Long-term, high-dose opioid prescription for chronic non-cancer pain in primary care

Bailey, John; Gill, Simon; Poole, Rob

BJGP open

DOI:
DOI:10.3399/BJGPO.2021.0217

E-pub ahead of print: 21/06/2022

Peer reviewed version

BJGP OPEN

Long-term, high-dose opioid prescribing for chronic non-cancer pain in primary care

Bailey, John; Gill, Simon; Poole, Rob

DOI: https://doi.org/10.3399/BJGPO.2021.0217

To access the most recent version of this article, please click the DOI URL in the line above.

Received 12 November 2021
Revised 23 May 2022
Accepted 16 June 2022

Author Accepted Manuscript

This is an 'author accepted manuscript': a manuscript that has been accepted for publication in BJGP Open, but which has not yet undergone subediting, typesetting, or correction. Errors discovered and corrected during this process may materially alter the content of this manuscript, and the latest published version (the Version of Record) should be used in preference to any preceding versions

Long-term, high-dose opioid prescribing for chronic non-cancer pain in primary care

John Bailey, Simon Gill and Rob Poole

Corresponding author:

John Bailey (BA), Research Officer

Centre for Mental Health and Society, Bangor University

Wrexham Academic Unit, Technology Park

Wrexham, LL13 7YP

03000 847086

Simon Gill (MPharm), Pharmacist

Betsi Cadwaladr University Health Board

Rob Poole (FRCPsych), Professor of Social Psychiatry

Centre for Mental Health and Society, Bangor University

Hon. Consultant Psychiatrist

Betsi Cadwaladr University Health Board

Table1. UK studies of opioid prescribing in primary care.

Study	Study period	Location	Study population	Findings
[1] NTA (2011)	1991-2009	England	All prescriptions	Five-fold increasing prescribing of opioids. Regional variations in prescribing.
[32] Ruscitto et al (2015)	1995-2010	Tayside	Primary care	Increase in opioid prescribing. Larger increase in "strong"[1] opioid prescribing. Associated factors: polypharmacy; social deprivation.
[2] Curtis et al (2019)	1998-2018	England	Primary care	Increases in prescribing between 1998 and 2016. Increase in ME amount prescribed much greater. Prescriptions decreased after 2016. Associated factor: geographical variation.
[13] Zin et al (2014)	2000-2010	England	Primary care	"Huge" increase in "strong"[1] opioid prescribing. Majority (88%) for non-cancer pain.
[33] Cartagena Farias et al (2017)	2000-2015	England	Primary care Non-cancer pain	Increasing numbers of people prescribed opioids. Prescribing for longer periods. Associated factors: age, social deprivation, regional variation.
[34] Bedson et al (2016)	2002-2013	England	Primary care Musculoskeletal pain	Long-term prescribing increased to 2009; slight decrease after 2011. Increased prescribing of long-acting opioids.
[35] Green et al (2012)	2004-2007(?)[2]	North Staffordshire	Primary care Joint pain Aged >50	Factors associated with increased rates of prescription. Factors associated with "strong"[1] opioid use.
[36] Foy et al (2016)	2005-2012	West Yorkshire	Primary care Non-cancer pain	Prescribing of weaker opioids doubled. Six-fold increase in "stronger"[1] opioid prescribing. Patient and prescriber factors associated with stepping up to "stronger"[1] opioids.
[11] Davies et al (2019)	2005-2015	Wales	Primary care Non-cancer pain	Large increase in prescribing of "strong"[1] opioids.

Study	Study period	Location	Study population	Findings
				Associated factors: age; social deprivation; anxiety or depression diagnosis.
[37] Jani et al (2020)	2006-2017	England	Primary care	Increased prescribing of opioids – codeine, morphine, tramadol, oxycodone. Initiated high doses tend to be maintained. Associated factors: social deprivation; regional variation; polypharmacy.
[38] Mordecai et al (2018)	2010-2014	England	Primary care	Increase in amount (in ME) prescribed. Associated factors: social deprivation; regional variation.
[39] Ponton & Sawyer (2018)	2012(?)[2]	South East England	Primary care Patients prescribed high doses	Identified patients prescribed doses ≥120mg ME of "strong"[1] opioids as candidates for specialist input.
[40] Ashaye et al (2018)	2011-2012	London and Midlands	Primary care Musculoskeletal pain	Long-term prescribing common. Possible overprescribing in over a quarter of patients receiving "strong"[1] opioids.
[41] Public Health England (2019)	2015-2018	England	Primary care	Prescriptions and proportion of population prescribed opioids declining from historically high rates. High rates of long-term prescribing. Associated factor: social deprivation; polypharmacy.
[42] Bastable & Rann (2019)	2018	East England	Primary care Patients prescribed high doses	Identified patients prescribed opioid doses ≥120mg ME. Co-prescribing of z drugs, benzodiazepines and GABA drugs.

