- Co-prescription of an opioid with a benzodiazepine was common despite potentially dangerous drug interactions.

There is good evidence for the efficacy of opioids in acute and cancer pain, and variable evidence of short-to medium-term efficacy in chronic non-cancer pain.[1,2] There are no good long-term studies of the efficacy of opioids for patients with chronic pain.[3] Despite this, in many regions, most notably North America, western and central Europe, Australia and New Zealand, there is evidence of increasing prescribing of opioids,[3–9] although with significant variation between countries. Concerns have been raised about a worldwide 'opioid epidemic' and about the potential and actual risks.[10–13] The reasons for greatly increased prescribing are complex, and might include the wider range of opioids and routes of administration available, changes in social and cultural factors that encourage prescribing, and an aging population with a higher incidence of pain. Much of the published opioid prescribing data originate in North America, where there have been parallel increases in serious adverse outcomes. These include increasing rates of opioid misuse and dependence and unintentional fatal overdose. In the USA, ~63% of overdose deaths in 2015 involved a prescription opioid.[10,14–18] It is unclear how this translates to the UK and Europe, where healthcare systems differ.

Reservations have been expressed about the effectiveness of opioid drugs for long-term management of persistent painful conditions, such as low back pain[16] and fibromyalgia,[19] especially in situations in which dose-related harms might outweigh benefits.[20,21] The most recent European guidelines specifically recommended against their use for fibromyalgia.[19] Systematic reviews find minor adverse events (such as nausea, constipation, and headache) are common,[22] although other serious adverse events associated with longer-term use (especially high doses) can occur, including prescription opioid dependence,[22] impaired cognitive function,[23] endocrine dysfunction,[24] and opioid-induced hyperalgesia.[25,26]

These serious adverse outcomes, or harms, are also associated with co-prescription of opioids with benzodiazepines, as both are central nervous system and respiratory depressants and can decrease respiratory drive. Concurrent use is likely to put patients at greater risk of potentially fatal overdose and dependence, and clinicians are advised to avoid co-prescribing.[3,27]

In primary care, prescribing of weak opioids is relatively common, with 8% of the Norwegian population being prescribed codeine in a single year.[28] In a 3 yr study of new users of weak opioids, 7% received a prescription at least once per year, although only 0.3% and 0.08% developed prescription patterns indicating 'persistent' and 'problematic' opioid use, respectively.[29] These findings suggest that, despite the high and increasing use of weak opioids in the population, the majority of patients are able to stop opioid treatment when their acute pain condition resolves, and challenges the perception of a high risk of misuse.[29,30] There is also evidence that many patients with severe pain are not prescribed opioid analgesics and in those with persistent opioid use, strong or very strong pain is reported despite this treatment.[30] In the context of increasing rates of opioid prescribing, there is therefore conflicting evidence about the safety and appropriateness of prescribing for chronic pain.

We aimed to describe national opioid prescription rates in Scotland, seeking sociodemographic factors associated with variations in prescribing and indicators of quality of prescribing, specifically co-prescribing of benzodiazepines. To explain these at an individual level, we examined the association between receipt of opioid prescriptions and the presence and severity of chronic pain.

Methods

Data sources

National level data

The National Health Service (NHS) in Scotland is a publicly-funded healthcare system that is universally used by the 5.3 million residents. It is administered through 14 geographical NHS Boards. In 2009, the Prescribing Information System was developed as a national individual level dataset of prescriptions issued, dispensed and reimbursed within the community in Scotland.[31] All prescribing data are stored securely by the Information Services Division (ISD), part of NHS National Services Scotland (http://www.isdscotland.org/). Data held on each prescription include the date, strength, formulation and quantity of both generic and proprietary drugs issued. Data on reimbursed prescription items were used in this study. A full history of all prescription items for an individual patient are grouped using a unique NHS person identifier [Community Health Index (CHI) number]. The CHI number can also be linked to other datasets and provides basic demographic information including sex, year of birth and postcode.[31]

NHS Scotland spends £1.3 billion a year on medicines, with around £1 billion of the expenditure spent on medicines dispensed in primary care (http://www.gov.scot/Publications/2015/07/4244/8). General practitioners (GPs) account for more than 95% of community prescribing and CHI capture from prescriptions is high at 98.7% for GP prescribers.[31]

We examined 10 yr prescribing trends (2003–2012) for all opioid drugs across Scotland. Taking a snapshot of 1 yr (2012), we analysed the rates and variations of prescribing by:

(i) the number of patients who received at least one opioid prescription during the year;
(ii) age and sex of patients;
(iii) Scottish Index of Multiple Deprivation (SIMD) for patients' place of residence for 2012. SIMD is based on residential postcode and grouped into quintiles, ranking those areas from most deprived (ranked 1) to least deprived (ranked 5)[32] and by urban/rural classification based on the Scottish Government Urban Rural Classification (http://www.gov.scot/Topics/Statistics/About/Methodology/UrbanRuralClassification);
(iv) all geographical NHS Board areas in Scotland (n=14);
(v) GP practices (n=1007), which were also stratified into high, medium and, low prescribers based on tertile values of the number of defined daily doses (DDDs) of opioids per day, prescribed by the practice;
(vi) co-prescribing with opioids, to examine:
  (a) potential for increase in serious CNS side effects as a result of co-prescribing of benzodiazepines;
  (b) indicators of effective management of common side effects (constipation and nausea) with co-prescribing of laxatives and antiemetics.

