Grŵp Strategaeth Meddyginiaethau Cymru Gyfan
All Wales Medicines Strategy Group

# Persistent Pain Resources

## Medicines Used in Persistent Pain

**October 2016**
**(December 2020 - Updated to include information from MHRA drug safety updates published in September 2020)**

This document has been prepared by multiprofessional collaborative group, with support from the All Wales Prescribing Advisory Group (AWPAG) and the All Wales Therapeutics and Toxicology Centre (AWTTC). This document has subsequently been endorsed by the All Wales Medicines Strategy Group (AWMSG).

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## EXECUTIVE SUMMARY

- Persistent, also known as chronic, pain is usually defined as occurring when pain has been present for three months or more[1].
- Prevalence of persistent pain varies widely depending on the definition used and how it is measured. An estimated 14 million people in the UK live with persistent pain[2]; this equates to over 600,000 people in Wales.
- Persistent pain can have a significant impact on quality of life and the ability of patients to undertake everyday activities[3].
- Opioid analgesics are increasingly being used to treat persistent pain; however, their safety and efficacy in the long-term management of pain is uncertain, as is the propensity for these medicines to cause problems of tolerance, dependence and addiction[4].
- Strong opioid* use as a whole is increasing within NHS Wales, and accounted for 716,756 items in the year to March 2016, an increase of 11% from the previous year.
- Medicines commonly used in the treatment of persistent pain, such as tramadol, gabapentin, pregabalin, and fentanyl and buprenorphine patches, have prompted recent reviews following concerns regarding safety and risk of misuse and diversion[5-8]. In September 2020, following a review of the risks of dependence and addiction associated with prolonged use of opioid medicines (opioids) for non-cancer pain, the Medicines and Healthcare products Regulatory Agency (MHRA) recommends that before prescribing opioids, healthcare professionals should discuss with the patient the risks and features of tolerance, dependence, and addiction, and agree together a treatment strategy and plan for end of treatment[9]. Also, following a review of the risks associated with use of opioid medicines for non-cancer pain, the Commission on Human Medicines (CHM) has recommended that fentanyl transdermal patches are contraindicated in opioid-naive patients in the UK[10].
- Medicines used in persistent non-malignant pain conditions have featured in the National Prescribing Indicators (NPIs)[11-13]. During the development of the NPIs for 2016–2017, it was identified that signposting resources to support non-specialist prescribers in this complex therapeutic area would help to promote appropriate prescribing in line with the prudent prescribing initiatives[14].
- The resources are aimed at non-specialist prescribers and those involved in medicines review in primary care. The resources signpost to appropriate, relevant and up-to-date information on the prescribing of medicines in persistent pain and include key messages pulled from national and local guidance. They also aim to address the inappropriate prescribing of medicines in pain management and reduce the risks associated with misuse and diversion.
- The signposted resources include information on the non-pharmacological management of persistent pain, and issues surrounding opioid/strong opioid prescribing and prescribing for neuropathic pain.

* See National Prescribing Indicators 2015–2016 for details of CASPA drug baskets.

## PERSISTENT PAIN RESOURCES OVERVIEW

The resources signpost to and pull together key messages from appropriate, relevant and up-to-date information, focussing on the care of patients with persistent (also known as chronic) pain conditions in non-specialist settings. They provide information on the non-pharmacological and pharmacological management of persistent pain, including issues surrounding opioid/strong opioid prescribing and prescribing for neuropathic pain.

These resources do not aim to produce prescriptive guidance or formularies. Rather, they aim to direct non-specialist prescribers involved in the care and medication reviews of patients with persistent pain to the most up-to-date and useful evidence-based resources and highlight the main messages from national and local guidance.

**Areas of focus**
The resources will focus on four main areas:

1. Persistent pain – understanding the condition;
2. Non-pharmacological management of persistent pain conditions;
3. Opioid/strong opioid prescribing in persistent pain conditions;
4. Neuropathic pain.

**Aim**
The aim of these resources is to:

- Raise awareness of the issues surrounding the management of persistent pain conditions and support patients, carers and healthcare teams in understanding the potential benefits and harms of medicines used in pain management.
- Provide prescribers with the information needed to support the appropriate management of persistent pain conditions.
- Address inappropriate prescribing of medicines in pain management and reduce the risks associated with misuse and diversion.