[1] Drugs categorised as "strong" vary between studies, but always include morphine, oxycodone and fentanyl.

[2] This is estimated from the published text, which does not indicate the data collection period

Table 2.

Searching practice records for prescriptions for opioid medication

The two GP practices studied in this research used different database systems (**Vision** and **EMIS**) to record practice information. Different search terms were enabled in these systems to access information about drug prescriptions.

In the **Vision** system, the search terms were:

Drug Class of type Opioid Analgesics, and

Drug Class of type Non-opioid and Compound Analgesics.

In the **EMIS** system, the search terms were:

The Drug is Opioid Analgesics, and

The Drug is Compound Analgesic Preparations.

These searches produced slightly differing results, but included, in both cases, all prescriptions for drugs listed by BNF as opioid analgesics, in the relevant time period; i.e. there were false positive results but no false negatives.

Table 4.

Longitudinal high-dose prescribing data from Practice A

	2017	2018	2019	2020	2021
Registered patients	14,355	14,584	14,797	15,809	16,140
≥60<120mgME	27(1.88)[a]	25(1.71)[a]	24(1.62)[a]	23(1.45)[a]	24(1.49)[a]
≥120mgME	34(2.37)	37(2.54)	37(2.50)	36(2.28)	36(2.23)
≥120mgME>1year	25(1.74)	28(1.92)	30(2.03)	32(2.02)	31(1.92)

[a] n/1000 registered patients.

Table 5.

Age profile of LTHD patients in the two practices in the index week 2017

Practice A

Age	**0-24**	**25-34**	**35-44**	**45-54**	**55-64**	**65-74**	**75-84**	**> 85**
Patients in age group	4006	1729	1735	2404	1772	1524	902	283
% of all patients in age group	28	12	12	17	12	11	6	2
n = long-term, high dose users	0	1	2	7	5	3	5	2
n/1000 patients	0	0.58	1.15	2.91	2.82	1.97	5.54	7.07

Practice B

Age	**0-24**	**25-34**	**35-44**	**45-54**	**55-64**	**65-74**	**75-84**	**> 85**
Patients in age group	2632	1170	1119	1236	972	836	410	106
% of all patients in age group	31	14	13	15	11	10	5	1
n = long-term, high dose users	0	2	4	3	3	0	3	0
n/1000 patients	0	1.71	3.57	2.43	3.09	0	7.32	0

Combined

Age	**0-24**	**25-34**	**35-44**	**45-54**	**55-64**	**65-74**	**75-84**	**> 85**
Patients in age group	6638	2899	2854	3640	2744	2360	1312	389
% of all patients in age group	29	13	12	16	12	10	6	2
n = long-term, high dose users	0	3	6	10	8	3	8	2
n/1000 patients	0	1.03	2.10	2.75	2.91	1.27	6.10	5.14

Table 6.

Procedure for identifying patients prescribed LTHD opioids from routinely collected prescription data.

1. Identify all patients prescribed morphine, oxycodone, fentanyl, or buprenorphine.
2. From 1, identify all patients prescribed one of these drugs at ≥120mgME daily dose.
3. From 2, identify patients prescribed these drugs and these doses 1 year previously.

Table 3.