We included all individuals who received a prescription for an opioid from a GP in the period of the study. As ISD data were not associated with the clinical indication for the prescribing, we were unable to exclude individuals for whom pain was not the main indication, or those with cancer.

As these data are anonymised, ethical approval was not required.

Individual level data—Generation Scotland: Scottish Family Health Study

We conducted a prescribing linkage examining the association between receipt of opioids and severity of chronic pain using data from Generation Scotland: Scottish Family Health Study (GS:SFHS) for GS participants who were residents in NHS Greater Glasgow and Clyde, NHS Fife or NHS Tayside. GS:SFHS is a general population-based cohort of extended families, with detailed clinical data and DNA from 23 960 individuals, recruited through primary care between 2006 and 2011, mainly from Tayside and Glasgow. A detailed description of GS:SFHS, including recruitment, data collection and baseline epidemiology, has been published.[33]

In GS:SFHS, chronic pain was defined as reported pain or discomfort persisting longer than 3 months,[34] completed at the time of recruitment to the study. The Chronic Pain Grade (CPG) questionnaire was used to assess pain severity based on intensity and pain-related disability in the previous 3 months.[35] The CPG is a seven-item instrument that classifies severity into four hierarchical grades: Grade I (low disability-low intensity), Grade II (low disability-high intensity), Grade III (high disability-moderately limiting), and Grade IV (high disability-severely limiting). Clinically significant chronic pain was defined as those with CPG II-IV, representing those with high pain intensity, high pain-related disability, or both, and participants were categorised as 'no chronic pain', 'mild' (CPG I) and 'severe' chronic pain (CPG II–IV). We stratified this analysis by age, sex, and potency of prescribed opioids.

Individual GS:SFHS participants' prescribing data were linked using CHI by the Health Informatics Centre (HIC) at the University of Dundee and NHS Greater Glasgow and Clyde then pseudo-anonymised and stored in the HIC Safe Haven. GP prescribing for the cohort in the 6 months before and after their questionnaire submission was analysed.

Prescribing data

Prescribing data from ISD included both the number of prescription items and the number of DDDs. DDD is a World Health Organisation standard quantitative unit of measurement defined as the assumed average maintenance dose per day for the medication's main indication in adults (http://www.whocc.no/atc_ddd_index/). DDD was calculated by ISD analysts based on WHO definitions.

ISD data for 2012 by NHS Board were analysed as: (i) DDDs per 1000 population per day, and (ii) prescription items per 1000 population. GS:SFHS analysis was based on the number of dispensed prescriptions.

Opioids and benzodiazepines

Opioid drugs in Chapter 4.7.2 of the British National Formulary[36] were included, subdivided according to the categories of 'strong' and 'weak' opioids with strong opioids classified as controlled drugs in 2012.[36] *Strong opioids* were buprenorphine, dipipanone, fentanyl, hydromorphone, methadone, morphine, oxycodone, papaveretum, pentazocine, pethidine and tapentadol. *Weak opioids* were codeine, dihydrocodeine, meptazinol and tramadol. 'Combination, products' such as co-codamol were categorised according to the strength of the parent opioid (e.g. codeine). Benzodiazepines included chlordiazepoxide, diazepam, loprazolam, lorazepam, lormetazepam, nitrazepam, oxazepam, and temazepam.

Statistical analysis

Mainly descriptive analyses were conducted on the national level data released by ISD. Multilevel modelling at NHS Board level was conducted, and a two-level linear regression model was used with GP practices nested within NHS Boards to examine factors associated with variations in prescribing rates. The first step was a null model (a model with no covariates), which served as a baseline for the other models. The null model was used to detect how much unexplained variation stems from NHS Board level. The intraclass correlation was calculated to determine the relevance of the NHS Board. The next model (Final model) added the effects of the SIMD quintile and urban/rural classification. For this, the outcome was number of DDDs per 1000 population per year. Negative binomial regression was performed to estimate the effect of age and sex on opioids prescribing rates overall. χ^2 tests were performed to examine associations between categorical variables (pain severity and receipt of an opioid prescription) in the GS:SFHS linkage; and Kruskal–Wallis and Mann–Whitney tests examined comparisons between the number of prescriptions in the three pain groups. Data were analysed using SAS (SAS Institute, USA), SPSS for Windows, v. 22 (IBM, USA),

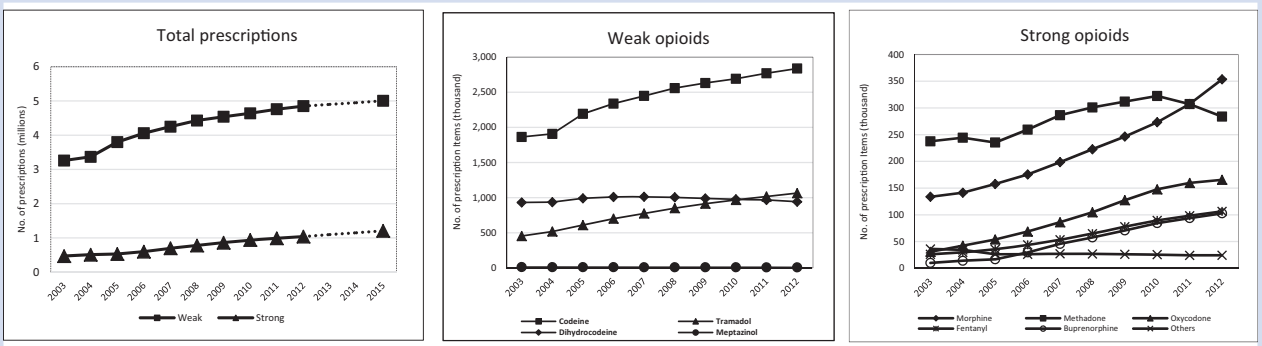

Fig 1. Trends in opioids prescribing in Scotland (2003–2012).

