Grŵp Strategaeth Meddyginiaethau Cymru Gyfan
All Wales Medicines Strategy Group

National Prescribing Indicators 2022–2025

Supporting Safe and Optimised Prescribing

January 2022

(May 2022 – 'Yellow Cards' section updated with baseline year for targets corrected to 2021–2022)

(September 2022 – 'Best value biological medicines' section updated with named ranibizumab biosimilars)

(January 2023 – 'Best value biological medicines' section updated with bevacizumab removed from basket of included medicines)

(October 2023 – Document updated to reflect that the 2022–2023 NPIs have been extended to 2022–2025)

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

Please direct any queries to AWTTC:

All Wales Therapeutics and Toxicology Centre
The Routledge Academic Centre
University Hospital Llandough
Penlan Road
Llandough
Vale of Glamorgan
CF64 2XX

awttc@wales.nhs.uk
029 218 26900

The information in this document is intended to help healthcare providers make an informed decision. This document should not be used as a substitute for professional medical advice and although care has been taken to ensure the information is accurate and complete at the time of publication, the All Wales Therapeutics and Toxicology Centre (AWTTC) and All Wales Medicines Strategy Group (AWMSG) do not make any guarantees to that effect. The information in this document is subject to review and may be updated or withdrawn at any time. AWTTC and AWMSG accept no liability in association with the use of its content.

Information presented in this document can be reproduced using the following citation:
All Wales Medicines Strategy Group, National Prescribing Indicators 2022–2023: Supporting Safe and Optimised Prescribing. January 2022 (Updated October 2023).

Contents

Introduction

This document was originally published in January 2022 to set out the background, evidence, measures and targets for the National Prescribing Indicators 2022–2023. However, in September 2022, AWMSG agreed that the review and update of the NPIs should change from annually, to every three years. This change will enable health boards to develop longer term plans for utilising the NPIs, by providing assurance that indicators will be in place for a minimum of three years. As a result of this the 2022–2023 National Prescribing Indicators were subsequently extended and will be referred to as the 2022–2025 National Prescribing Indicators throughout this document.

The document has been updated to reflect the measures and targets for 2023–2024 and will be further updated to reflect any changes for 2024–2025. Further details on the measures, targets and drug baskets for 2023–2024 can be found in the NPI Specification document.

Prescribing indicators are used to highlight therapeutic priorities for NHS Wales and compare the ways in which different prescribers and organisations use particular medicines or groups of medicines. Prescribing indicators should be evidence-based, clear, easily understood and allow health boards, primary care clusters, GP practices and prescribers to compare current practice against an agreed standard of quality. Ideally, they should be validated by a group of experts, and should recommend the direction that prescribing should move, even if it is not possible to specify an exact value that represents 'good practice'. They should usually be standardised to allow comparison between health boards, primary care clusters, or practices serving different sized populations. Weighting can also consider the age and demographics of the population.

In October 2003, the All Wales Medicines Strategy Group (AWMSG) agreed that National Prescribing Indicators (NPIs) were useful tools to promote rational prescribing across NHS Wales, and since then, NPIs have evolved to include secondary care in addition to primary care. It was agreed that NPIs should address efficiency as well as quality and that targets should be challenging but achievable, and applicable at practice level. In order to undertake monitoring, the NPIs draw on a variety of data sources such as CASPACluster, Medusa, Audit+ and the Medicines and Healthcare products Regulatory Agency (MHRA).

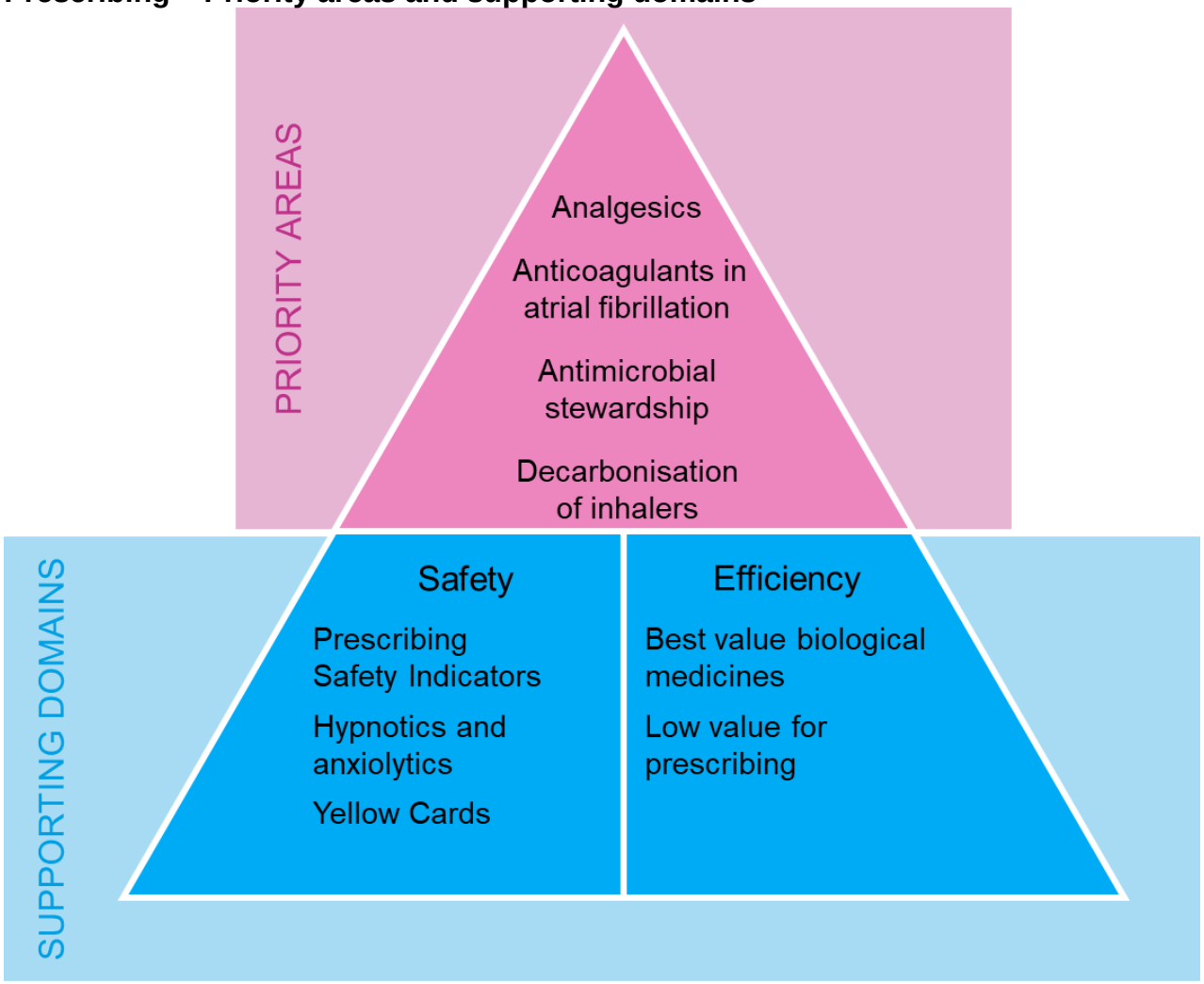
For 2022–2025, the 2020–2021 National Prescribing Indicators: Supporting Safe and Optimised Prescribing have been refreshed with a focus on four priority areas, supported by safety and efficiency domains as shown in Figure 1. The refresh continues with the philosophy of prudent healthcare, enabling higher quality and value through reducing variation, waste and harm, in addition to contributing to two themes in the Quadruple Aim of *A Healthier Wales*, Welsh Government's plan for health and social care[1], namely:

- Population health and wellbeing – better prevention and self-management
- Higher value health and social care – rapid improvement and innovation, enabled by data, focussed on outcomes.

The actions of *A Healthier Wales* (AHW) were revised in September 2020 to support the stabilisation and recovery of services following the Covid-19 pandemic, as well as elements of AHW brought to the forefront by the pandemic. An action within the

Determinants of Health theme focuses on driving good practice to reduce health inequalities and outcomes[2]. Implementation of the NPIs supports this action, and in-depth analysis of the opioid burden, gabapentin and pregabalin, and antimicrobial stewardship NPIs will further support this aim.