Opioid prescribing in Practice A and Practice B in the index week 2017

	Practice A	Practice B	Both practices
Number of patients in practice (all ages)	14,355	8,486	22,841
Prescriptions for opioids: *including compound drugs*	914	734	1,648
non-compound drugs	389	275	664
Patients prescribed opioids: *including compound drugs*	821(5.7%)[a]	667(7.9%)[a]	1,488(6.5%)[a]
non-compound drugs	337(2.3%)	246 (2.9%)	583(2.6%)
Patients with estimated daily dose ≥120mgME	34[b](2.37)[c]	19(2.24)[c]	53(2.32)[c]
As above + use for more than a year	**25(1.74)**	**14(1.65)**	**39(1.71)**
Patients with dose ≥60mg & <120mgME in one drug	28[d](1.95)	21(2.47)	49(2.15)
As above + other opioid(s)	15(1.04)	4(0.47)	19(0.83)

[a] *% of all practice patients prescribed these drugs.*

[b] *In this practice there were an additional 4 patients with a cancer diagnosis.*

[c] *Number/thousand patients.*

[d] *In this practice there was 1 additional patient with a cancer diagnosis.*

Abstract

Background: Opioid prescriptions for chronic pain have risen sharply over the last 25 years; harms associated with these drugs are related to dose and length of use.

Aim: The main aim of this study was to identify patients prescribed long-term, high doses of opioids in the community and to assess the prevalence of such use.

Design and Setting: An observational study of opioid prescribing in two demographically dissimilar GP practices was carried out.

Method: Details of opioid prescriptions were collected for 22,841 patients, of whom 1488 (6.5%) were being prescribed opioids on the census date. Exhaustive examination of the data identified all patients who were prescribed oral morphine equivalent doses of 120mg/day or more for one year or longer.

Results: All these patients were being prescribed ≥120mg/day as a single drug; morphine, oxycodone, fentanyl or buprenorphine, irrespective of opioid polypharmacy. Across both practices, 1.71/1000 patients were identified as long-term, high-dose users of opioid medication for chronic non-cancer pain. Prevalence was similar in the two practices. Repetition of the process until January 2021 showed no change in the pattern.

Conclusion: This study offers confirmation that a significant group of patients are prescribed long-term opioid medication for chronic pain at doses which are unlikely to be effective in reducing pain but are likely to have harmful consequences. The findings offer a simple, reliable and practical method of data extraction to identify these patients individually from routinely collected prescribing data, which will help in monitoring and treating individuals and establishing the problem prevalence.

How this fits in

Whilst there is much concern about the increasing prescribing of opioid medication in recent years, little is known about those patients prescribed high doses in the long term. A detailed examination of prescribing for chronic non-cancer pain at the individual patient level informed the development of a simple method for identifying those prescribed sustained high doses. This allows for the identification for monitoring and intervention of those patients most likely to be at risk of harm resulting from opioid doses which are likely to be ineffective in reducing pain.

Introduction

UK opioid prescribing has increased substantially since 1990[1,2], with similar changes internationally[3] especially in North America[4-6]. There is widespread concern in the UK related to severe problems in the USA,[7-10] where there has been an epidemic of opioid use and resulting harm arising, in part, from the indiscriminate prescribing and diversion of pain medication. There is little evidence for problems of the scale and severity experienced in the USA occurring outside North America. Most opioid prescribing in the UK is for chronic non-cancer pain (CNCP)[11-13] despite a lack of evidence of effectiveness[14-19] and the risk of direct and indirect harms[15,17,19-26]. Epidemiological evidence shows that opioids for CNCP are associated with worse functioning and quality of life[27-30] and clinical experience suggests is this is particularly true with high doses.

An emerging consensus suggests that opioid treatment for chronic pain should be approached with care rather than with unbridled enthusiasm[31]. However, we must now cope with the consequences of past over-enthusiasm. It is important find practical ways to identify patients in primary care on long-term high-dose regimens.

Table 1 about here

Studies of opioid prescribing in the UK are summarised in **Table 1**. Overall prescribing may have decreased but rates remain much higher than they were 25 years ago[2,11,41]. In contrast, prescribing of stronger drugs has increased[2,11,36,38], as has the number of people prescribed long-term opioids[33,41]. These studies illustrate persistent concerns about use of opioid medication in the UK population. However, to properly understand, and then address, the problem, individual-level information is needed. Aggregated population-level statistics showing 100 prescriptions issued cannot distinguish between 100 people with one prescription each, 10 people with 10 prescriptions each, or one person with 100 prescriptions, each of indicates a different clinical situation. There is also a need for a method to identify individual patients on these regimens within practice populations to facilitate evaluation and intervention.