and R, v. 3.2.0 (R Foundation for Statistical Computing, Austria).

Results

National data

Prescribing of both weak and strong opioids increased steadily over the 10 yr period 2003–2012. The number of strong opioid prescription items more than doubled, from 474 385 in 2003 to 1 036 446 in 2012 (Fig. 1). Weak opioid prescribing increased from 3 261 547 prescription items to 4 852 583 million. Additional aggregate data obtained from ISD show that the number of prescriptions continued to increase, with 1 206 187 strong opioid prescriptions and 5 005 405 weak opioids dispensed in 2015 (Fig. 1).

In 2012, 938 674 individuals in Scotland were prescribed an opioid (18% of the population), with codeine being the most commonly prescribed drug (>658 000 individuals), followed by tramadol (>206 000). Morphine was the most commonly prescribed strong opioid (>40 000 people, Supplementary Table S1).

Sociodemographic factors

The age and sex distributions of prescribing of weak and strong opioids are shown in Fig. 2. With weak opioids, rates varied significantly with increasing age ($P<0.001$) and with sex, with higher rates of prescribing found among women ($P<0.001$). With strong opioids prescribing, rates increased significantly with age ($P<0.001$), but there was no significant difference found for sex ($P=0.192$).

People living in the most deprived SIMD quintile were three and four times more likely to be dispensed a prescription for a weak or strong opioid, respectively, than patients in the least deprived areas (Fig. 2).

NHS boards and GP practices

There was clear variation in prescribing rates between NHS Boards of both weak and strong opioids (Fig. 3, Suppplementary Figure 2, and Supplementary Tables S2 and S3). There was also variation in prescribing rates between GP practices (Fig. 3). The median rate of prescribing of strong opioids was highest in NHS Dumfries, although there was a substantial range of prescribing rates within and between Health Boards.

There was significant variation in the mean number of DDDs per 1000 population across NHS Boards ($P<0.05$). The intraclass correlation was calculated for strong (0.11) and for weak (0.27) opioid prescribing, indicating that 11% and 27% of total variance in these prescribing rates was a result of variation between NHS Board areas for strong and weak opioids, respectively. Then, after adjusting for deprivation (SIMD quintile) and urban/rural classification (Supplementary Figure 1, Supplementary Table S4a,b), for strong opioid prescribing the intraclass correlation for GP practice variance was 0.092. This indicates that 9% of the GP practice variance in prescribing rates is explained by deprivation and urban/rural classification (Supplementary Table S4d). For weak opioids, the multilevel linear regression model identified deprivation (SIMD quintile) as a significant predictor ($P<0.05$) of number of DDDs per 1000 population per year (Supplementary Table S4a,c). After adjustment for deprivation, the proportion of variance of weak opioids prescribing at GP level was 0.13, indicating that 13% of the GP level variance can be explained by deprivation.

Co-prescribing of opioids and benzodiazepines

Overall, co-prescribing of benzodiazepines was more common for women than for men (Fig. 4). Almost 19% of women aged 30–45 yr who were prescribed a weak opioid were also prescribed a benzodiazepine, and 38% of women were co-prescribed a strong opioid and a benzodiazepine. In younger age groups (<25 yr) there were slightly higher rates of such co-prescribing in men compared with women.

Co-prescriptions to manage common side effects

With strong opioids, 50% or more of patients were co-prescribed a laxative from age 60 yr, but there were lower rates of such co-prescribing with weak opioids (Supplementary Fig. S3). Prescribing rates of antiemetics were lower than of laxatives. There was a significant difference in both age and sex ($P<0.001$) for all co-prescribing of strong and weak opioids with laxatives and antiemetics; higher rates of co-prescribing to manage side effects occurred for women.

GS:SFHS linkage

Data linkage was conducted for the 17 404 GS participants who had received any prescription from a GP. We linked the