Figure 1. National Prescribing Indicators: Supporting Safe and Optimised Prescribing – Priority areas and supporting domains



The measures for each of the priority and supporting areas, together with the background and evidence, reporting methods and data sources are included within this document.

Method used to review and update NPIs

An NPI Task and Finish Group of the All Wales Prescribing Advisory Group (AWPAG) was established to review the 2020–2021* NPIs and discuss potential changes for 2022–2023.

Prior to the NPI Task and Finish Group meeting, a questionnaire was sent to health board medicines management teams, prescribing leads, GPs, cluster pharmacists, secondary care prescribers and pharmacists, and Medicines and Therapeutics Committees. This asked for comment on the continued relevance of the 2020–2021

* Due to the workload pressure across NHS Wales during the COVID-19 pandemic, the NPIs for 2020–2021 were carried forward into 2021–2022.

NPIs and additional priority areas that may be appropriate to monitor. This information then fed into the discussions of the NPI Task and Finish Group.

The 2022–2023 NPIs proposed by the NPI Task and Finish Group were discussed at AWPAG in September 2021 and approved by AWMSG in November 2021.

Key changes for 2022–2025

NPIs for retirement:

- Proton pump inhibitors (PPIs), measured as DDDs per 1,000 PUs.
- Long-acting insulin analogues, measured as the items/number of long-acting insulin analogues as a percentage of total long and intermediate-acting insulin prescribed.

Retired indicators will continue to be monitored as Local Comparators on SPIRA for two years.

NPIs for inclusion:

- High strength opioids, to be included within the opioid burden priority area.
- Decarbonisation of inhalers, to be included as a new priority area.

Measures

ADQ: The average daily quantity (ADQ) is a measure of prescribing volume based upon prescribing behaviour in England. It represents the assumed average maintenance dose per day for a medicine used for its main indication in adults. ADQ is not a recommended dose but an analytical unit to compare prescribing activity.

DDD: The defined daily dose (DDD) developed by the World Health Organization is a unit of measurement whereby each medicine is assigned a value within its recognised dosage range. The value is the assumed average maintenance dose per day for a medicine when used for its main indication in adults. A medicine can have different DDDs depending on the route of administration.

PU: Prescribing units (PUs) were adopted to take account of the greater need of elderly patients for medication in reporting prescribing performance in primary care. Patients aged 65 years and over are counted as three prescribing units; patients under 65 years and temporary residents are counted as one.

STAR-PU: Specific therapeutic group age–sex related prescribing units (STAR-PUs) are designed to measure prescribing weighted for age and sex of patients. There are differences in the age and sex of patients for whom medicines in specific therapeutic groups are usually prescribed. To make such comparisons, STAR-PUs have been developed based on costs of prescribing or items within therapeutic groups.

- Where possible, measures used should be accessible to all medicines management teams through CASPACluster, SPIRA, Audit+ or Medusa.
- The ADQ and STAR-PU measurements are used for certain indicators instead of the DDD measurement and PU weighting in order to benchmark with the ‘Medicines optimisation: key therapeutic topics’ (MO KTT) comparators in England. ADQ measurements are available on CASPACluster and STAR-PU

measurements are updated on a quarterly basis by the NHS Wales Shared Services Partnership (NWSSP): Primary Care Services.
- Digital Health and Care Wales (DHCW) will provide Audit+ data on the Prescribing Safety Indicators, which will be accessed by the Welsh Analytical Prescribing Support Unit (WAPSU) at a health board and cluster level.
- The MHRA will provide data on Yellow Card reporting which will be analysed by WAPSU.
- Secondary care medicines data will be supplied by DHCW through the Medusa data warehouse.
- Where data are provided by external sources, WAPSU cannot be held accountable for errors in data provided or delay in provision of data.
- An NPI specification document detailing drug baskets used will be available on the awttc.nhs.wales website.

Targets

- Details of NPI targets are listed in Tables 1 and 2.
- NPI targets should be challenging but achievable and, unless otherwise stated, based on the principle of encouraging all health boards, local cluster groups and practices to achieve prescribing rates in the best quartile. In these instances, the target is therefore not an absolute value and can be achieved if there is movement towards the threshold set.
  - For primary care NPIs with a threshold, this will normally be set at the 75th percentile (i.e. the prescribing rate of the best performing 25% of practices), for the quarter ending 31st December 2021.
  - Unless otherwise stated, the primary care thresholds are based on prescribing data for all general practices in Wales.

Tables 1 and 2 detail the ‘priority area’ and ‘supporting domain’ NPIs for 2022–2025 respectively, with units of measure and targets where applicable.

Evidence

The evidence, prescribing data (where available), and supporting prescribing messages are outlined in the body of the document.

Table 1. Priority area NPIs for 2022–2025

National Prescribing Indicator	Applicable to:	Unit(s) of measure	Target for 2022–2025	Data source
Priority areas				
Analgesics	Primary care	Opioid burden user defined group (UDG) DDDs per 1,000 patients† High strength opioids (UDG) DDDs per 1,000 patients†	Maintain performance levels within the lower quartile, or show a reduction towards the quartile below.	NWSSP
		Tramadol DDDs per 1,000 patients	Maintain performance levels within the lower quartile, or show a reduction towards the quartile below.	NWSSP
		Gabapentin and pregabalin DDDs per 1,000 patients	Maintain performance levels within the lower quartile, or show a reduction towards the quartile below.	NWSSP
Anticoagulants in atrial fibrillation	Primary care	The number of patients with AF and a CHA_2DS_2-VAS_C score of 2 or more who are currently prescribed an anticoagulant, as a percentage of all patients with AF.	To increase the number of patients with AF and a CHA_2DS_2-VAS_C score of 2 or more prescribed an anticoagulant.	DHCW
		The number of patients diagnosed with AF who are prescribed an anticoagulant and have received an anticoagulant review within the last 12 months, as a percentage of all patients diagnosed with AF who are prescribed an anticoagulant.	To increase the number of patients who are prescribed an anticoagulant and have received an anticoagulant review within the last 12 months.	
		The number of patients diagnosed with AF who are prescribed antiplatelet monotherapy, as a percentage of all patients diagnosed with AF.	To reduce the number of patients with AF prescribed antiplatelet monotherapy.	

† These measures previously used ADQs however due to a lack of ADQ values for a number of opioids, the measures were changed to use DDDs from Q1 2023–2024

National Prescribing Indicator	Applicable to:	Unit(s) of measure	Target for 2022–2025	Data source
Priority areas				
Antimicrobial stewardship	Primary care	Total antibacterial items per 1,000 STAR-PUs	Health board target 2023-2024: a quarterly reduction of 10% against a baseline of April 2019–March 2020‡. GP Practice target: Maintain performance levels within the lower quartile, or show a reduction towards the quartile below.	NWSSP
		Number of 4C antimicrobial (co-amoxiclav, cephalosporins, fluoroquinolones and clindamycin) items per 1,000 patients§	GP Practice target: Maintain performance levels within the lower quartile, or show a reduction towards the quartile below.	NWSSP
Decarbonisation of inhalers	Primary care	The number of dry powder inhalers (DPI) and soft mist inhalers (SMI) as a percentage of all inhalers prescribed.	Maintain performance levels within the upper quartile, or show an increase towards the quartile above.	NWSSP

‡ Previous target for 2022–2023 was a 5% reduction against a baseline of April 2019–March 2020.
§ Health board target for 2022–2023 only was a quarterly reduction of 10% against a baseline of April 2019–March 2020.