**Contents**
The resources include:

- Executive Summary and Introduction
- Medicines Used in Persistent Pain – prescribing data and safety information
- Signposting to Persistent Pain Resources – summary, resources for healthcare professionals, including guidance and audits, resources for patients, including patient information leaflets and videos
- Ten Key Messages:
  - Managing persistent pain
  - Non-pharmacological management
  - Neuropathic pain
  - Strong opioids
- Management of Persistent Pain – Shared Decision-Making Toolkit
- Management of Persistent Pain – Educational Slide Set

## CONTENTS

## 1.0 INTRODUCTION

Pain is a common and distressing condition, which is often categorised as either acute or persistent (also known as chronic). Acute pain can occur as a result of trauma, surgery or an acute illness. Persistent, or chronic, pain has historically been defined as occurring when pain has been present for three months or more. However, it is now recognised that persistent pain can present as a complex problem before this time[15].

### 1.1 Persistent pain

Prevalence of persistent pain varies widely depending on the definition used and how it is measured. An estimated 14 million people in the UK live with persistent pain[2]; this equates to over 600,000 people in Wales.

Persistent non-malignant pain covers a wide range of painful conditions affecting patients physically, psychologically and socially. These conditions can have a significant impact on quality of life and the ability of patients to undertake everyday activities[3]. People with persistent pain need a multi-disciplinary approach to help them manage and cope with the effects of their pain so that they can maintain the highest possible quality of life and are able to function day-to-day.

Persistent pain can range from mild to severe and is not necessarily a sign of existing tissue damage. Rather, it may relate to changes in the peripheral and central nervous system that occur over time, so that the pain signalling becomes self-sustaining over a prolonged period[1]. Unrelieved persistent pain has become a more significant problem as pain prevalence has increased: for example, with an ageing population and with more cancer and trauma survivors[15]. Persistent pain can be difficult to treat and unrelieved persistent pain is a major socio-economic burden for the health service and the community[15].

These Persistent Pain Resources are intended to provide non-specialist prescribers and other healthcare professionals involved in the care and medication reviews of patients with access and signposting to relevant, evidence-based and up-to-date resources brought together from a variety of local and national sources.

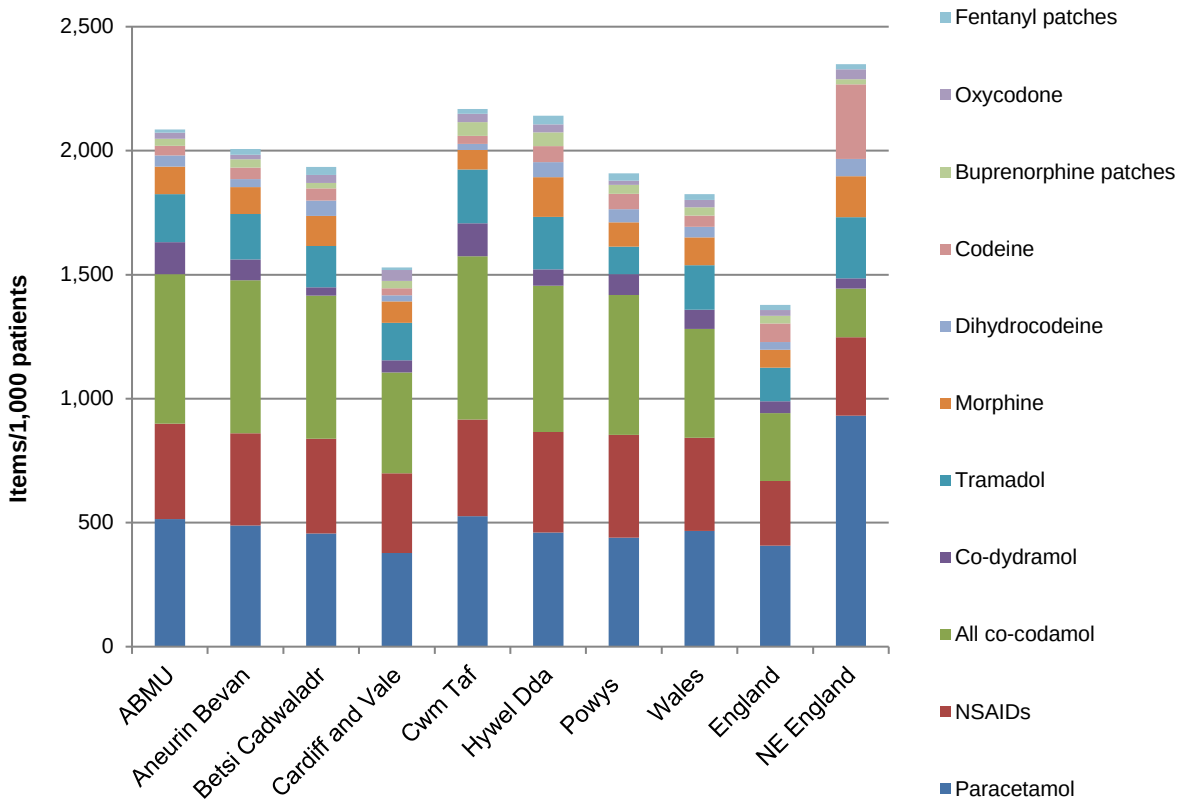
## 2.0 MEDICINES USED IN PERSISTENT PAIN