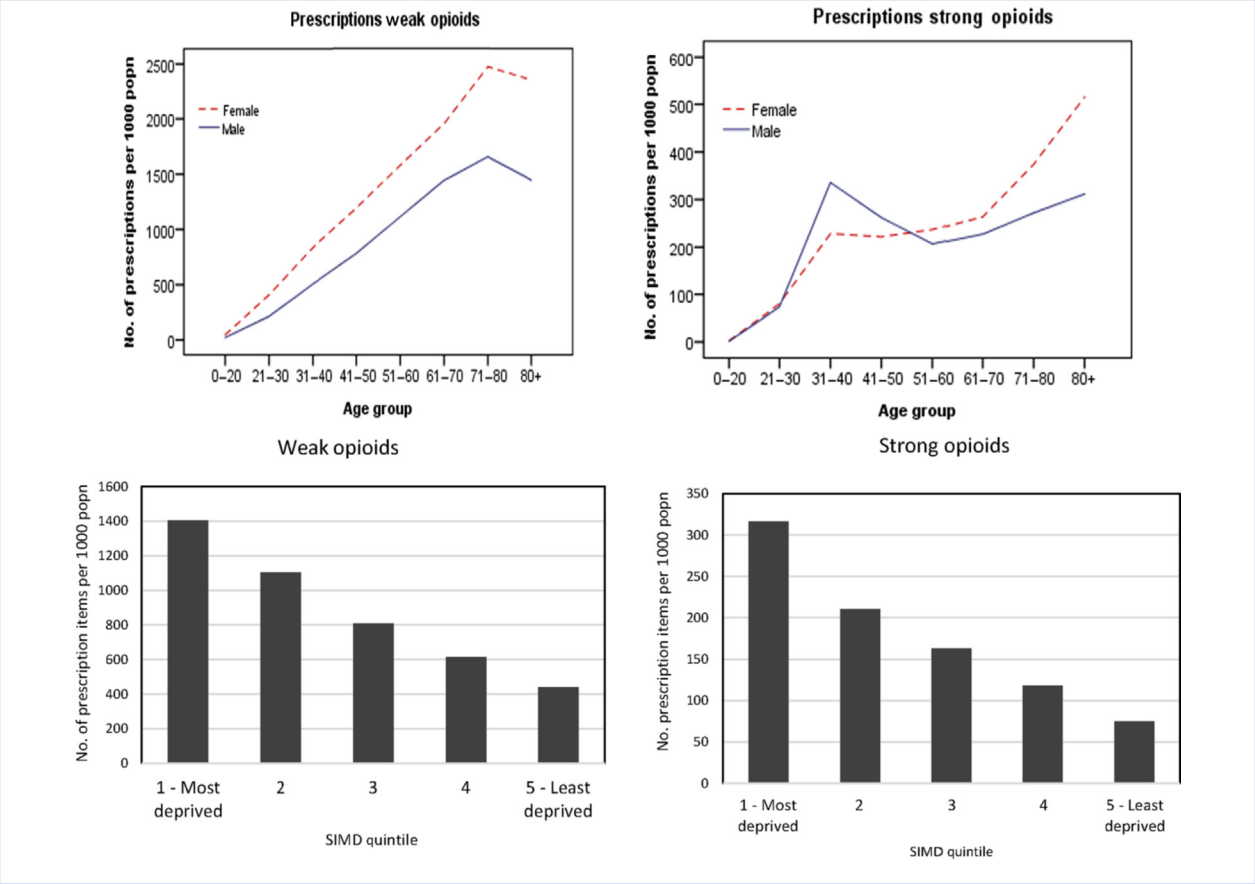

Fig 2. Opioid prescribing and sociodemographic characteristics [age and sex; Scottish Index of Multiple Deprivation (SIMD)]. 1=most deprived, 5=least deprived.

GS:SFHS questionnaire and prescribing data of those individuals who had received a prescription 6 months before or after attending their research clinic appointment and identified 11 041 individuals who had also completed the chronic pain identification questions. In total, 6448 (58.4%) reported no chronic pain, 2305 (20.9%) were classed as CPG I (mild chronic pain) and 2288 (20.7%) as CPG II–IV (severe chronic pain).

The characteristics and the opioids prescribed for these GS participants are shown in Table 1. Their mean age was 48.3 yr [standard deviation 15.4; range: 18–99 yr; median (interquartile range) 50 (37–60) yr], and 63.7% (7033/11 041) were women.

There was a significant association between pain severity and receipt of at least one opioid prescription (χ^2 test, $P<0.001$). Almost 90% (5788/6448) of those reporting no chronic pain did not receive any opioid prescription and nor did 53% (1215/2288) of those who reported 'severe pain'. A weak opioid (and no strong opioid) was prescribed to 998 individuals (43.6%) in the severe pain group and for 338 (14.7%) the opioid was tramadol. Only 3% who reported severe pain received a strong opioid during the 6 months before and after the clinic visit. Benzodiazepines were co-prescribed to 9.5% (mild pain) and 14.5% (severe pain) of GS:SFHS participants who also received a weak opioid, and to 29.3% of individuals who reported severe chronic pain and were prescribed a strong opioid.

Among participants with severe chronic pain who received weak (998) or no opioid prescriptions (1215), we also explored other commonly prescribed analgesics during the 12-month period. Of those with severe pain and a weak opioid, 302 participants were prescribed a non-steroidal anti-inflammatory drug, 124 were prescribed a gabapentinoid, and 224 were prescribed paracetamol; overall, 49.4% (493/998) were prescribed another analgesic. Of those with severe pain and no opioid, 293 participants were prescribed other analgesics: 207 were prescribed an non-steroidal anti-inflammatory drug; 25 were prescribed a gabapentinoid; 115 were prescribed paracetamol. The remaining 50.6% (505/998) and 75.8% (922/1215) of those with severe pain and weak or no opioids, respectively, were prescribed no analgesics during the 6 months before and after their report of severe chronic pain.