Table 2. Supporting domain NPIs 2022–2025

National Prescribing Indicator	Applicable to:	Unit of measure	Target for 2022–2025	Data source
Supporting Domain: Safety				
Prescribing Safety Indicators	Primary care	Number of patients identified	No target set	DHCW
Hypnotics and anxiolytics	Primary care	Hypnotic and anxiolytic UDG ADQs per 1,000 STAR-PUs	Maintain performance levels within the lower quartile, or show a reduction towards the quartile below	NWSSP
Yellow Cards	Primary care	Number of Yellow Cards submitted	One Yellow Card per 2,000 GP practice population	MHRA
	Health board		One Yellow Card per 2,000 health board population 10% or greater increase from baseline (previous financial year) for Yellow Cards submitted by secondary care 25% or greater increase from baseline (previous financial year) for Yellow Cards submitted by members of the public	
	Community pharmacy		No target set. Reported as the number of Yellow Cards submitted by health board	
Supporting Domain: Efficiency				
Best value biological medicines	Primary + secondary care	Quantity of best value biological medicines prescribed as a percentage of total 'biosimilar' plus 'reference' product.	Increase the appropriate use of cost-efficient biological medicines, including biosimilar medicines	NWSSP DHCW
Low value for prescribing	Primary care	Low value for prescribing UDG spend per 1,000 patients	Maintain performance levels within the lower quartile or show a reduction towards the quartile below	NWSSP

Please note: Implementation of the recommended NPIs does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer. This is supported by the philosophy of prudent healthcare and *A Healthier Wales*, Welsh Government's plan for health and social care[1].

1.0 Priority areas

1.1 Analgesics

Analgesic medicines have been the mainstay of the treatment of pain for decades. Pain can be defined as acute or chronic, depending on the length of time the person has experienced pain. Chronic pain, also known as persistent pain, is usually defined as occurring when pain has been present for three months or more[3], and can be further categorised as chronic primary pain (CPP) or chronic secondary pain (CSP). CPP is pain with no clear underlying cause, or pain (or its impact) that is out of proportion to any observable injury or disease, with an estimated prevalence of 1%-6%[4]. CSP is pain caused by an underlining condition, for example rheumatoid arthritis or endometriosis. Chronic primary pain and chronic secondary pain can coexist[4]. In April 2021, NICE published a guideline for *Chronic Pain (primary and secondary) in over 16s: assessment of all chronic pain and management of chronic primary pain,* which advocates a number of non-pharmacological options for the management of chronic primary pain, rather than analgesics[4].

A number of analgesic medicines with different mechanisms of action and licensed indications are available; however, these NPIs focus on total opioid use; high strength opioids; tramadol; and gabapentin and pregabalin. These have been included as indicators as concerns have been raised regarding the appropriate use and review of these medicines, in addition to the potential for dependence, diversion and misuse.

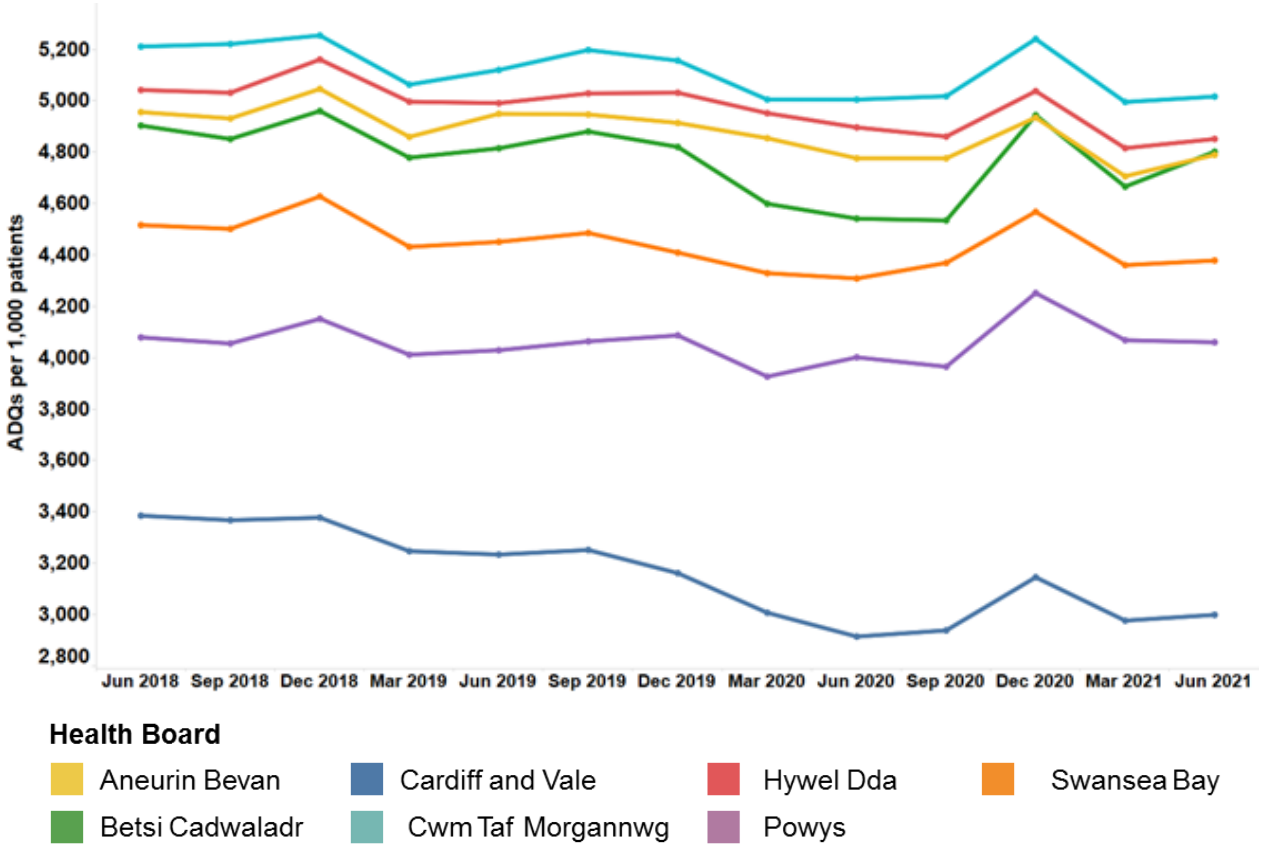
There is increasing evidence that many analgesics, including opioids, gabapentin and pregabalin, have the potential for harm and abuse. Cases of dependency have been described and there are reports of an increasing street value and risk of drug misuse[5]. Patients should be given information on the potential benefits of their medicine, and its risks and reported side effects, including the potential for such medicines to lead to abuse or dependence[5]. In September 2019, due to the growing problem of dependence and addiction to prescription medicines, Public Health England published a review of the evidence for dependence on and withdrawal from prescribed medicines, which included opioids and gabapentinoids. The review made a number of recommendations, including: increasing the availability and use of data on the prescribing of medicines that can cause dependence or withdrawal to support greater transparency and accountability and help ensure practice is consistent and in line with guidance; and improving information for patients on prescribed medicines and other treatments, and increasing informed choice and shared decision making between clinicians and patients[6]. It is anticipated that this priority area will support these recommendations.

1.1.1 Opioid burden

Purpose:
To encourage the appropriate use and review of opioids in primary care, minimising the potential for dependence, diversion, misuse and ADRs.
Units of measure 2022–2025*:
2022–2023: 1. Opioid burden UDG ADQs per 1,000 patients. 2. High strength opioids UDG ADQs per 1,000 patients **2023–2025:** 1. Opioid burden UDG DDDs per 1,000 patients. 2. High strength opioids UDG DDDs per 1,000 patients
Target for 2022–2025:
Maintain performance levels within lower quartile, or show a reduction towards the quartile below.

Note
Monitoring of trends in total analgesic prescribing and other analgesics should be undertaken alongside these NPIs in order to assess the overall picture of analgesia prescribing in Wales.

