Opioid prescribing practices, their association with chronic pain, and co-prescribing of benzodiazepines: a primary care data linkage study

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Short running title: Opioids, co-prescribing of benzodiazepines and chronic pain: a population based study.

Key words: prescribing, general practice, chronic pain, opioids, benzodiazepines, data linkage

Abstract

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

Methods: Electronic linkages of opioids prescribing: 1) national data from Information Services Division, NHS Scotland (2003-2012); and 2) individual data from Generation Scotland: Scottish Family Health Study. Descriptive analyses were conducted on national data, multi-level modelling to examine factors associated with variations in prescribing rates. Chi-square 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 and weak opioid prescribing increased from 3,261,547 to 4,852,583. 938,674 individuals in Scotland 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 (<0.05), with much of this explained by deprivation. 40% of females aged 25-40 prescribed a strong opioid were also prescribed a benzodiazepine. There was significant association between pain severity and receipt of opioid prescription ($p<0.001$). Over 50% of people reporting severe pain were not prescribed any opioid analgesic.

Conclusions: This national study, using routine and individual data, found opioid prescribing in primary care to be common and increasing, but appearing generally appropriate in relation to pain severity. Co-prescribing of opioids and benzodiazepines, was common.

Introduction

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 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 ever-increasing prescribing of opioids,[3-9] though 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 may include the wider range of opioids and routes of administration available; changes in social and cultural factors which encourage prescribing; and an aging population with a higher incidence of pain. Much of the published opioid prescribing data originates in North America, where there have been parallel increases in serious adverse outcomes. These include rising 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 markedly.

Alongside these warnings of potential problems related to increases in opioid prescribing, reservations have been expressed about the effectiveness of these drugs for the long-term management of persistent painful conditions, such as low back pain [16] and fibromyalgia,[19] especially in situations in which dose-related harms may 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), including prescription opioid dependence,[22] impaired cognitive function,[23] endocrine dysfunction[24] and opioid-induced hyperalgesia [25 26] may occur.

These serious adverse outcomes, or harms, are also associated with co-prescription of opioids with benzodiazepines (BZDs), 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] A three-year study of new users of weak opioids, found 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 rising rates of opioid prescribing, there is therefore conflicting evidence about the safety and appropriateness of prescribing for chronic pain.

In this study we aimed to describe national opioid prescription rates, seeking socio-demographic factors associated with variations in these, and indicators of quality of prescribing, specifically the co-prescribing of BZDs. Then, 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 NHS in Scotland is a publicly-funded healthcare system and is universally used by the 5.3 million residents. It is administered through 14 geographical NHS Boards. In 2009, the Prescribing Information System (PIS) 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 that are 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 the ten year prescribing trends (2003-2012) for all opioid drugs across Scotland. Taking a snapshot of one year (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=1,007), 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 due to co-prescribing of BZDs
  b. indicators of effective management of common side effects (constipation and nausea) with co-prescribing of laxatives and anti-emetics

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.

Individual level data – Generation Scotland: Scottish Family Health Study (GS:SFHS)

We conducted a prescribing linkage examining the association between receipt of opioids and severity of chronic pain was conducted using data from Generation Scotland: Scottish Family Health Study (GS:SFHS) for GS participants who were residents in NHS Greater Glasgow & 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 three months.[35] The CPG is a 7-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 and/or high pain-related disability. Therefore 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 & Clyde (GGC) then pseudo-anonymised and stored in the HIC Safe Haven. GP prescribing for the cohort in the six 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 Defined Daily Doses (DDDs). DDD is a World Health Organization 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 the WHO definitions.

ISD data for 2012 by NHS Board were analysed as (i) DDDs per 1,000 population per day and (ii) prescription items per 1,000 population. GS:SFHS analysis was based on the number of dispensed prescriptions.