The aim of this study is to develop a practical method to identify all patients on long-term high-dose opioid regimens within primary care and to describe patterns of opioid prescribing in two practice populations.

Method

The criteria for long-term high-dose (LTHD) opioid prescribing were 1) daily oral morphine equivalent (ME) dose of 120mg or more (see[39,42]); 2) prescribed continuously for more than one year and 3) cancer patients were excluded. The Royal College of Anaesthetists[43] indicates that "The risk of harm increases substantially at doses above an oral morphine equivalent of 120mg/day, but there is no increased benefit" and the British Pain Society[44] has recommended that CNCP patients being prescribed opioids at this doses or above should be referred to specialist pain services. A one-year criterion was chosen as it is unequivocally long-term use.

A point prevalence study was carried out in two GP practices in North Wales. Practice (A) was a large, fully medically staffed practice in a market town with national average levels of social deprivation, as indicated by the Welsh Index of Multiple Deprivation (WIMD)[45]. It was not identified, either internally or externally, as an outlier regarding opioid prescribing, lying below the mean for the Local Health Board (LHB).

During data collection in practice A, we were asked to provide support on opioid prescribing to a second GP practice (B) in an ex-mining community, with higher WIMD[45] levels of social deprivation. It was entirely staffed by locum GPs and administered by the LHB. Opioid prescribing was close to the LHB mean.

Table 2 about here

Data was extracted from the practices' computerised records for all prescriptions of opioid analgesic medication, including compound drugs (see **Table 2** for details), dated between 1st October 2016 and 31st January 2017 (practice A) and 17th January and 15th May 2017 (practice B). The data included: age and sex; date of prescription; drug name, strength and dose direction; and quantity prescribed. The weeks beginning Monday 9th January 2017 (practice A) and Monday 24th April 2017 (practice B) were selected as the index week and all prescriptions issued in that week or for use in that week

were identified. PRN prescriptions dated in the month preceding the index week and/or records indicated continuing use, were included. An estimate of daily dose was made. For PRN prescriptions, this was calculated by dividing the total quantity of drug prescribed by the number of days between the two prescriptions nearest the index week. This method was also used where there was a clear difference between the use calculated and the amount specified in the dose direction; otherwise the dose as directed was used. Oral morphine equivalent (ME) doses were calculated using conversion tables from Palliative Care Guidelines Plus[46]; total 24-hour doses were calculated for individual drugs and for all opioids issued.

It was assumed that there were likely to be three ways in which total ME dose might exceed 120mg/day:

A. as a high dose of a single drug;

B. as a relatively high dose of one drug with a dose of a second drug;

C. as lower doses of several opioid drugs in combination.

Three sets of criteria were applied sequentially to the collected data to identify three (non-mutually exclusive) patient groups:

A. those prescribed a daily dose of a single drug ≥120mgME;

B. those prescribed a daily dose of a **single drug** between 60mgME and 119mgME and other opioid(s);

C. those prescribed three or more different opioids. (This iteration identified very few cases not found in A or B, none of which had doses approaching 120mgME. It was subsequently discontinued.)

All LTHD patients were identified. Those with a cancer diagnosis were excluded. Comparison data on these patients for the corresponding period a year earlier was collected.

In practice A, additional data was collected from review of LTHD patient records: indication for use of opioid; non-opioid analgesic or adjuvant medications; referral history to secondary care pain services: and longitudinal opioid prescription histories.

The LHB policy is that opioid replacement for substance misuse must be prescribed by specialist services, not GPs; no opioid prescriptions for substance misuse were identified.

When the data had been collated, the findings were presented to a meeting of practice A staff. Prescribers' comments elicited and recorded. This was not possible in practice B because of unstable medical staffing.

The exercise was repeated yearly in practice A in the corresponding week from 2018 to 2021. One repeat audit was conducted in practice B in October 2020.

Service users from PÂR-NCMH[47] were consulted during the planning of this research.

Results

Table 3 summarises opioid prescribing data from the two primary care practices. In both practices, all patients identified as LTHD reached the threshold dose through prescription of **a single drug** at

≥120mgME. No patient crossed the dose threshold only when doses of different opioids were aggregated.

Table 3 about here

Combining figures from the two practices showed a LTHD prevalence of 1.71/1000 patients (practice A: 1.74/1000; practice B: 1.65/1000).