There was a positive association between reported pain severity and the number of opioid prescriptions dispensed (Fig. 5; Kruskal–Wallis Test: $P<0.001$ and $P=0.002$ for weak and strong opioids, respectively). Participants reporting mild chronic pain were dispensed more prescriptions than those without chronic pain, and those reporting severe chronic pain had were most frequently dispensed prescriptions.

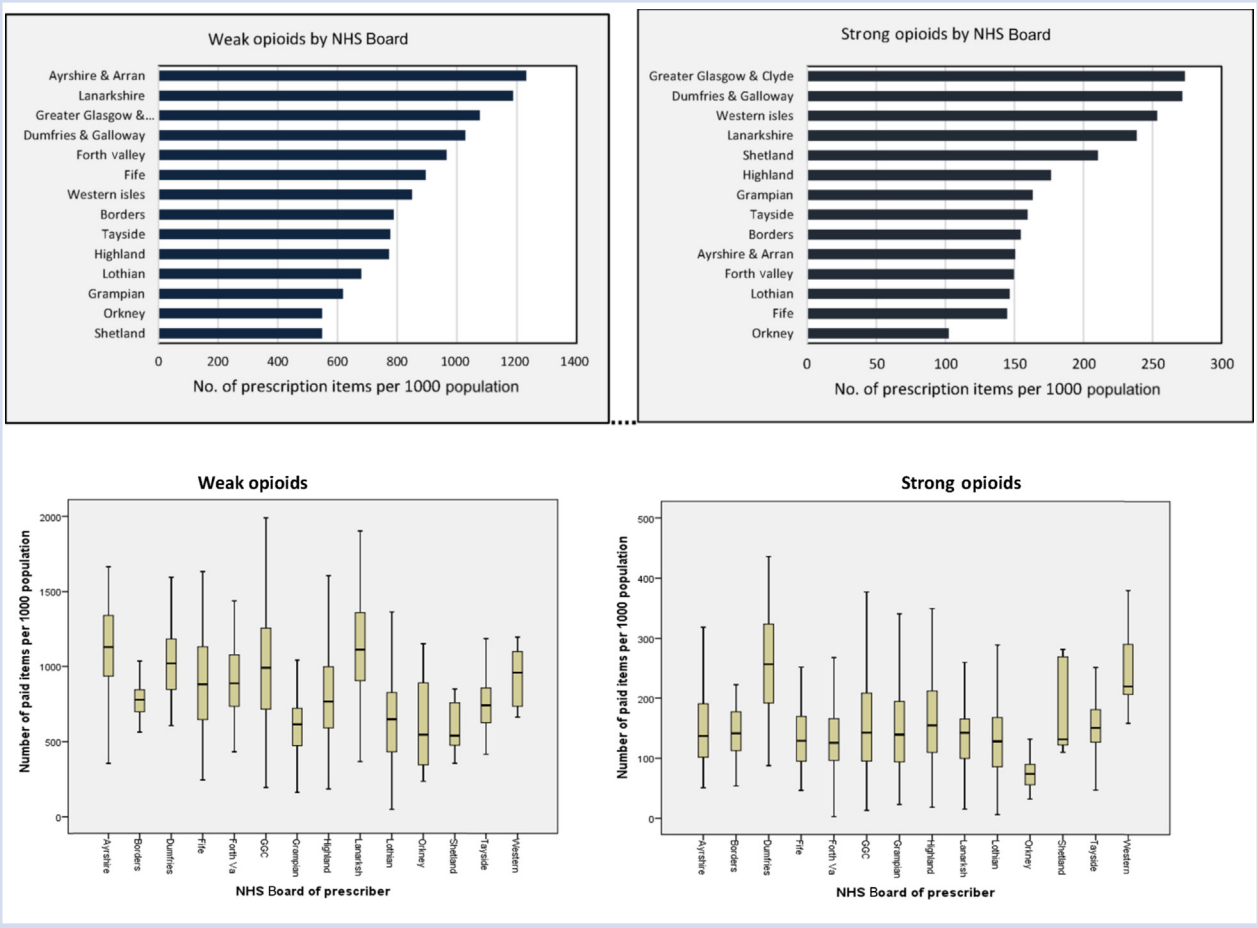

Fig 3. Opioid prescribing by National Health Service (NHS) Board of general practitioner prescriber for 2012.

Discussion

Using established clinical databases, we found increasing opioid prescribing over 10 yr in Scotland, with variation by age, sex, economic deprivation, GP practices, and NHS Board of practice location. There was significant variation in prescribing of both weak and strong opioids across NHS Boards with much of this explained by deprivation. Similar increases in opioid prescribing have been reported elsewhere in the UK and internationally.[4–8]