Opioids & Benzodiazepines

Opioid drugs in Chapter 4.7.2 of the British National Formulary (BNF)[36] were included, subdivided according to the BNF categories of "strong" and "weak" opioids with all strong opioids classified as controlled drugs in 2012.[36] S*trong 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, temazepam.

Statistical analysis

Mainly descriptive analyses were conducted on the national level data released by ISD. Multi-level 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. Therefore the intra-class 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 1,000 population per year. Negative binomial regression was performed to estimate the effect of age and sex on opioids prescribing rates overall. Chi-square 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, SPSS for Windows (v22) and R (v3.2.0).

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

RESULTS

National data

Prescribing of both weak and strong opioids increased steadily over the ten year period 2003-2012. The number of strong opioid prescription items more than doubled, from 474,385 in 2003 to 1,036,446 in 2012 (Figure 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 (Figure 1).

In 2012, 938,674 individuals in Scotland were prescribed an opioid (18% of the population) with codeine 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 1).

Sociodemographic factors

The age and sex distributions of prescribing of weak and strong opioids are shown in Figure 2. With weak opioids, rates varied significantly with increasing age ($p<0.001$) and with gender, 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 gender ($p=0.192$).

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. (Figure 2).

NHS Boards and GP practices

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

There was significant variation in the mean number of DDDs per 1,000 population across NHS boards ($p<0.05$). The intra-class correlation was calculated for strong (0.11) and for weak (0.27) opioids prescribing, indicating that 11% and 27% of total variance in these prescribing rates was due to variation between NHS Board areas, for strong and weak opioids respectively. Then, after adjusting for deprivation (SIMD quintile) and urban/rural classification (Supplementary Table 4a b), for strong opioid prescribing the intra-class 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 4d). For weak opioids, the multilevel linear regression model identified deprivation (SIMD quintile) as a significant predictor ($p<0.05$) of number of DDDs per 1,000 population per year (Supplementary Table 4a & 4c). After adjustment for deprivation, the proportion of variance of weak opioids prescribing at GP level was found to be 0.13, indicating that 13% of the GP level variance is explained by deprivation.

Co-prescribing of opioids and benzodiazepines

Overall co-prescribing of BZDs was more common for females than for males (Figure 4). Almost 19% of females aged 30-45 years, who were prescribed a weak opioid, were also prescribed a BZD, and 38% of

women were co-prescribed a strong opioid and a BZD. In younger age groups (<25 years) there were slightly higher rates of such co-prescribing in males compared to females.

Co-prescriptions to manage common side effects

With strong opioids, 50% or more of patients were co-prescribed a laxative from age 60 years, but there were lower rates of such co-prescribing with weak opioids *(*Supplementary Figure 3*)*. Prescribing rates of anti-emetics 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 anti-emetics; higher rates of co-prescribing to manage side effects occurred for females.

Generation Scotland: Scottish Family Health Study linkage

Data linkage was conducted for the 17,404 GS participants who had received any prescription from a GP. We linked the GS:SFHS questionnaire and prescribing data of those individuals who had received a prescription six 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, 6,448 (58.4%) reported no chronic pain, 2,305 (20.9%) were classed as CPG I (mild chronic pain) and 2,288 (20.7%) as CPG II-IV (severe chronic pain).

The characteristics and the opioids prescribing for these GS participants are shown in Table 1. Their mean age was 48.3 years (SD (15.4) Range: 18 - 99 years; Median (IQR) = 50 (37 - 60) years.) and 63.7% (n=7,033/11,041) were women.

There was a significant association between pain severity and receipt of at least one opioid prescription (chi-squared test, $p<0.001$). Almost 90% (n=5,788/6,448) of those reporting no chronic pain did not receive any opioid prescription and nor did 53% (n=1,215/2,288) 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 six 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 almost a third (29.3%) of individuals who reported severe chronic pain and were prescribed a strong opioid.