Medicines commonly used in the treatment of persistent pain, such as tramadol, gabapentin, pregabalin, and fentanyl and buprenorphine patches, have prompted recent reviews following concerns regarding safety and risk of misuse and diversion[5-8].

### 2.1 All analgesics

Figure 1 gives a breakdown of analgesic prescribing for the health boards in Wales, and shows that tramadol and morphine account for the largest proportion of opioid prescribing (excluding combination products such as co-codamol) in all of the health boards. Figure 1 indicates that there is considerable variation between the health boards in the amount of opioid items prescribed. Wales appears to have higher prescribing of co-codamol products than England and NE England. However, NE England has considerably higher prescribing of codeine and paracetamol separately.

**Figure 1. Analgesic prescribing breakdown for health boards in Wales, England and NE England – April 2015–March 2016[*]**




[*] The data displayed was correct at the time of original publication (October 2016), and has not been updated as part of the December 2020 update that was made to include information from MHRA Drug Safety Updates published in September 2020. This data will be updated as part of a full review due to be carried out in 2021.

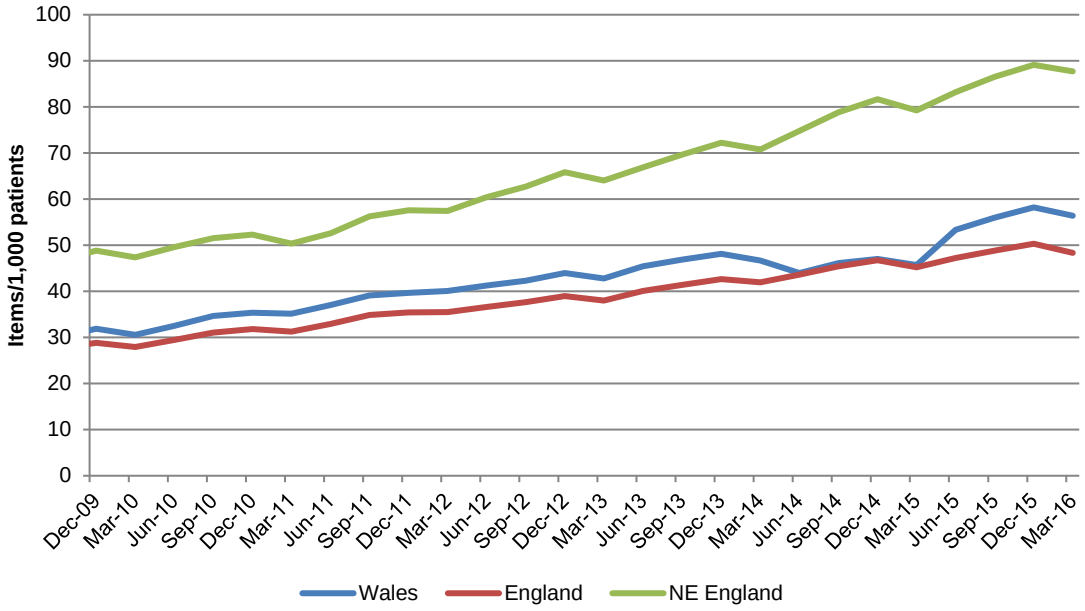
## 2.2 Opioids

Opioid analgesics are increasingly being used to treat persistent pain; however, their safety and efficacy in the long-term management of pain is uncertain, as is the propensity for these medicines to cause problems of tolerance, dependence and addiction[4]. In September 2020, following a review of the risks of dependence and addiction associated with prolonged use of opioid medicines (opioids) for non-cancer pain, the MHRA recommends that before prescribing opioids, healthcare professionals should discuss with the patient the risks and features of tolerance, dependence, and addiction, and agree together a treatment strategy and plan for end of treatment[9]. Also, following a review of the risks associated with use of opioid medicines for non-cancer pain, the Commission on Human Medicines (CHM) has recommended that fentanyl transdermal patches are contraindicated in opioid-naive patients in the UK[10].