All the LTHD patients were prescribed morphine, oxycodone or fentanyl transdermal patches. In **practice A**:

- 8 on morphine (Highest daily ME 619mg).
- 6 on oxycodone (Highest daily ME 480mg).
- 11 on fentanyl (Highest daily ME 540mg).

14 out of 25 also had PRN opioid prescriptions. When PRN was added, the highest daily ME was 778mg.

In **practice B**:

- 4 on morphine (Highest daily ME 480mg)
- 5 on oxycodone (Highest daily ME 320mg)
- 5 on fentanyl (Highest daily ME 540mg)

3 out of 14 patients also had PRN opioid prescriptions.3

Table 4 summarises high dose opioid prescribing in practice A between 2017 and 2021. LTHD rates increased from 1.74/1000 to 1.92/1000 during this period. In practice B, this rate decreased from 1.65/1000 to 1.26/1000 in 2020. It can be seen from the **Supplementary File** that once high doses were reached, they tended to be maintained and that in January 2021 there were a small number of LTHD buprenorphine prescriptions (3 [6%] of all the LTHD patients from Practice A).

Table 4 about here

In **practice A**, LTHD patients' ages ranged from 32 to 88 years (mean 61.1, median 58). 15 (60%) were female. In **practice B**, ages ranged from 30 to 80 years (mean 51.7, median 44.5). Five (36%) were female. **Table 5** gives detailed age distributions.

Table 5 about here

Practice A data showed indications for opioids: musculoskeletal pain in 21/25 and chronic abdominal pain in 4/25. 9/25 had never been referred, at any point, to secondary care pain services. 19/25 were prescribed non-opioid analgesics or adjuvant medications:

- Amitriptyline 7
- Other antidepressants 11 (2 antidepressants in two instances)
- Benzodiazepines 4
- Hypnotics 1
- Gabapentinoids 7 (1 patient with a diagnosis of epilepsy)
- NSAIDs 4
- Ketamine 1

It was possible to determine the duration of continuous opioid use for 23/25 patients (the other two patients were on high-dose opioids on registration with the practice). Regular non-compound

opioids were initiated 42 to 240 months before the index week (median 126). Initiation of doses ≥120mgME was 13 to 198 months earlier (median 106).

Findings from the first year's data were presented a group of practice A GPs and other staff. They expressed surprise at the number of LTHD patients (they had expected few or none). The consensus was that patients experience adverse drug effects at doses below 120mg ME/day, and that a lower dose-threshold might be more appropriate. Problems with adjuvant medications were raised. Conversations about opioids were described as difficult for prescribers and patients, sometimes leading to conflict. Refusal to increase dose or strength and raising cessation or reduction of opioids were difficult topics. There was a perceived lack of alternatives. Prescribers did not feel they had full control of opioid prescribing. The GPs were asked if there were any LTHD patients who experienced satisfactory levels of pain relief without negative effects, none could be identified.

Discussion

Summary

Our findings show that LTHD opioid use for CNCP can be identified in primary care records by searching for prescriptions of morphine, fentanyl, oxycodone or buprenorphine at or above 120mgME/day and examining prescriptions a year previously. This method (see **Table 6**) is less laborious than that used in previous UK studies.

Table 6 about here

As indicated in **Table 3,** examination of opioid prescribing data for practices A and B identified all LTHD patients. A rate of 1.71/1000 patients was calculated for the practices combined. Unadjusted extrapolation would suggest that there might be over 100,000 patients prescribed LTHD opioid medication in the UK, but this figure not epidemiologically reliable. It is a crude estimate. These patients are at risk of harm and functional impairments with very limited pain relief.

Our criteria were conservative: most of the literature accepts 120mgME as the threshold for limited analgesic benefit and high risk of harm[43]. One-year duration was chosen pragmatically. It is likely that some patients experience negative effects at lower doses and shorter durations. **Table 3** sets out data for high doses for less than a year and daily doses between 60 and 120mgME.

Our study shows that some patients follow LTHD regimens for many years. No judgements about drug effectiveness can be made from our findings, but there is a real possibility that harms outweigh benefits for these patients.

We found frequent use of adjunctive pain medications alongside high dose opioids. Many of these have sedative effects that compound the effects of opioids.