Figure 2. Trend in opioid burden ADQs per 1,000 patients to quarter ending June 2021



* These measures previously used ADQs however due to a lack of ADQ values for a number of opioids, the measures were changed to use DDDs from Q1 2023–2024

Figure 3. Opioid burden ADQs per 1,000 patients Welsh health boards and English CCGs – Quarter ending June 2021

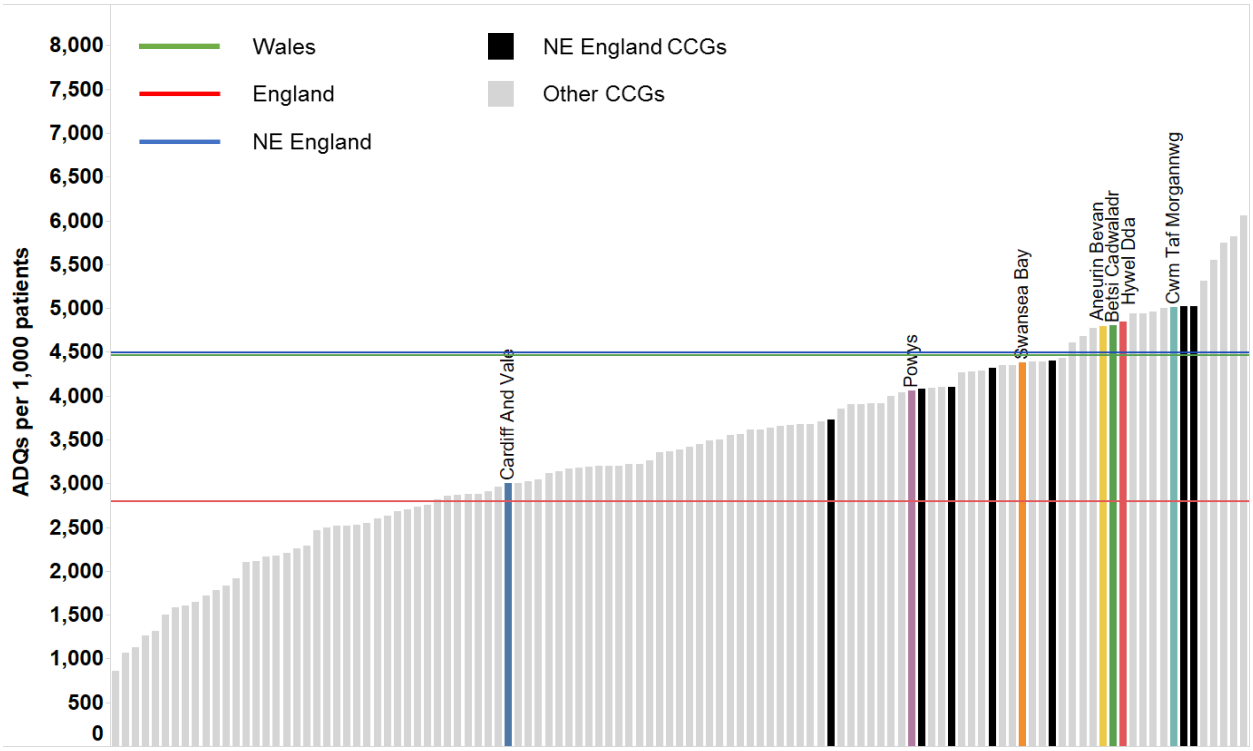
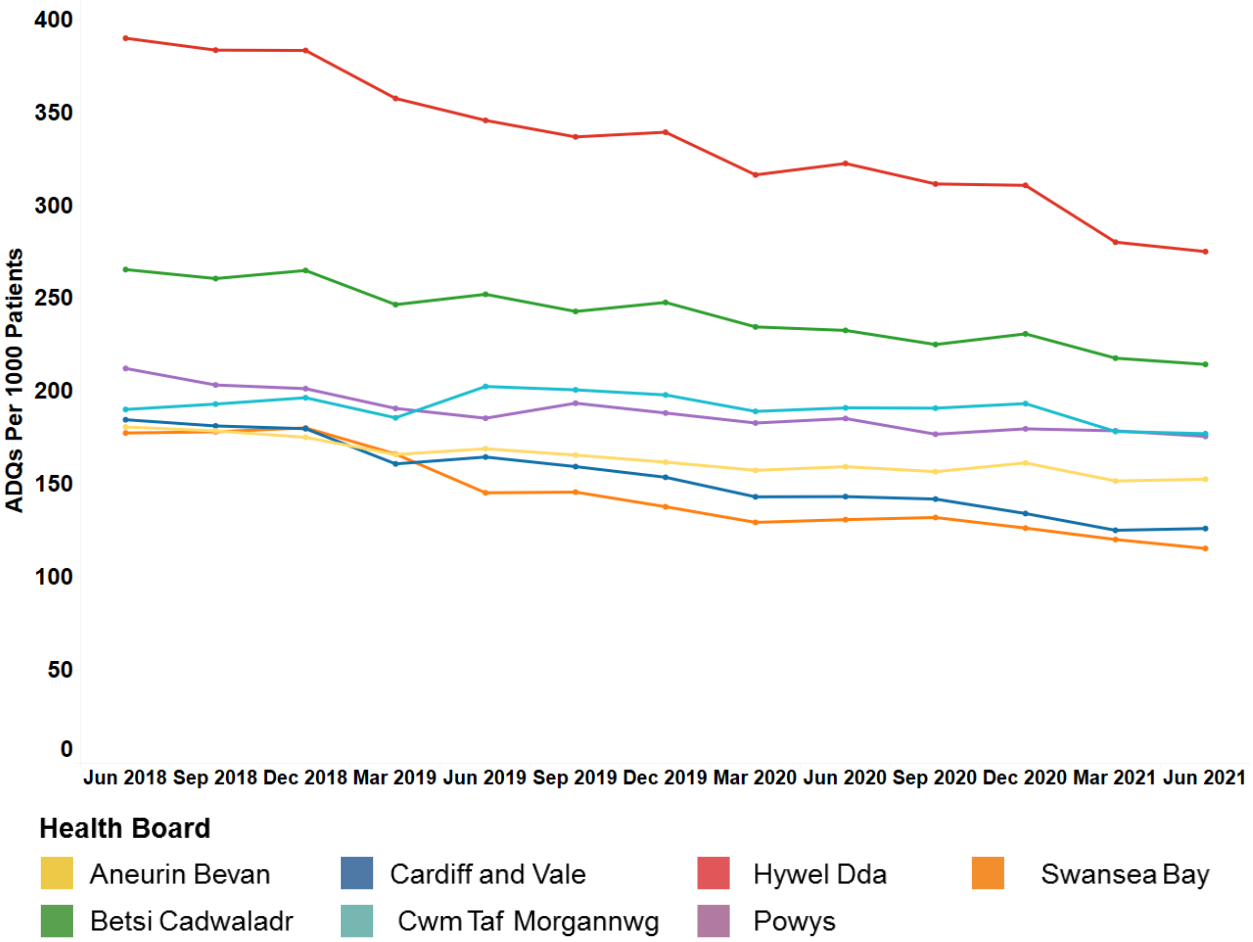


Figure 4. Trend in high strength opioid ADQs per 1,000 patients to quarter ending June 2021



Background and evidence

Opioid analgesics have long been used as the gold standard to treat severe pain, most notably for acute pain and in palliative care[7]. The WHO analgesic ladder, which advocates a stepwise approach from non-opioid analgesics to opioids for mild to moderate pain, followed by opioids for moderate to severe pain, was developed with the aim of helping patients with cancer achieve freedom from pain[8], but has often been used as a guide to the treatment of chronic pain. This has resulted in patients receiving increasing doses of strong opioids, however, it has never been validated in this setting[9], and this simple approach is not appropriate for chronic pain, which is highly complex[10].

Due to a lack of evidence of effectiveness, opioids are not recommended as a treatment option for the management of chronic primary pain. NICE states that opioids should not be initiated to manage chronic primary pain due to a lack of evidence of effectiveness[4]. In addition, evidence from non-randomised studies on the use of long-term opioids for chronic pain suggests an increased risk of dependence, although it is acknowledged that there were limitations on the studies[4].

Opioid analgesics have well established side effects including constipation, nausea and vomiting, and respiratory depression, and repeated administration may cause tolerance and dependence[11]. Whilst concerns regarding tolerance and dependence should be no deterrent in the control of pain in terminal illness[11], consideration should be given to this when prescribing for other causes of pain. A systematic review in 2015 suggested that rates of misuse of opioids in patients treated for chronic pain ranged from 21% to 29% and that addiction resulted in between 8% and 12% of patients taking opioids[12].