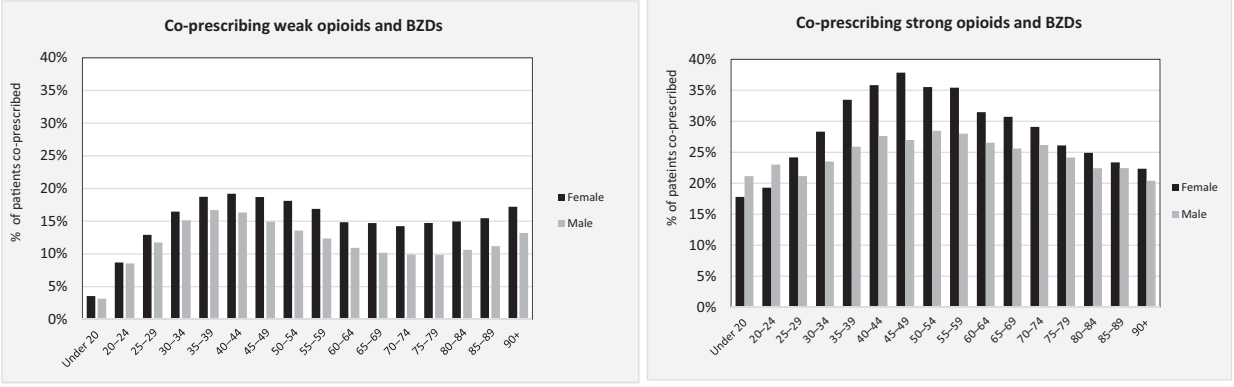

Fig 4. Co-prescribing of opioids with benzodiazepines (BZDs).

Table 1 Characteristics of Generation Scotland: Scottish Family Health Study participants and their receipt of an opioid prescriptions within 6 months before or after self-reported pain, *n* (%). Notes: Mild pain = Chronic Pain Grade (CPG) I; Severe pain = CPG II–IV; Strong opioids prescribing includes methadone and buprenorphine, which are often prescribed for substance misuse replacement therapy. There was a total on 81 individuals prescribed these drugs (12 with no pain; three with mild pain and 10 with severe pain). [a] % of Generation Scotland participants co-prescribed a benzodiazepine within pain and opioid group

	No chronic pain	Mild pain	Severe pain	Total (%)
Sex				
Female	3989 (61.9)	1401 (60.8)	1643 (71.8)	7033 (63.7)
Male	2459 (38.1)	904 (39.2)	645 (28.2)	4008 (36.3)
Total (%)	6448 (58.4)	2305 (20.9)	2288 (20.7)	11 041 (100)
Age (yr)				
<25	795 (12.3)	94 (4.1)	104 (4.5)	993 (9.0)
25–44	2141 (33.2)	609 (26.4)	574 (25.1)	3324 (30.1)
45–64	2766 (42.9)	1252 (54.3)	1268 (55.4)	5286 (47.9)
≥65	746 (11.7)	350 (15.2)	342 (14.9)	1438 (13.0)
No opioid	5788 (89.8)	1927 (83.6)	1215 (53.1)	8959 (81.1)
Weak opioid	639 (9.9)	368 (16.0)	998 (43.6)	1976 (17.9)
Strong opioid	21 (0.3)	10 (0.4)	75 (3.3)	106 (1.0)
Co-prescribing with benzodiazepines				
Weak opioid and benzodiazepine[a]	57 (8.9)	35 (9.5)	149 (14.9)	241 (12.2)
Strong opioid and benzodiazepine[a]	1 (4.5)	0	22 (29.3)	23 (21.7)

Overall, approximately 18% of the population received an opioid prescription in 2012, which is a higher proportion than reported in other countries, although similar to some figures on the prevalence of chronic pain.[37] Many of these prescriptions will have been for acute pain and short-term use or at initiation of analgesic prescribing,[38] although we are unable to determine the extent of this and were unable to link to clinical data nationally. Epidemiological data from the USA and Denmark have shown that 3–5% of the population use prescribed opioids regularly for treatment of chronic pain.[39–41]

Opioid prescribing was more common in areas of greatest deprivation, consistent with other research.[7,21,42,43] In a Canadian study, Gomes and colleagues[21] found that socioeconomically disadvantaged patients were prescribed more opioid drugs, more often, and at higher doses. We also found that opioid prescribing generally increased with age and that women had higher rates than men. Chronic pain studies have consistently shown that more women report chronic pain than men[44,37] and that women are more likely to consult a GP with pain.[45] There was significant variation in prescribing between NHS Boards and between GP practices; however, after adjusting for geographical and deprivation factors, this variance was considerably reduced. Similar results have been reported by Ruscitto and colleagues,[7] suggesting both that further research is required to explain this association, and that any intervention to address increasing opioid prescribing should look to incorporate relevant sociodemographic factors rather than focusing primarily on individual GPs.

We found co-prescribing of benzodiazepines, particularly with strong opioids, to be relatively common, particularly among women where up to 38% received co-prescriptions. These findings are particularly relevant given the recent publication of the Food and Drug Administration safety communication announcing serious risks and death associated with co-prescribing.[46] It is recommended that clinicians should avoid co-prescribing opioid analgesic medication and benzodiazepines whenever possible.[3,36] Concurrent use of benzodiazepines and opioids has been found in 31–61% of drug-related deaths.[47–49] Benzodiazepines have no clear role in analgesia, there are better anxiolytic therapies, and they are addictive.[3] Using guidelines to address such problematic prescribing has the potential to optimise care and improve patient safety using evidence-based practice.[17]

In general, we found that opioids were prescribed in relation to reported presence and severity of chronic pain, although with no information available about the efficacy of the prescribed opioids. We found 40% of those reporting severe chronic pain were not prescribed any opioids or other common analgesics in the 6 months before and after the assessment point. These findings are consistent with data from Norway: among individuals reporting severe chronic pain, most did not use opioids and even among patients prescribed opioids, most continued to report severe pain.[30] Discontinuation of opioids is common,[50] and there are likely to be a number of factors explaining why people with severe chronic pain are not prescribed opioids, including lack of perceived efficacy or unpleasant and unacceptable physical effects, psychological effects, or both. Some patients prefer to use other strategies to self-manage pain.[51] GPs have reported difficulty in assessing pain levels and have concerns about lack of education/knowledge, duration of use of strong opioids and possible side effects, tolerance, and addiction.[52,53] These concerns lead to the possibility that severe chronic pain, as reported by the GS:SFHS participants, is actually under-treated despite the observed increase in overall rates of opioid prescribing or indeed other analgesics.