Strong opioid use as a whole is increasing within NHS Wales, and accounted for 716,756 items in the year to March 2016, an increase of 11% from the previous year.

Figure 2 shows the increasing prescribing trend for strong opioids* in Wales, England and the North East (NE) of England, and Figure 3 shows the trends for the Welsh health boards. Since the quarter ending September 2011, the number of items prescribed in Wales has increased by 46%. Prescribing has increased by 46% in England and by 52% in NE England.

**Figure 2. Strong opioid prescribing trends for Wales, England and NE England Quarter ending December 2009 to quarter ending March 2016†**




* Strong opioids are defined as per the 2015–2016 NPIs and include buprenorphine, dipipanone, fentanyl, hydromorphone, morphine, oxycodone, pentazocine, pethidine, tapentadol (excluding injection formulations and buprenorphine preparations prescribed for the management of opioid dependence).

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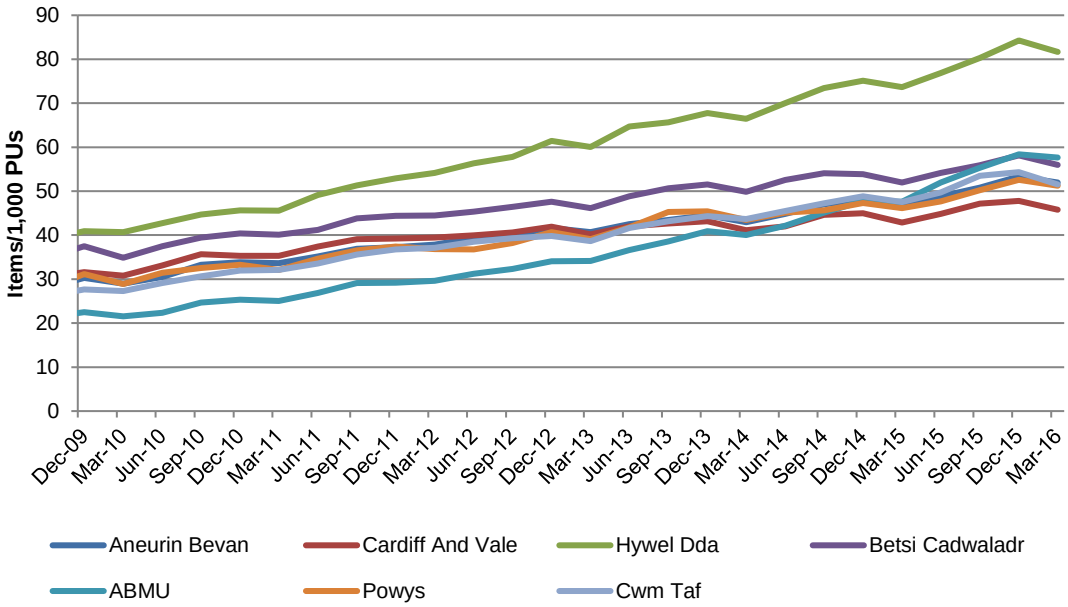
**Figure 3. Strong opioid prescribing trends of the Welsh health boards Quarter ending December 2009 to quarter ending March 2016***




## 2.3 Tramadol

Deaths related to tramadol in England and Wales increased from 83 in 2008[16] to 240 in 2014[17]. Advice published by the Advisory Council on the Misuse of Drugs (ACMD) in February 2013 highlighted the risks associated with misuse and diversion[5]. In October 2013, the All Wales Medicines Strategy Group (AWMSG) published the *Tramadol Educational Resource Materials*, providing healthcare professionals with resources to review the prescribing of tramadol in NHS Wales[18]. In June 2014, tramadol was controlled as a Class C drug under the Misuse of Drugs Act 1971[19] and placed within Schedule III to the Misuse of Drugs Regulations 2001, but with exemption from the safe custody requirements[20].