The feedback meeting with practice A GPs suggested that LTHD prescribing can arise without the prescriber intending it, confirming uncertainty over the locus of control. The discussion confirmed previous findings regarding difficult doctor-patient interactions about opioids[48,49]. The prescribers were unable to identify any LTHD patient with good pain relief and no adverse effects on functioning.

Strengths and limitations

Our study's main limitation is sample size. Small-scale studies are susceptible to sampling error. The findings should not be over-interpreted. We have presented purely descriptive findings. Set against

this, the size of the study allowed collection and analysis of detailed data the individual patient level with direct counts of cases rather than estimates from a sample of the population of interest. This is a necessary step in developing practical methods to generate large individual level datasets and to identify individual patients for medication review. Replication in other locations with different demographics would be helpful. We are particular aware of the lack of ethnic diversity in the area studied. Our findings are indicative, but a larger study is necessary for fully generalisable findings. Our method will facilitate larger scale studies of LTHD opioid use.

Comparison with existing literature

Two previous studies sought to identify patients prescribed high-dose opioids for CNCP[39,42]. Their methods did not measure duration and made extensive demands on clinical and administrative staff time. Our method is less laborious and captures the group of greatest concern.

Rates of LTHD prescribing in practice A in **Table 4** are consistent with other evidence on potent, high dose and long-term opioid prescribing[2,11,33,38,41]. Increasing levels of such prescribing suggest that prescriber awareness of LTHD opioids because of this study was insufficient to alter prescribing. Decreased LTHD prescribing in practice B may be a result of pharmacist prescribing support provided in the absence of permanent medical staff.

The number of patients prescribed opioids, sex ratio and average age in practice A are similar to a recent primary care study[33]. The results for practice B are different. Research has shown that higher overall rates of opioid prescribing are associated with older-age patients[11,13,33]. **Table 5** shows higher *rates* in people over 75 years, the *number* is evenly spread across those over 40 years.

Research has shown higher levels of opioid prescribing in deprived areas[2,11,32,33,38,41]. Accordingly, rates of overall opioid prescribing were higher in socially deprived practice B. However, rates of LTHD use were similar in the practices. Our prevalence finding is higher than previous studies. This may reflect differences in method, geographical differences, change in prevalence over time, or all three. However, it does not support a recent reduction in high-dose opioid prescribing. It underlines the need for evidence-based interventions to reduce high dose prescribing.

Implications for research and practice

Our method is practical and reliably identifies LTHD patients in UK primary care. It has utility in auditing such regimens and in identifying at-risk patients. It has potential to unpick the fine grain epidemiology of the problem.

Our findings indicate factors that should be explored in future studies: social deprivation; age; duration of high-doses regimens; indications for opioids; adjunctive medications; and better prescribing strategies. Such studies will be important in the development of better pain management strategies in primary care (see[50]).

Additional information

Funding: There was no external funding for this research.

Ethics: The research was registered as audit of routinely collected anonymised data by the LHB R&D department. It did not require NHS or University ethical approval. Bangor University CBLESS Research Ethics Committee gave approval for the collection of staff meeting data. All staff gave prior informed consent.

Competing interests: The authors report no competing interests in the carrying out and reporting of this research.

References

1. National Treatment Agency for Substance Misuse (NTA). Addiction to medicine. http://webarchive.nationalarchives.gov.uk/20120502165324/http://www.nta.nhs.uk/uploads/addictiontomedicinesmay2011a.pdf (2011, accessed October 2020).

2. Curtis HJ, Croker R, Walker AJ, et al. Opioid prescribing trends and geographical variation in England, 1998–2018: a retrospective database study. *Lancet Psychiatry* 2019; 6(2), 140-150.

3. Berterame S, Erthal J, Thomas J, et al. Use of and barriers to access to opioid analgesics: a worldwide, regional, and national study. *Lancet* 2016; 87, 1644-1656.

4. Okie S. A flood of opioids, a rising tide of deaths. *N Engl J Med* 2010; 363(21), 1981-1985.

5. Manchikanti L, Helm S, Fellows B, et al. Opioid epidemic in the United States. *Pain Physician* 2012; 15, ES9-ES38.

6. Fischer B, Jones W, Vojtila L, et al. Patterns, changes, and trends in prescription opioid dispensing in Canada, 2005-2016. *Pain Physician* 2018, 21 (3), 344-353.