The completeness rate of ISD community pharmacy dispensed data is high and contains all GP opioids prescribing across Scotland. This produced a large and nationally comprehensive study population, minimising selection bias and enabling analysis at individual, practice and NHS Board levels. This is an advantage compared with studies that are restricted by prescription data from health insurance plans and claims data.[43,54] The analysis of national prescribing was limited because of its aggregate format. This was necessary to maintain anonymity and minimise risk of potential disclosure of individual patients or prescribers, resulting in mainly descriptive analysis and restricting the possibility of more complex statistical analyses.

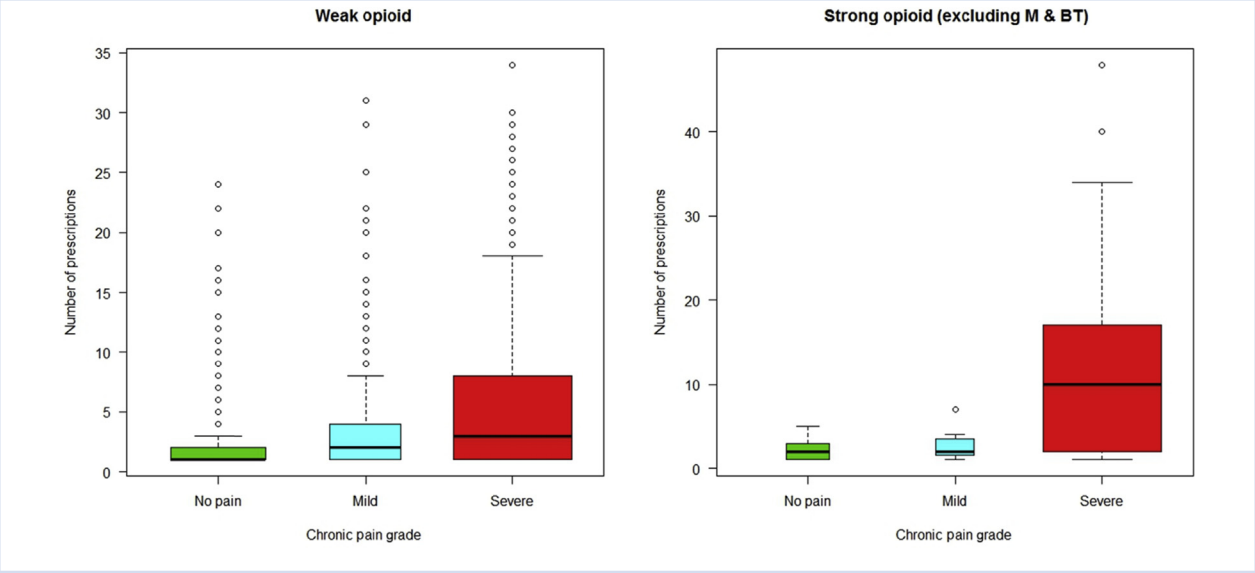

Fig 5. Boxplots for number of prescriptions by pain severity group for weak/strong opioids. Weak opioid prescriptions: The number of prescriptions in the three groups are significantly different Kruskal–Wallis Test: $P<0.001$. Pairwise comparisons (Mann–Whitney test) No pain *vs* Mild pain ($P<0.001$); No pain *vs* Severe pain ($P<0.01$) and Mild *vs* Severe pain ($P<0.001$) The patients with mild chronic pain had more frequent prescription of than those without chronic pain, where those with severe chronic pain had the most frequent weak opioid prescription. Strong opioid prescriptions: the number of prescriptions in the three groups are significantly different Kruskal–Wallis test: $P=0.002$. Pairwise comparisons (Mann–Whitney test) for prescriptions of strong opioids found no significant difference for No pain *vs* Mild pain ($P=0.621$). There were significantly more prescriptions for No pain *vs* Severe pain ($P=0.004$) and Mild *vs* Severe pain ($P=0.022$). Methadone (M) and buprenorphine (BT) were excluded from this analysis, as these are most commonly prescribed for managing substance misuse.

We aimed to explore all opioid prescribing, including methadone and buprenorphine, although we recognise that these are commonly used in opioid maintenance therapy. Data from ISD lacked clinical details and we were unable to discern opioid prescriptions with specific diagnoses including cancer. Including people with cancer might inflate the overall prescribing rates and average rates per head for strong opioids as, particularly near the end of life, people with cancer receive much higher than standard doses to control pain. It would only take one or two people in a general practice being treated in this way for a few months to create the apparent impression of very high prescribing. When comparing NHS Boards and GP practices, this is likely to flatten out, and adjustment for age and deprivation will have further reduced the effects of this.