The Advisory Panel on Substance Misuse (APoSM) published a report on tramadol in September 2015 and a report considering other prescription-only analgesics (including opioids) is scheduled to be published in 2016. The APoSM report *Reducing the harms associated with prescription-only analgesics: Tramadol* made several recommendations to address the issue of deaths associated with tramadol and other prescription-only medicines[21]:

- AWMSG should consider retaining the tramadol NPI as one of the NPIs in Wales for at least a further two years, to highlight the importance of safe and appropriate prescribing of this medicine in primary care in NHS Wales.
- The All Wales Therapeutics and Toxicology Centre (AWTTC) and the Wales Centre for Professional Pharmacy Education (WCPPE) should consider updating and re-issuing the educational and audit resources concerning tramadol prescribing in light of the experience gained since its publication, including the information contained in the APoSM Review.
- AWTTC should ensure that a case study involving tramadol and opioid prescribing is incorporated into the case-based Prudent Prescribing workshops being delivered to all health boards in Wales in 2015–2016.
- A further audit of deaths associated with tramadol in Wales should be conducted in 2015–2016 to examine the impact of the interventions that have been, and will be implemented.

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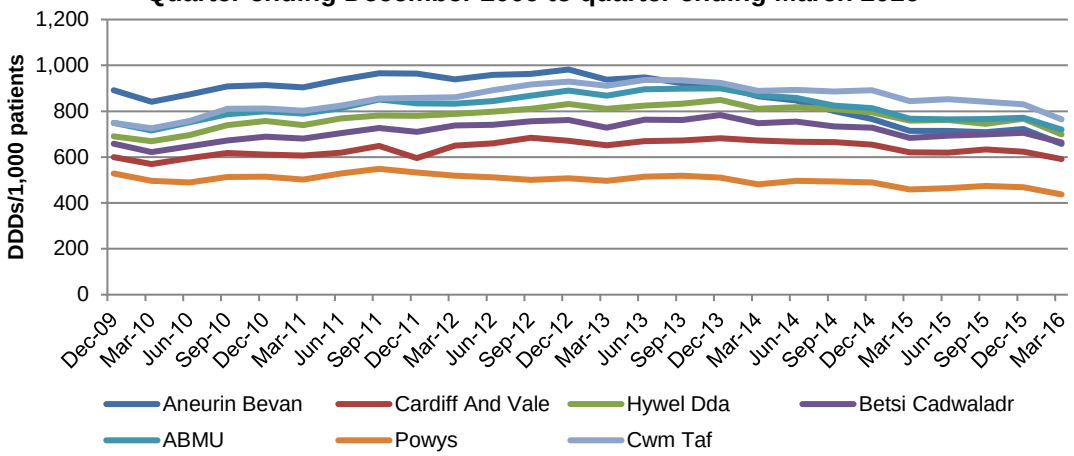
- APoSM should further examine the issues associated with analgesics (including opioid analgesics) other than tramadol in order to make recommendations in the future to improve safe, effective and appropriate use of these enormously important and clinically valuable medicines.

Figure 4 shows the prescribing trend for tramadol in Wales. Tramadol prescribing in NHS Wales started to plateau towards the end of 2013, having risen year-on-year for several years previously, and started to decrease from 2014. Tramadol prescribing decreased significantly (7%, p<0.005) between 2013–2014 and 2014–2015.

**Figure 4. Tramadol prescribing trend of the Welsh health boards Quarter ending December 2009 to quarter ending March 2016***