7. Dhalla IA, Persaud N and Juurlink DN. Facing up to the prescription opioid crisis. *BMJ* 2011; 343: d5142

8. Stannard C. Opioids in the UK: what's the problem? *BMJ* 2013; 347: f5108.

9. Kotecha MK and Sites BD**.** Pain policy and abuse of prescription opioids in the USA: a cautionary tale for Europe. *Anaesthesia* 2013; 68(12), 1210-1215.

10. Weisberg DF, Becker WC, Fiellin, DA, et al. Prescription opioid misuse in the United States and the United Kingdom: Cautionary lessons. *Int J Drug Policy* 2014; 25(6), 1124-1130.

11. Davies E, Phillips C, Rance J et al. Examining patterns in opioid prescribing for non-cancer-related pain in Wales: preliminary data from a retrospective cross-sectional study using large datasets. *Br J Pain* 2019; 13, 145-158.

12. Health and Social Care Information Centre. Prescriptions dispensed in the community: England 2002-2012. https://files.digital.nhs.uk/publicationimport/pub11xxx/pub11291/pres-disp-com-eng-2002-12-rep.pdf (2013, accessed October 2020).

13. Zin CS, Chen L-C and Knaggs R. Changes in trends and pattern of strong opioid prescribing in primary care. *Eur J Pain* 2014; 18, 1343-1351.

14. Noble M, Treadwell JR, Tregear SJ et al. Long-term opioid management for chronic noncancer pain. *Cochrane Database Syst Rev* 2010; 1: CD006605.

15. Manchikanti L, Vallejo R, Manchikanti KN, et al. Effectiveness of long-term opioid therapy for chronic non-cancer pain. *Pain Physician* 2011, 14, E133-E156.

16. Chan BKB, Tam LK, Wat CY, et al. Opioids in chronic non-cancer pain. *Expert Opin Pharmacother* 2011; 12(5),705-720.

17. Chou R, Turner JA, Devine EB et al. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. *Ann Int Med* 2015; 162(4), 276-286.

18. Els C, Jackson TD, Hagtvedt R, et al. High-dose opioids for chronic non-cancer pain: an overview of Cochrane Reviews. *Cochrane Database Syst Rev* 2017; 10: CD012299.

19. Chou R, Hartung D, Turner J, et al. Opioid Treatments for Chronic Pain. Comparative Effectiveness Review No. 229. Agency for Healthcare Research and Quality; April 2020 : https://doi.org/10.23970/AHRQEPCCER229

20. Benyamin R, Trescot AM, Datta , et al. Opioid complications and side effects. *Pain Physician* 2008, 11(2Suppl), S105-S120.

21. Labianca R, Sarzi-Puttini P, Zuccaro SM et al. Adverse effects associated with non-opioid and opioid treatment in patients with chronic pain. *Clin Drug Investig* 2012; 32(Suppl. 1), 53-63.

22. Els C, Jackson TD, Kunyk D, et al. Adverse events associated with medium- and long-term use of opioids for chronic non-cancer pain: an overview of Cochrane Reviews. *Cochrane Database Syst Rev* 2017; 10: CD012509.

23. Lee M, Silverman SM, Hansen H, et al. A comprehensive review of opioid-induced hyperalgesia. *Pain Physician* 2011; 14(2), 145-161.

24. Brush DE Complications of long-term opioid therapy for management of chronic pain: the paradox of opioid-induced hyperalgesia. *J Med Toxicol* 2012; 8(4), 387-392.

25. Vowles KE, McEntee ML, Julnes PS, et al. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. *Pain* 2015; 156(4), 569-576.

26. Bedson J, Chen Y, Ashworth J, et al. Risk of adverse events in patients prescribed long-term opioids: A cohort study in the UK Clinical Practice Research Datalink. *Eur J Pain* 2019; 23(5), 908-922.

27. Eriksen J, Sjøgren P, Bruera E et al. Critical issues on opioids in chronic non-cancer pain: An epidemiological study. *Pain* 2006; 125(1-2), 172-179.

28. Jensen MK, Thomsen AB, and Højsted J. 10-year follow-up of chronic non-malignant pain patients: Opioid use, health related quality of life and health care utilization. *Eur J Pain* 2006; 10(3), 423-433.