Other UK research has found 84% of prescriptions for strong opioids were prescribed for chronic non-malignant pain.[8] Including those without pain as the main indication means those receiving opioid replacement therapy for drug addiction were included—this is likely to have similar inflationary effects as the inclusion of those with cancer, particularly in more deprived areas, and areas where methadone prescribing is through GP prescribing rather than directly through substance misuse services. We could not apply this information to the dataset and could therefore not adjust for it, although adjustment for deprivation (and age) will again have partly mitigated this. Other non-pain indications are likely to have much smaller effect (e.g. codeine linctus for cough, codeine for diarrhoea).

Patient level data obtained from the GS:SFHS linkage included reported chronic pain severity, with a high rate of accurate linkage to opioid prescribing. Overall 68% of those with any reported chronic pain were not prescribed an opioid, although we are unable to account for weak opioids available over-the-counter, which is likely to have resulted in an underestimate of opioid use. There are few studies of this type of linkage between prescribing data and reported pain in a general population sample. In a study by Fredheim and colleagues,[30] 85% of Norwegian patients with chronic non-malignant pain did not use opioids at all and, in Denmark, Kurita and colleagues[39] reported a chronic pain prevalence of 27%, of whom 13% were prescribed an opioid.

The structure of the NHS in the UK and the gatekeeper status of GPs means that it is difficult for patients to undertake 'doctor-shopping' and obtain prescriptions from multiple prescribers, as is possible in other countries.[10,55] Given this GP gatekeeper role, our interpretation is that the high rates of use of opioids and the extent of misuse that now exists in regions such as North America should not be seen as a ubiquitous problem. Opioids, particularly strong opioids, are also used much less frequently in many European countries,[4,16] including Portugal,[41] Norway,[30] and Denmark,[39] than in the USA. Long-term or high levels of opioid prescribing for pain should only occur after full biopsychosocial assessment and in conjunction with a specialist according to latest guidelines,[56–58] avoiding co-prescribing of benzodiazepines. Caution is required when prescribing long-term opioids for chronic pain in view of the potential harms and limited evidence of long-term benefit. The Royal College of Anaesthetists highlights this, with approaches to managing risks and benefits, and emphasises the need to adopt a biopsychosocial approach to managing chronic pain.[57]

Future research

Evidence on long-term opioid therapy for chronic pain is limited but suggests an increased risk of serious harms that appears to be dose-dependent.[59] More research is needed to identify factors associated with clinical indications for increases in prescribing, and subsequent problem use following prescription in primary care with a view to identifying these and preventing misuse and related outcomes. This is likely to benefit patient safety, high-risk prescribing, and polypharmacy programmes. Further research is also needed to establish the long-term efficacy of opioids, as it is not possible to ascertain this from current evidence.

Conclusions

This national study, using routine and individual data, found opioid prescribing in primary care to be common and increasing. Patients prescribed a strong opioid were likely to have severe pain, which might indicate appropriate prescribing to attempt to manage this pain. There was also a considerable number of patients with severe pain not prescribed an opioid or other analgesics. The appropriateness or otherwise of this is difficult to define with current data, but might represent under-prescribing of opioids when indicated. This highlights the importance of guidance for prescribing safely and effectively,[3,56,58] the need to establish protocols for appropriate person-centred prescribing and for the continued development of alternative interventions that are more effective and safer than long-term opioids in chronic painful conditions. Chronic painful conditions present by far the most prevalent causes of disability in the Global Burden of Disease Report,[60] and it is important that we are equipped to address this with better public and professional understanding of chronic pain prevention and management, and appropriate, safe, and effective prescribing of opioids.

Authors' contributions

Project conception and design: B.H.S., L.C., S.G., G.J.M., M.G.S., A.B., P.D.
Extraction and compilation of ISD data: G.W.
Statistical analysis: R.M., H.W., N.T.
Statistical analysis advice: P.D.
Submission draft: N.T.
Critical data review, comments on all subsequent drafts, final version of manuscript approval: all authors.
Guarantors for the study: B.H.S., L.C.

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Declaration of interest

N.T., R.M., H.W. and T.G.H. have no competing interests to declare. S.G. has received funds for talks from Lilly and Pfizer in the previous 3 yr. G.J.M. has received funds (via the British Society for Rheumatology (BSR)) from AbbVie, UCB and Pfizer for the conduct of the BSR Biologics Register in Ankylosing Spondylitis and has received honoraria from AbbVie and Janssen for talks on 'The use of real world evidence'. M.G.S. has received research support, consulting fees, or honoraria in the past 3 yr from Astellas, Grünenthal, NAPP, and Pfizer. A.B. has received educational grants from Schering Plough and research project funding from Schering-Plough, Merck Serono, Lundbeck, and Indivior, on behalf of his institution. P.T.D. has received research grants from GSK, Shire Pharmaceuticals, and Novo Nordisk. P.T.D. is a member of the New Drugs Committee of the Scottish Medicines Consortium. L.C. has received funding from Grunenthal and Astellas in support of education and scientific meetings and is an editor with the *British Journal of Anaesthesia*. B.H.S. has received research funding and consultancy fees, on behalf of his institution, from Pfizer Ltd, for research into the genetics of chronic pain.

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Supplementary material

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