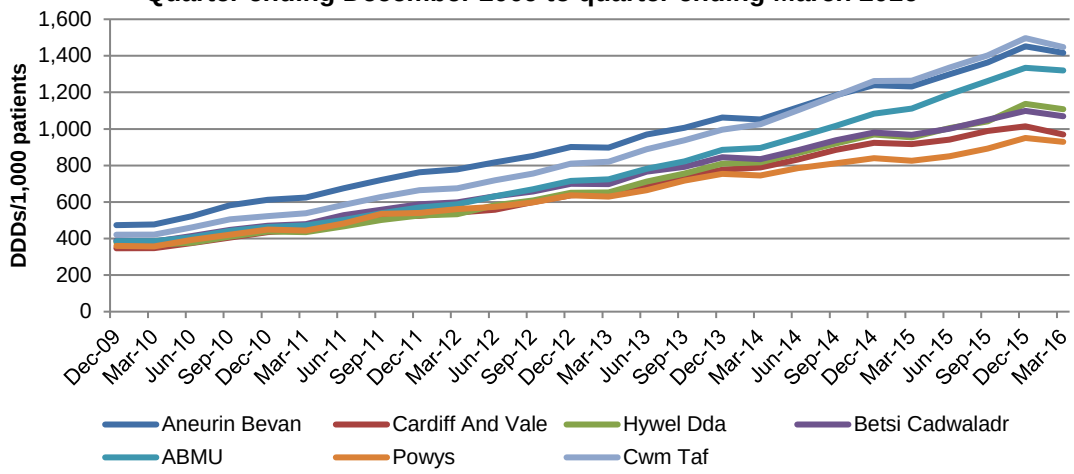



## 2.4 Gabapentin and pregabalin

ACMD published advice in January 2016 concerning gabapentin and pregabalin, highlighting the potential risk of dependence, misuse and diversion of these medicines and the importance of appropriate prescribing to minimise these risks[6]. The number of drug-related deaths where gabapentin and pregabalin were mentioned on the death certificate have increased from 1 and 4 deaths in 2009, to 26 and 38 deaths in 2014 for both gabapentin and pregabalin respectively[6].

Figure 5 shows the prescribing trend for gabapentin and pregabalin in Wales. Gabapentin and pregabalin prescribing has increased in NHS Wales by 16% from 2014–2015 to 2015–2016.

**Figure 5. Gabapentin and pregabalin prescribing trend of the Welsh health boards Quarter ending December 2009 to quarter ending March 2016***

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***Prescribing data***

The prescribing data presented below provide some context and an overview of the recent prescribing trends in medicines used for the treatment of persistent, also known as chronic, non-malignant pain conditions. The data are compiled from the Comparative Analysis System for Prescribing Audit (CASPA) database*, which captures prescribing information from WP10 and WP10HP prescriptions. The data are not linked to specific patient details or indications; caution should therefore be applied when interpreting the data. However, prescribing data can provide useful insight into prescribing behaviours, and emerging trends and comparisons can highlight areas for potential review.

***SPIRA***

In July 2016, the Server for Prescribing Information Reporting and Analysis (SPIRA) was made available. SPIRA provides an online interactive programme for comparative analysis of NPI information. As medicines used in persistent non-malignant pain conditions have featured in the NPIs for a number of years[11-13], SPIRA will be useful for future analysis of prescribing data for these medicines.

It is essential that medicines used in the treatment of persistent pain are monitored within the wider context of pain management. Monitoring trends for all analgesic medicines will ensure that variations or changes in prescribing in NHS Wales can be addressed. Tramadol, gabapentin and pregabalin prescribing will be monitored as part of the NPIs for 2016–2017[13], and morphine prescribing as a percentage of strong opioid prescribing will continue to be monitored as a Local Comparator.

## 3.0 CURRENT GUIDANCE

**A full list of useful resources and guidance is available in the Signposting to Persistent Pain Resources document.**

The Persistent Pain Resources aim to bring together key prescribing messages from local and national resources, and facilitate the sharing of good practice in NHS Wales.

Whilst there has been a lot of work done recently in health boards in Wales on guidelines focusing on a variety of specific areas of pain prescribing, there is currently no comprehensive central point of reference for non-specialist prescribers to access the available resources for the management of persistent pain. Although some patients will require access to specialist secondary and tertiary care pain services, the majority of persistent pain patients will be managed in the community or primary care[22]. See local advice for referral criteria to specialist services.

As of January 2016, the Faculty of Pain Medicine of the Royal College of Anaesthetists (RCoA) hosted the *Opioids Aware* online resource (funded by Public Health England). This resource was developed by UK healthcare professionals and policymakers, and provides information to support safe and effective decisions in the prescribing of opioid medicines for pain[1].

In September 2020, following a review of the risks of dependence and addiction associated with prolonged use of opioid medicines (opioids) for non-cancer pain, the MHRA recommends that before prescribing opioids, healthcare professionals should discuss with the patient the risks and features of tolerance, dependence, and addiction, and agree together a treatment strategy and plan for end of treatment[9].

* CASPA provides a record of all WP10 prescriptions (issued by GPs in Wales for patients receiving NHS treatment) and WP10HP prescriptions (issued by hospitals in NHS Wales) forwarded to Prescribing Services, NWSSP, for processing and payment following dispensing.

The National Institute for Health and Care Excellence (NICE) has published guidance in a number of areas known to be associated with persistent pain, such as osteoarthritis[23], low back pain and sciatica[24], and neuropathic pain[25]. Welsh Government published its '*Service Development and Commissioning Directive for Chronic Non-malignant Pain*' in 2008, which sets out to improve the service provision and care for people living with persistent pain[3].