Among the participants with severe chronic pain who received weak (n=998) or no opioid prescriptions (n=1,215), 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 (NSAID), 124 were prescribed a gabapentinoid and 224 were prescribed paracetamol and so, 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 NSAID; 25 were prescribed a gabapentinoid; 115 were prescribed paracetamol. The remaining 50.6% (505/998) and 75.8% (922/1,215) of those with severe pain and weak or no opioids, respectively, were prescribed no analgesics during the six 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 (Figure 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 the most frequently dispensed prescriptions.

Discussion

Using established clinical databases, we found increasing opioid prescribing over 10 years, at a national level, with variation by age, gender, 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]

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 [ref]. Many of these prescriptions will have been for acute pain and short-term use or at initiation of analgesic prescribing [37] although we are unable to determine the extent of this and were unable to link to clinical data nationally. Epidemiological data from the United States and Denmark have shown that 3% to 5% of the population use any prescribed opioids regularly for treatment of chronic pain.[38-40]

Opioids prescribing was more common in areas of greatest deprivation, consistent with other research.[7 21 41 42] In a Canadian study, Gomes (2011) 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 [43 44] 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 *et al* (2014), suggesting both that further research is required to explain this association, and that any intervention to address rising opioids prescribing should look to incorporate relevant socio-demographic factors, rather than focusing primarily on individual GPs.

In our work, we found co-prescribing of BZDs, 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 FDA 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 BZDs and opioids has been found in 31%–61% of drug-related deaths.[47-49] BZDs 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 six 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: a lack of perceived efficacy or unpleasant and unacceptable physical and/or psychological effects. Some patients may 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, the duration of use of strong opioids and possible side effects, tolerance, and addiction.[52 53] These concerns may 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 prescribing of opioids across Scotland. This produced a large and nationally comprehensive study population, minimising selection bias and enabling analysis at individual, practice and NHS Board level. This is an advantage compared to studies that are restricted by prescription data from health insurance plans and claims data.[42 54] The analysis of the national prescribing was limited due to 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. We aimed to explore all opioids prescribing and included methadone and buprenorphine prescribing, 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 may inflate the overall prescribing rates, and average rates per head, for strong opioids as, particularly near the end of life, people with cancer may 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, though adjustment for deprivation (and age) will again have partly mitigated. 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 opioids 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 to buy over-the-counter, which is likely to have resulted in an under-estimate of opioid use. There are few studies of this type of linkage between prescribing data and reported pain, in a general population sample. In the study by Fredheim et al (2014), 85% of Norwegian patients with chronic non-malignant pain did not use opioids at all and in Denmark, Kurita et al (2012) reported a chronic pain prevalence of 27%, of whom, 13% were prescribed an opioid.

The structure of the National Health Service (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 countries 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 [40], Norway [30] and Denmark [38] than in US. Long term or high levels of prescribing of opioids for pain should only be after full assessment and in conjunction with a specialist, according to latest guidelines [56-58] and with co-prescribing of BZDs avoided. Caution is required when prescribing opioids, or any medicine, long-term for chronic pain, in view of the potential harms. 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 the current evidence.

Conclusions

This national study, using routine and individuals' data, found opioid prescribing in primary care to be common and increasing. Patients prescribed a strong opioid were likely to have severe pain, which may indicate appropriate prescribing to attempt to manage this pain. There were, 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 may 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 may be 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 as well as appropriate, safe and effective prescribing of opioids.

Contributions: This project was conceived and designed by BHS, LC, SG, GJM, MGS, AB, and PD. GW extracted and complied the ISD data. RM, HW and NT performed statistical analysis and PD advised on the analysis. NT drafted the submission. All authors reviewed the data critically, commented substantially on all subsequent drafts and approved the final version of the manuscript. BHS and LC are the guarantors for the study.

Acknowledgements: We acknowledge the input and participation of patients and third sector organisations in the development of this project through the Scottish Pain Research Community. We thank Jackie Caldwell and Iain Bishop of eDRIS at ISD Scotland for their advice and expertise with the national prescribing datasets. We are grateful to the families who took part in GS:SFHS, the GPs and Scottish School of Primary Care for their help in recruiting them, and the whole Generation Scotland team, which includes academic researchers, clinic staff, laboratory technicians, clerical workers, statisticians and research managers.