29. Sjøgren P, Gronbaek M, Peuckmann V, et al. A population-based cohort study on chronic pain: the role of opioids. *Clin J Pain* 2010; 26(9), 763-769.

30. Birke H, Ekholm O, Sjøgren P et al. Long-term opioid therapy in Denmark: A disappointing journey. *Eur J Pain* 2017; 21(9), 1516-1527.

31. Stannard C. Where now for opioids in chronic pain? *Drug Ther Bull* 2018, 56 (10), 118-122.

32. Ruscitto A, Smith BH and Guthrie B. Changes in opioid and other analgesic use 1995–2010: Repeated cross-sectional analysis of dispensed prescribing for a large geographical population in Scotland. *Eur J Pain* 2015; 19, 596.

33. Cartagena Farias J, Porter L, McManus, S, et al. *Prescribing patterns in dependence forming medicines*. London: NatCen, 2017.

34. Bedson J, Chen Y, Hayward RA, et al. Trends in long-term opioid prescribing in primary care patients with musculoskeletal conditions: an observational database study. *Pain* 2016; 157(7), 1525-1531.

35. Green DJ, Bedson J, Blagojevic-Burwell M, et al. Factors associated with primary care prescription of opioids for joint pain. *Eur J Pain* 2013; 17(2), 234-244.

36. Foy R, Leaman B, McCrorie C, et al. Prescribed opioids in primary care: cross-sectional and longitudinal analyses of influence of patient and practice characteristics. *BMJ Open* 2016; 6, e010276.

37. Jani M, Birlie Yimer B, Sheppard t, et al. Time trends and prescribing patterns of opioid drugs in primary care in UK primary care patients with non-cancer pain: A retrospective cohort study. PLoS Med 2020; 17(10), e1003270.

38. Mordecai L, Reynolds C, Donaldson LJ, et al. Patterns of regional variation of opioid prescribing in primary care in England: a retrospective observational study. *Br J Gen Pract 2018;* 68(668): e225-e233.

39. Ponton R and Sawyer R. Opioid prescribing in general practice: use of a two-stage review tool to identify and assess high-dose prescribing. *Br J Pain* 2018; 12(3), 171-182.

40. Ashaye T, Hounsome N, Carnes D, et al. Opioid prescribing for chronic musculoskeletal pain in UK primary care: results from a cohort analysis of the COPERS trial. *BMJ Open* 2018; 8: e019491.

41. Taylor S, Annand F, Burkinshaw P, et al. *Dependence and withdrawal associated with some prescribed medicines: an evidence review*. London: Public Health England, 2019.

42. Bastable R and Rann S. Opioids Aware: a general practice audit of high-dose opioid prescribing NHS England Midlands and East. *Br J Gen Pract Open* 2019; Jul 1;3(2).

43. RCoA, Faculty of Pain Medicine. Opioids aware: a resource for patients and healthcare professionals to support opioid prescribing for pain. www.rcoa.ac.uk/facultyof-pain-medicine/opioids-aware (2015, accessed October 2020).

44. The British Pain Society. *Opioids for persistent pain: Good Practice.* London: The British Pain Society, 2010.

45. Welsh Government. Welsh Index of Multiple Deprivation (full Index update with ranks): 2014. https://gov.wales/welsh-index-multiple-deprivation-full-index-update-ranks-2014 (2015, accessed October 2020).

46. Palliative Care Guidelines Plus. *Opioid dose converter.* http://book.pallcare.info/index.php?op=plugin&src=opiconv (2016, accessed October 2020).

47. PÂR-NCMH. Partnerships in research (PÂR). https://www.ncmh.info/help-with-research/par/ (2020, accessed October 2020).

48. Hughes HK, Korthuis PT, Saha S, et al. A mixed methods study of patient–provider communication about opioid analgesics. *Patient Educ Couns* 2015; 98 453–461.

49. McCrorie C, Closs SJ, House A, et al. Understanding long-term opioid prescribing for non-cancer pain in primary care: a qualitative study. *BMC Fam Pract* 2015; 16(1), 121-129.

50. Bailey J, Nafees S, Jones L, et al. Rationalisation of long-term high-dose opioids for chronic pain: development of an intervention and conceptual framework. *Br J Pain* 2021; 15(3), 326-334.