When prescribing analgesics, it is important that prescribers consider the dose equivalence of the different medicines. Additionally, there may be some variation in the effectiveness of an analgesic between patients, and so it is suggested that prescribers start lower than the equivalent dose, monitoring and titrating slowly, tailoring the treatment to the individual. Equivalence tables are available from a number of sources and may differ locally; it is therefore important to refer to local guidelines when appropriate. Equivalence tables from the British National Formulary (BNF) are included in Appendix 1.

## 4.0 EXAMPLES OF GOOD PRACTICE

Aneurin Bevan University Health Board has published a persistent pain strategy outlining issues around the community management of people with persistent pain, with particular focus on safe and effective prescribing. The strategy outlines the implementation of a package of measures to improve quality and patient safety in the management of persistent pain. Aneurin Bevan University Health Board has also shown the greatest reduction in tramadol prescribing following audit and review, with an 11% decrease from September 2014 to September 2015.

Betsi Cadwaladr University Health Board promotes the use of a written, structured agreement in complex patients, in conjunction with its local guidelines (see Appendix 2A&B), and in line with advice published by the Faculty of Pain Medicine of the RCoA. The written, structured agreement and accompanying documents aim to promote communication about the care of patients receiving opioid treatment for persistent non-malignant pain. The resources were developed in consultation with the local Pain Management Service and GPs to support the safe prescribing of strong opioids for persistent non-malignant pain and to help reduce the risk of problem drug use.

## 5.0 ACKNOWLEDGEMENTS

We would like to acknowledge the work of health boards and local specialist teams in Wales involved in producing various guidance and resources, the Welsh Pain Society and the RCoA Faculty of Pain Medicine, as well as other national organisations. Guidelines, patient information and policy documents have been reviewed and the key messages have been included in these resources, alongside signposting to the full guidance or most relevant resource.

We are always interested to hear about initiatives that have led to good outcomes in health boards in NHS Wales. Please send good news stories from your health board to awttc@wales.nhs.uk.

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## APPENDIX 1: DOSE EQUIVALENCES

It is important to consider dose equivalence when comparing the prescribing of different analgesics. Additionally, there is some variation in the effectiveness of an analgesic between patients, and so it is suggested that prescribers start lower than the equivalent dose, monitoring and titrating slowly, tailoring the treatment to the individual. Equivalence tables are available from a number of sources and may differ locally; it is therefore important to refer to local guidelines when appropriate.

Table 1 below gives an example of a clinical practice guide from the BNF for the dose equivalence of some commonly prescribed opioids. Tables 2 and 3 give **approximately** equivalent 24-hour doses of oral morphine for buprenorphine and fentanyl patches.

**Table 1. Equivalent doses of opioid analgesics[26]**

| Analgesic | Route | Dose |
|---|---|---|
| **Codeine** | PO | 100 mg |
| **Diamorphine** | IM, IV, SC | 3 mg |
| **Dihydrocodeine** | PO | 100 mg |
| **Hydromorphone** | PO | 2 mg |
| **Morphine** | PO | 10 mg |
| **Morphine** | IM, IV, SC | 5 mg |
| **Oxycodone** | PO | 6.6 mg |
| **Tramadol** | PO | 100 mg |
| PO=by mouth; IM=intramuscular; IV=intravenous; SC=subcutaneous | | |

**Table 2. Buprenorphine patch equivalences[26]**

| **Buprenorphine patches are *approximately* equivalent to the following 24-hour dose of oral morphine*.** | | | |
|---|---|---|---|
| morphine salt 12 mg daily | ≡ | BuTrans® '5' patch | 7-day patches |
| morphine salt 24 mg daily | ≡ | BuTrans® '10' patch | 7-day patches |
| morphine salt 48 mg daily | ≡ | BuTrans® '20' patch | 7-day patches |
| morphine salt 84 mg daily | ≡ | Transtec® '35' patch | 4-day patches |
| morphine salt 126 mg daily | ≡ | Transtec® '52.5' patch | 4-day patches |
| morphine salt 168 mg daily | ≡ | Transtec® '70' patch | 4-day patches |

**Table 3. Fentanyl patch equivalences[10,26]**

| **72-hour fentanyl patches are *approximately* equivalent to the following 24-hour dose of oral morphine*.** | | | |
|---|---|---|---|
| morphine salt 30 mg daily | ≡ | fentanyl '12' patch | 3-day patches |
| morphine salt 60 mg daily | ≡ | fentanyl '25' patch | 3-day patches |
| morphine salt 120 mg daily | ≡ | fentanyl '50' patch | 3-day patches |
| morphine salt 180 mg daily | ≡ | fentanyl '75' patch | 3-day patches |
| morphine salt 240 mg daily | ≡ | fentanyl '100' patch | 3-day patches |

* Fentanyl equivalences in this table are for patients on well-tolerated opioid therapy for long periods; for patients who are opioid naive or who have been stable on oral morphine or other immediate release opioid for only several weeks, see further information on fentanyl transdermal route in the BNF. Conversion ratios vary and these figures are a guide only. Morphine equivalences for transdermal opioid preparations have been approximated to allow comparison with available preparations of oral morphine.