A briefing paper by the BMA, *Chronic Pain: supporting safer prescribing of analgesics,* notes that too many people with chronic pain are prescribed opioids at high doses. The dose above which harms outweigh benefits is 120mg oral morphine equivalent in 24 hours. Increasing opioid load above this dose is unlikely to yield further benefits but exposes the patient to increased harm[13]. A table providing approximate equivalence values for opioids can be found in Appendix 1.

Despite the lack of evidence for use in chronic non-cancer pain, research in the UK has found an escalation of strong opioid prescribing in primary care, predominantly for non-cancer patients[7]. A retrospective cohort study, looking at opioid prescribing in primary care in Wales between 2005 and 2015, found that the annual number of prescriptions for opioids increased by 44%, while the total daily oral morphine equivalent per 1,000 patients increased by 95%[14]. During the same period, the number of opioid related deaths increased from 82 in 2005 to 141 in 2015. Since then, the number of opioid related deaths in Wales has fluctuated, with the most recent data reporting a total of 121 deaths[15]. A November 2018 briefing statement to health professionals on the management of opioid medications, issued by the Faculty of Pain Medicine of the Royal College of Anaesthetists, highlights that there is professional and governmental concern regarding misuse of prescription medicines and the number of prescriptions of opioid analgesics. Key messages from the briefing statement include the urgent need to screen and assess people on opioids, and to make clinical decisions about opioid reduction and optimal pain management[16].

NICE guidance recommends that if a person with chronic primary pain is already taking an opioid analgesic, this should be reviewed[4]. As part of the shared decision making process, it should be explained that there is a lack of evidence for these medicines for

chronic primary pain. A plan for continuing safely should be agreed if the patient reports benefit at a safe dose and few harms, or the risks of continuing should be explained if they report little benefit or significant harm[4]. Where this is the case, the patient should be encouraged and supported to reduce and stop the opioid if possible[4].

The decision to taper and stop an established opioid regimen needs to be discussed carefully with the patient, and should include an explanation of the rationale for stopping opioids including the potential benefits of opioid reduction (avoidance of long-term harms and the ability to engage in self-management strategies); agreeing outcomes of opioid tapering; arrangements for monitoring and support during opioid taper; and documented agreement of the tapering schedule. The dose of drug can be tapered by 10% weekly or fortnightly[13].

Chronic pain is a complex condition, which has a substantial impact on the lives of those affected. The relief of pain should be seen as a clinical priority, yet the prescribing of opioids is often not the most appropriate or effective treatment option for many patients with chronic pain, and can risk exposing patients to unnecessary harm[9]. Complete pain relief is rarely achieved, therefore management should focus not only on reduction in pain intensity but also on improved function. An estimated 49% of patients in the UK suffering from chronic pain also suffer from depression[9], and there is variable interplay between biological, psychological and social factors[17]. NICE recommends consideration of an antidepressant, although off label use, in the pharmacological management of chronic primary pain, to help with quality of life, pain, sleep and psychological distress, even in the absence of a diagnosis of depression[4].

This NPI promotes a prudent approach to prescribing opioid analgesics, taking into account the indication, risks and benefits, and encouraging timely review of patients prescribed opioids for chronic pain.

Useful resources

- NICE guideline Chronic pain (primary and secondary) in over 16s: assessment of all chronic pain and management of chronic primary pain
- MHRA Opioids e-learning module
- RCoA Faculty of Pain Medicine (2019) Opioids Aware: Tapering and stopping opioids
- AWMSG (2022) Resources for pharmacological management of pain
- RCoA Faculty of Pain Medicine (2019) Opioids Aware
- RCoA Faculty of Pain Medicine (2019) Checklist for Prescribers

1.1.2 Tramadol

Purpose:
To encourage the appropriate use and review of tramadol in primary care, minimising the potential for dependence, diversion, misuse and ADRs.
Unit of measure:
Tramadol DDDs per 1,000 patients.
Target for 2022–2025:
Maintain performance levels within lower quartile, or show a reduction towards the quartile below.

Note
Monitoring of trends in total analgesic prescribing and other analgesics should be undertaken alongside these NPIs in order to assess the overall picture of analgesia prescribing in Wales.

Figure 5. Trend in tramadol DDDs per 1,000 patients to quarter ending June 2021

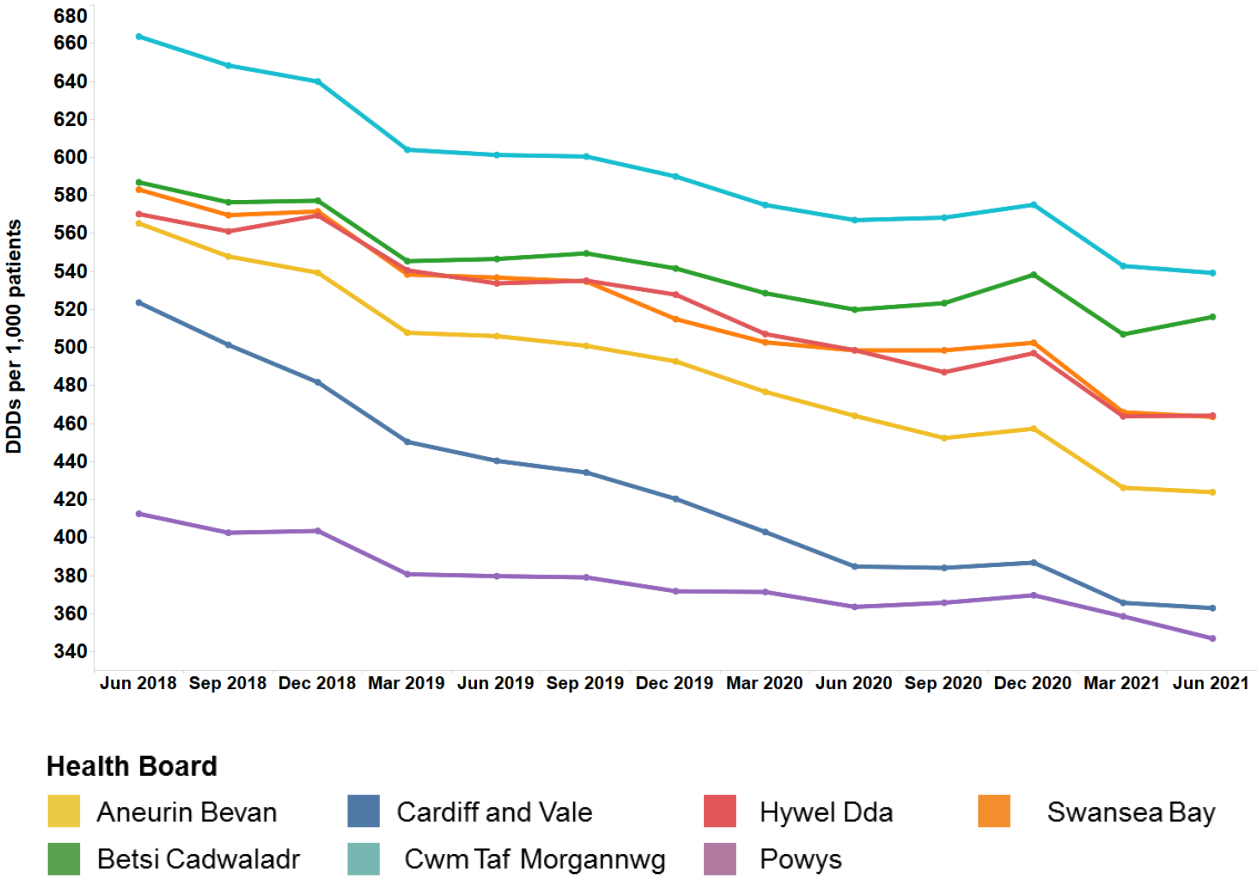
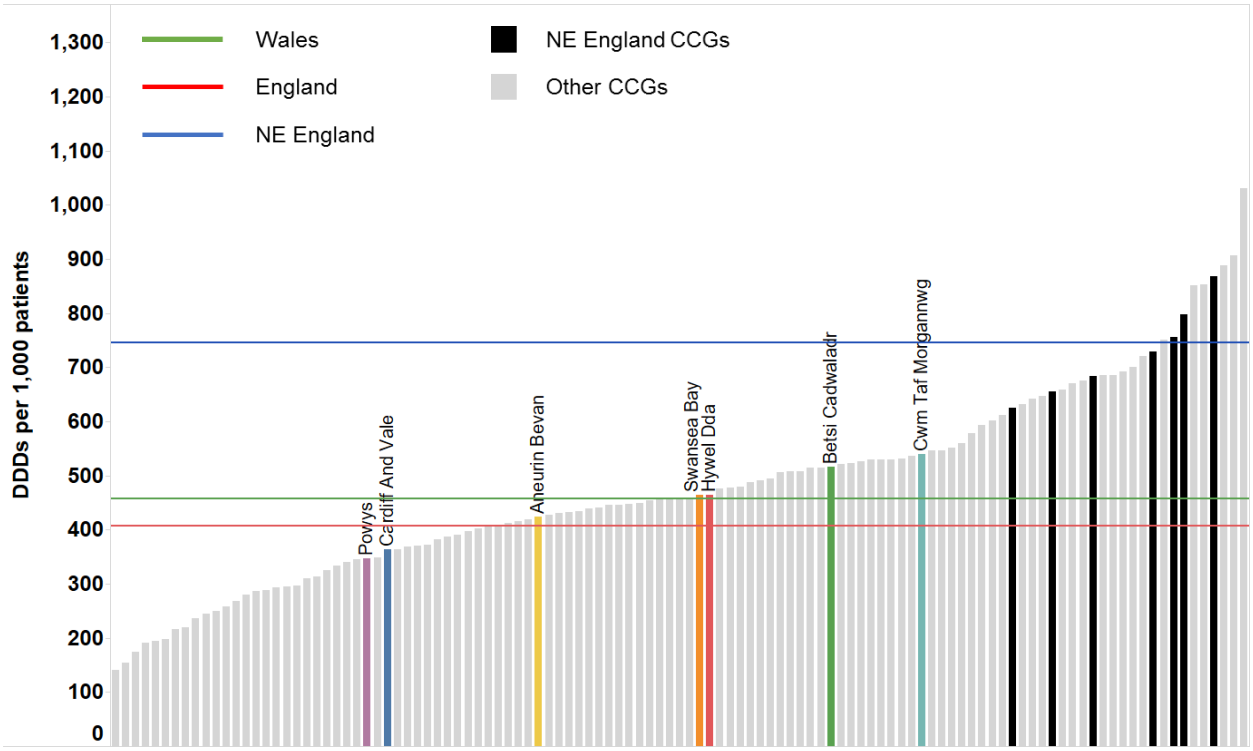