Declaration of Interests: NT, RM, HW and TGH have no competing interests to declare. SG has received funds for talks from Lilly & Pfizer in the previous three years. GJM 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". MGS has received research support, consulting fees, or honoraria in the past three years from Astellas, Grünenthal, NAPP and Pfizer. AB has received educational grants from Schering Plough and research project funding from Schering-Plough, Merck Serono, Lundbeck, and Indivior, on behalf of his institution. PTD has received research grants from GSK, Shire Pharmaceuticals, and Novo Nordisk. PTD is a member of the New Drugs Committee of the Scottish Medicines Consortium. LC has received funding from Grunenthal and Astellas in support of education and scientific meetings and is an editor with the British Journal of Anaesthesia. BHS has received research funding and consultancy fees, on behalf of his institution, from Pfizer Ltd, for research into the genetics of chronic pain.

Funding: This study was funded by the Chief Scientist Office, part of the Scottish Government Health Directorates (CZH-4-429).

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Table 1. Characteristics of the GS:SFHS participants and their receipt of an opioid prescription within six months before and/or after self-reported pain, n (%)

	No Chronic Pain	Mild pain	Severe pain	Total (%)
Gender				
Female	3,989 (61.9)	1,401 (60.8)	1,643 (71.8)	7,033 (63.7)
Male	2,459 (38.1)	904 (39.2)	645 (28.2)	4,008 (36.3)
Total (%)	6,448 (58.4)	2,305 (20.9)	2,288 (20.7)	11,041 (100)
Age				
<25 years	795 (12.3)	94 (4.1)	104 (4.5)	993 (9.0)
25-44 years	2,141 (33.2)	609 (26.4)	574 (25.1)	3,324 (30.1)
45-64 years	2,766 (42.9)	1,252 (54.3)	1,268 (55.4)(	5,286 (47.9)
65+ years	746 (11.7)	350 (15.2)	342 (14.9)	1,438 (13.0)
No opioid	5,788 (89.8)	1,927 (83.6)	1,215 (53.1)	8,959 (81.1)
Weak opioid	639 (9.9)	368 (16.0)	998 (43.6)	1,976 (17.9)
Strong opioid	21 (0.3)	10 (0.4)	75 (3.3)	106 (1.0)
Co-prescribing with BZDs				
Weak opioid & BZD**	57 (8.9)	35 (9.5)	149 (14.9)	241 (12.2)
Strong opioid & BZD**	1 (4.5)	0	22 (29.3)	23 (21.7)

Notes: Mild pain = Chronic Pain Grade (CPG) I; Severe pain = CPG II-IV; Strong opioids prescribing includes methadone & buprenorphine which are often prescribed for substance misuse replacement therapy. There were a total on 81 individuals prescribed these drugs (12 with no pain; 3 with mild pain and 10 with severe pain). **% of GS participants co-prescribed a BZD within pain and opioid group

Figure Legends

Figure 1. Trends in opioids prescribing in Scotland (2003-2012)

Figure 2. Opioids prescribing and sociodemographic characteristics (age & sex; Scottish Index of Multiple Deprivation)

Figure 3. Opioids by NHS board of GP prescriber for 2012

Figure 4. Co-prescribing of opioids with benzodiazepines

Figure 5. Boxplots for number of prescriptions by pain severity group for weak/strong opioids

Weak opioid prescriptions: The number of prescriptions in the 3 groups are significantly different Kruskal-Wallis Test: $p < 0.001$. Pairwise comparisons (Mann-Whitney test) No pain v Mild pain ($p < 0.001$); No pain v 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 3 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 v Mild pain ($p = 0.621$). There were significantly more prescriptions for No pain v 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.