## An illustrative example

Below is a case example of a pain medication history seen in a secondary care pain clinic referred from primary care:

- two co-codamol 30/500 tablets taken four times a day;
- two tramadol 50 mg capsules taken four times a day;
- one fentanyl 75 micrograms/hour transdermal patch applied every three days;
- morphine sulfate 10 mg/5 ml oral solution when required.

The morphine equivalence of this is:

- codeine 240 mg in 24 hours, which is equivalent to 24 mg morphine;
- tramadol 400 mg in 24 hours, which is equivalent to 40 mg morphine;
- fentanyl 75 micrograms/hour, which is equivalent to 180 mg morphine in 24 hours.

Total 244 mg morphine equivalence in 24 hours, plus however much morphine oral solution is being taken.

## APPENDIX 2A: BETSI CADWALADR OPIOID REVIEW PRO-FORMA EXAMPLE 2010

**OPIOID MEDICATION REVIEW**
**To be completed in conjunction with the patient assessment tool at each review (monthly during the initial drug titration)** for patients receiving strong opioid therapy for the management of chronic non-malignant pain

| **PATIENT SPECIFIC DETAILS / Addressograph** | |
|---|---|
| G. No: | Consultant: |
| Name: | Address: |
| DoB: | |

| **Checklist ( tick as appropriate)** | | | |
|---|---|---|---|
| **Assessment:** | | **Compliance** | |
| □ | Adequate analgesia<br>Improvement vs. treatment goals<br><br>**If no improvement, review activity and treatment goals and consider whether appropriate to continue opioid** | □<br>□<br>□ | Taking medication as recommended<br>Difficulty with tablets<br>Referral to pharmacist |
| **Side effects:** | | **Outcome:** | |
| □<br>□<br>□<br>□<br><br><br>□<br><br><br>□<br>□<br>□<br>□<br>□<br>□<br>□<br>□<br>□ | Nausea<br>Itching<br>Sedation<br>Dizziness<br>**These side effects may reduce with time - reduce dose or consider alternative opioid if symptoms persist**<br><br>Constipation<br>**Manage actively with dietary advice & stimulant laxative therapy**<br><br>Confusion<br>Memory loss<br>Weight gain<br>Weight loss<br>Sweating<br>Urine retention<br>Hallucinations<br>Respiratory depression<br>Hormonal effects<br>**Consider stopping or reducing the dose if side effects occur** | <br><br><br><br><br><br><br><br>□<br>□<br>□ | <br><br><br><br><br><br><br><br>Continue<br>Increase dose as per protocol<br>Reduce dose as per protocol |
| **Comments** | | | |
| **Date of next review:…… or Discharge from pain service……** | | | |

| **Completed by:** | |
|---|---|
| Signed (healthcare professional): | |
| Print Name: | |
| Designation: | |
| Date: | |
| Contact Number: | |

## APPENDIX 2B: BETSI CADWALADR OPIOID TREATMENT PLAN EXAMPLE 2010

### OPIOID TREATMENT PLAN

***Pain Management Service**: To be completed at time of discharge or outpatient review and a copy sent to the GP.*
***GP initiating treatment:** Complete treatment plan and file in patient's notes*
*Date of review:*

| **PATIENT SPECIFIC DETAILS / Addressograph** | |
|---|---|
| Patient Hospital No: | Consultant: |
| Name: | Address: |
| DoB: | |
| **Treatment Plan** | |
| Opioid recommended:<br>(Drug name: give BRAND name where applicable): | |
| Initial dose and frequency: | |
| Indication/reason for opioid therapy: | |
| Treatment goals: | |
| Maximum dose limit: (Consider specialist referral for patients who fail to derive benefit from large doses of opioids)[1] | |
| Recommended treatment for flare up/breakthrough pain:<br>(include both drug and non drug management) | |
| **Date of next review:……..** | |
| **Completed by:** | |
| Signed (healthcare professional): | |
| Print Name: | |
| Designation: | |
| Date: | |
| Contact Number: | |