Figure 6. Tramadol DDDs per 1,000 patients Welsh health boards and English CCGs Quarter ending June 2021



Background and evidence

Tramadol is an opioid analgesic licensed for the treatment of moderate to severe pain. Tramadol produces analgesia by two mechanisms: an opioid effect and an enhancement of the serotonergic and adrenergic pathways[11]. It has fewer of the typical opioid side effects (notably, less respiratory depression, less constipation and less addiction potential); psychiatric reactions have been reported[11]. The unique dual-action pharmacological profile of tramadol increases the risk of adverse effects seen in overdose[18].

In 2013, the Advisory Council on the Misuse of Drugs recommended that the UK Government should reclassify tramadol as a class C substance, and place it within Schedule III of the Misuse of Drugs Regulations 2001, due to concerns regarding abuse, dependence and an increasing number of deaths involving tramadol[18]. The changes came into force in June 2014, and since then, the number of deaths involving tramadol in Wales has fluctuated annually[15]. The number of deaths in 2019, where tramadol was noted on the death certificate, reduced by 50% from 14 deaths in 2018 to 7 deaths in 2019[15]. Despite the recent reduction in deaths, concerns remain regarding the potential for abuse and dependence.

Dizziness and nausea are the most commonly reported adverse effects, with headache, drowsiness, vomiting, constipation, dry mouth, fatigue and sweating also frequently reported[19]. Rare adverse effects include hallucinations, confusion, sleep disturbance, anxiety and nightmares, as well as cases of dependence and withdrawal[19]. To minimise the risk of convulsions, patients with a history of epilepsy or those susceptible to seizures should only be treated with tramadol if there are compelling reasons to do so[19]. In addition, tramadol should be used with caution in patients taking concomitant medicines that can lower the seizure threshold, such as tricyclic antidepressants or

selective serotonin reuptake inhibitors (SSRIs)[19]. The use of tramadol is contraindicated in uncontrolled epilepsy and in patients receiving, or who have recently discontinued (within the previous two weeks) monoamine oxidase inhibitors[19].

If it is appropriate for a patient's tramadol to be stepped down or stopped, it is important to note that the dose must be reduced slowly to ensure the patient's safety and to minimise the risk of withdrawal symptoms and/or adverse reactions. Where physical dependence to tramadol develops, the withdrawal syndrome can be severe, with symptoms typical of opiate withdrawal sometimes accompanied by atypical symptoms including seizures, hallucinations and anxiety[18,20]. To encourage patient engagement and concordance, a suggested approach would be to reduce the dose at each reduction step, e.g. by one 50 mg dose, and to titrate according to how the patient manages, rather than by setting time limits for the next reduction. Every patient and their circumstances will be different, and a prudent and individually tailored approach is required[21].

This NPI does not measure the prescribing of tramadol and paracetamol combination products as there are no DDDs available; however, these products are included in the *Medicines Identified as Low Priority for Funding in NHS Wales – Paper 2*, due to a lack of advantage over the individual preparations, with prescribing data made available on SPIRA.

While there is a recognised place in pain management for tramadol, concerns regarding the risks associated with misuse and diversion have prompted a review of tramadol prescribing in NHS Wales. It must be noted that pain management is often complex and prescribers need to make evidence-based, informed decisions based on the individual needs of the patient. This NPI promotes a prudent approach to prescribing tramadol, taking into account the risks and benefits of tramadol and encouraging timely review.

Useful resources

Please note: Links here will be updated to reflect the latest available resources at the time of publication.

- AWMSG (2021) Tramadol educational resources
- AWMSG (2022) Resources for pharmacological management of pain

1.1.3 Gabapentin and pregabalin

Purpose:
To encourage the appropriate use and review of gabapentin and pregabalin in primary care, minimising the potential for dependence, diversion, misuse and ADRs.
Unit of measure:
Gabapentin and pregabalin DDDs per 1,000 patients.
Target for 2022–2025:
Maintain performance levels within lower quartile, or show a reduction towards the quartile below.

Note
Monitoring of trends in total analgesic prescribing and other analgesics should be undertaken alongside these NPIs in order to assess the overall picture of analgesia prescribing in Wales.

Figure 7. Trend in gabapentin and pregabalin DDDs per 1,000 patients to quarter ending June 2021

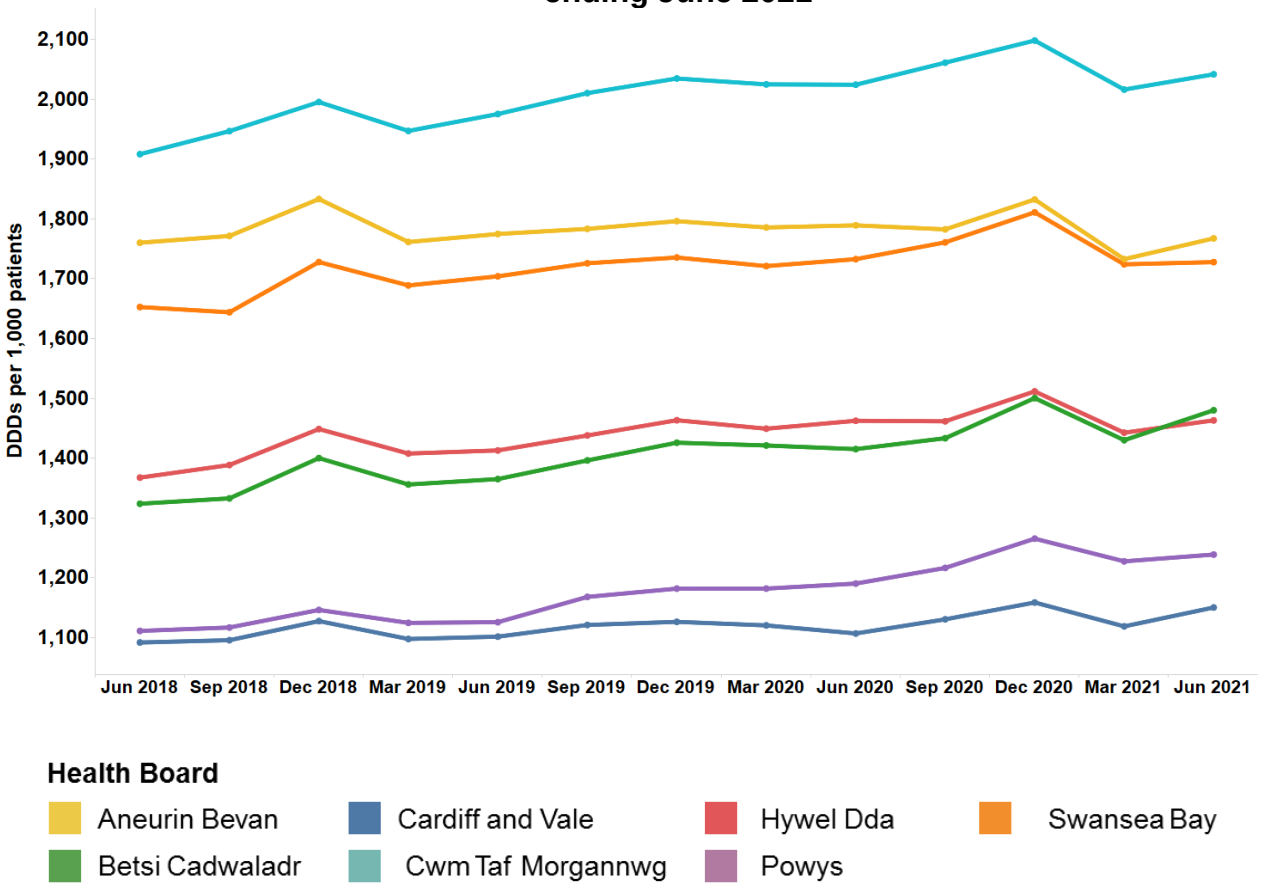
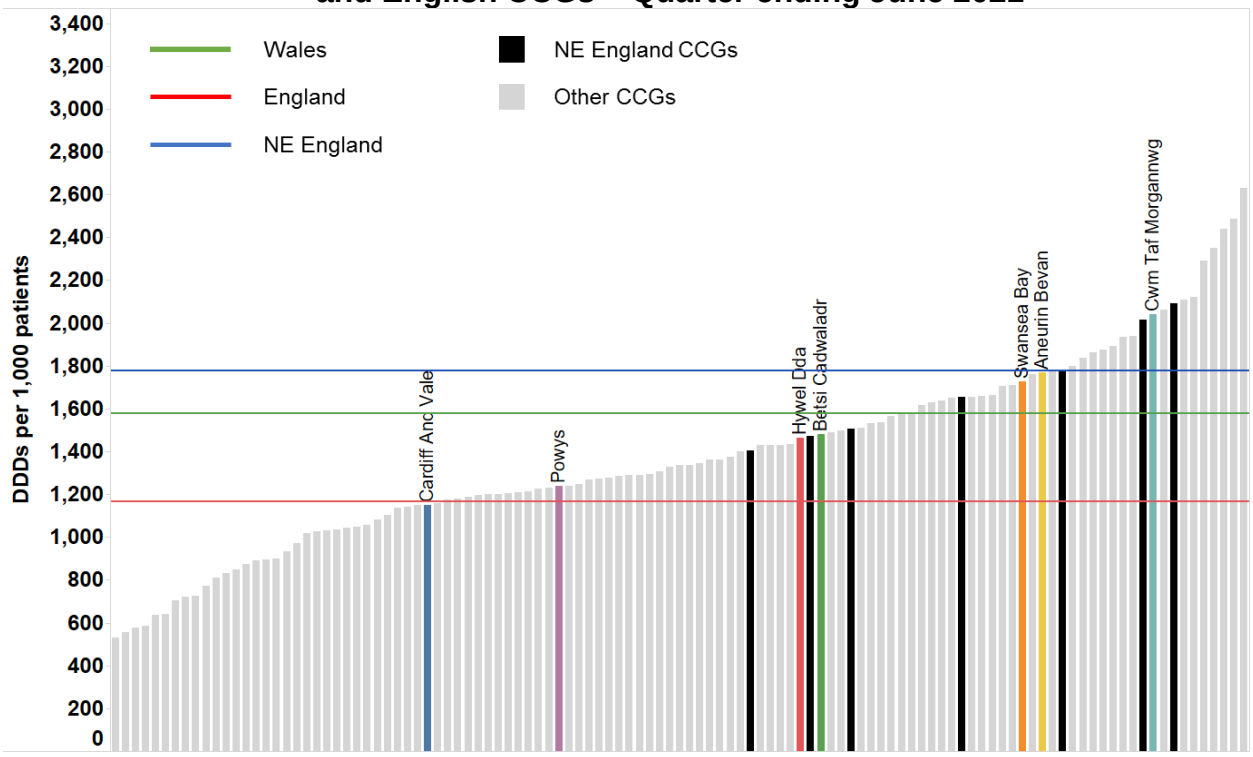


Figure 8. Gabapentin and pregabalin DDDs per 1,000 patients Welsh health boards and English CCGs – Quarter ending June 2021



Background and evidence

NICE recommends gabapentin or pregabalin as first-line options in the treatment of neuropathic pain, along with amitriptyline and duloxetine[22]. Gabapentin is licensed for peripheral neuropathic pain and epilepsy[23-25], whilst pregabalin is licensed for peripheral and central neuropathic pain, in addition to epilepsy and as a third line option for the treatment of generalised anxiety disorder (GAD)[26-29]. In April 2019, gabapentin and pregabalin were reclassified as Schedule 3 controlled drugs in response to recommendations made by the Advisory Council on the Misuse of Drugs, due to concerns regarding the potential risk of dependence, misuse and diversion[30].

Recent NICE guidance *Chronic pain (primary and secondary) in over 16s: assessment of all chronic pain and management of chronic primary pain* recommends that prescribers do no initiate gabapentinoids to manage chronic primary pain, as evidence suggest a lack of benefit, unless as part of a trial for complex regional pain syndrome[4]. As gabapentinoids are currently recommended for neuropathic pain, expert opinion within the committee suggested that complex regional pain syndrome (CRPS) is sometimes understood as a neuropathic pain disorder. Based on the expert opinion of some committee members they therefore decided to make a recommendation for research on the use of gabapentinoids for CRPS to inform future guidance. There is currently variation in the use of drugs to treat chronic primary pain. The recommendations are likely to have a resource impact in the short term because there may be increased resource use from helping people to stop treatments, particularly opioids and gabapentinoids.

There has been increasing use of gabapentin and pregabalin in primary care with prescribing data from the quarter ending March 2021, compared with the quarter ending March 2016, demonstrating an increase of over 33% in prescription items across Wales[31]. Current prescribing of gabapentin and pregabalin in Wales is high in

comparison with England, with 1,550 DDDs per 1,000 patients in Wales[31], compared with 1,149 DDDs per 1,000 patients in England[32] for the quarter ending March 2021. The number of deaths where gabapentin or pregabalin was mentioned on the death certificate has also increased, from a total of 9 deaths in Wales in 2016, to 13 deaths in 2019[15]. Increasing numbers of deaths in Northern Ireland involving pregabalin has led to its removal from the country's formulary for use in neuropathic pain. The Northern Ireland Health and Social Care Board made the decision in August 2021 due to a significant increase in deaths involving pregabalin, and the risks of dependence, misuse and diversion[33].

Dependence, diversion and misuse

The Summaries of Product Characteristics (SPCs) for both gabapentin and pregabalin highlight that cases of misuse, abuse and dependence have been reported. Caution should be exercised in prescribing either drug for patients with a history of substance abuse, and patients should be monitored for symptoms of misuse or dependence[23-28]. A Welsh Health Circular in 2016 noted that patients should be made aware of the risk of harms, including dependence[34]. Their mechanism for producing dependence is not yet well understood, though there may be direct or indirect effects on the dopaminergic 'reward' system[35]. An NHS Scotland resource, *Gabapentinoid Prescribing for Chronic Pain in Primary Care*, highlights that there appears to be more evidence of misuse than for dependence[35].

Misuse of gabapentin and pregabalin has been noted for some years in clients attending substance misuse services, and within prisons; currently, pregabalin appears to be more sought after for misuse than gabapentin[34]. Pregabalin may have a higher abuse potential than gabapentin due to its rapid absorption, faster onset of action and higher potency[30]. Pregabalin causes a 'high' or elevated mood in users[30], and individuals misusing gabapentin and pregabalin describe improved sociability, euphoria, relaxation and a sense of calm[36]. Pregabalin misusers achieve these effects by taking large quantities, ranging from 200 mg to 5 g as a single dose[36].

Individuals at risk of misusing or diverting gabapentinoids may include those with a history of substance misuse; patients who make specific requests for initiation of either gabapentin or pregabalin, particularly after release from prison; patients who repeatedly make requests for an early prescription or repeatedly report lost medication, and those who contact out of hours services for supplies of medication[35]. Prescribers must give careful consideration to the individual patient when prescribing gabapentinoids to minimise the risk of misuse, dependence and diversion and assessment of the risks and benefits is essential[35].

In September 2019, Public Health England published an evidence review; *Dependence and withdrawal associated with some prescribed medicines*, which noted that gabapentinoids have come to be used for a wider range of indications than is supported by the evidence or their licensing, and they have sometimes been prescribed in place of opioids or benzodiazepines in the likely-mistaken belief that they are less liable to misuse or dependence, and lack of awareness of the withdrawal problems that can arise when prescribing is stopped[6]. This is concerning given the increase in number of deaths associated with gabapentin and pregabalin, and highlights the importance of appropriate initiation, review, and tapering and stopping of medication where the patient is not benefitting or there are concerns regarding misuse or diversion.

With prevalence of neuropathic pain estimated to be between 7% and 10%[37], estimated prevalence of GAD estimated to be 5.9%[38] and prevalence of epilepsy at 1.0%[39], it is likely that the majority of gabapentin and pregabalin prescribed is for neuropathic pain, however the same considerations regarding the potential for dependence, misuse and diversion apply when prescribing for patients with GAD, and The Advisory Council on the Misuse of Drugs issued advice to prescribers in 2016 noting the importance of appropriate prescribing to minimise these risks[30].

Neuropathic pain

Neuropathic pain can be defined as pain that arises as a direct consequence of a lesion or diseases affecting the somatosensory nervous system[40], and can be very challenging to manage with only a minority of people experiencing a clinically relevant benefit from any one intervention[37].

Before initiating any treatment for neuropathic pain, it is good practice to assess the type, severity and impact of pain to guide management and gauge its success, and there are brief and well-validated tools available for use in non-specialist settings[41]. Tools to aid assessment of neuropathic pain include the Leeds assessment of neuropathic symptoms and signs (LANSS)[42] and the Pain Detect pain questionnaire[43].

No single drug works for all neuropathic pain, and given the diversity of pain mechanisms, patient's responses and diseases, treatment must be individualised[44]. When agreeing a treatment plan with the patient, pain severity, the underlying cause of pain, comorbidities, concurrent medications and vulnerability to adverse effects should be taken into account[22]. Patients should be informed that response to drug treatment in neuropathic pain is often inadequate, with no more than 40–60% of people obtaining partial pain relief[45]. A 2015 systematic review and meta-analysis found that the number needed to treat (NNT) for 50% pain relief was 7.2 for gabapentin and 7.7 for pregabalin[46], A recent Cochrane systematic review of pregabalin for neuropathic pain in adults concluded that pregabalin at daily oral doses of 300 mg to 600 mg can provide good levels of pain relief for some people with post-herpetic neuralgia and painful diabetic neuropathy, however evidence for use in other types of neuropathic pain is very limited. In addition, the review noted that more than half of patients treated with pregabalin will not attain worthwhile pain relief, and around 6 or 7 out of 10 will experience at least one adverse event[37].

NICE guidance on neuropathic pain in adults recommends early assessment once treatment has commenced. This should be followed by regular clinical reviews to assess and monitor effectiveness, including pain control, impact on lifestyle, physical and psychological wellbeing, adverse effects and continued need[22]. If the patient has not shown sufficient benefit within eight weeks of reaching the maximum tolerated dose, drug treatment should be reduced and stopped[44]. The SPCs for both gabapentin and pregabalin indicate that they can be discontinued gradually over a minimum of one week, independent of indication[24,27]; however, a more gradual dose taper allows observation of emergent symptoms that may have been controlled by the drug. Public Health England suggests reducing the daily dose by a maximum of 300 mg every four days in the case of gabapentin and by a maximum of 50–100 mg per week in the case of pregabalin[36].

If pain does not appear to be neuropathic in nature and is not currently well controlled, consider a change of treatment as gabapentin and pregabalin are only licensed for neuropathic pain[44]. Both gabapentin and pregabalin are commonly prescribed for non-

neuropathic pain syndromes; however, there is little evidence to support this practice[36]. A 2017 Canadian systematic review and meta-analysis highlighted that gabapentin and pregabalin are increasingly being used for non-specific chronic lower back pain, despite the significant risk of adverse effects without any demonstrated benefit[47]. This highlights the need for treatment to be reviewed when either pregabalin or gabapentin are prescribed outside of their licensed indications.

Neuropathic pain management is often complex and prescribers need to make evidence-based, informed decisions based on the individual needs of the patient. Overall, treatment gains in neuropathic pain with even the most effective of available treatments are modest[37]. Prescribers should be aware not only of the potential benefits of gabapentin and pregabalin, but also that they may be misused or diverted. Individuals who are misusing analgesics need to be distinguished from those who are using higher or more frequent doses because their symptoms are not being adequately treated. It is vitally important that any individual whose condition warrants an increase in pain relief is reassessed and subsequently receives the appropriate evidence-based prescribing[48]. The reclassification of gabapentin and pregabalin as class C controlled substances has resulted in stronger controls with regards to the prescribing and supply of these items and it is now illegal to be in possession of these drugs without a prescription.

This NPI promotes a prudent approach to prescribing gabapentin and pregabalin, taking into account the risks and benefits, and encouraging timely review.

Useful resources

Please note: Links here will be updated to reflect the latest available resources at the time of publication.

- PrescQIPP (2021) Neuropathic pain (log in required for access)
- SIGN (2019) SIGN 136. Management of chronic pain
- AWMSG (2022) Resources for pharmacological management of pain
- Public Health England (2014) Advice for prescribers on the risk of the misuse of pregabalin and gabapentin
- The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) Pain Scale

1.2 Anticoagulation in atrial fibrillation

Purpose:
To encourage the appropriate use and review of anticoagulants in patients with atrial fibrillation (AF).
Units of measure:
The number of patients diagnosed with AF who: 1. Have a CHA_2DS_2-VASc score of 2 or more who are currently prescribed an anticoagulant as a percentage of all patients diagnosed with AF. 2. Are currently prescribed an anticoagulant and have received an anticoagulant review (read codes 8BT3, 6A9, or 66QB) within the last 12 months, as a percentage of all patients diagnosed with AF who are prescribed an anticoagulant. 3. Are prescribed antiplatelet monotherapy, as a percentage of all patients diagnosed with AF.
Targets for 2022–2025:
1. To increase the number of patients with AF and a CHA_2DS_2-VASc of 2 or more prescribed an anticoagulant. 2. To increase the number of patients with AF who are prescribed an anticoagulant and have received an anticoagulant review (read codes 8BT3, 6A9, or 66QB) within the last 12 months. 3. To reduce the number of patients with AF prescribed antiplatelet monotherapy.

Figure 9. Percentage of patients with AF and a CHA_2DS_2-VASc score of 2 or more who are currently treated with anticoagulant therapy – quarter ending June 2021[49]

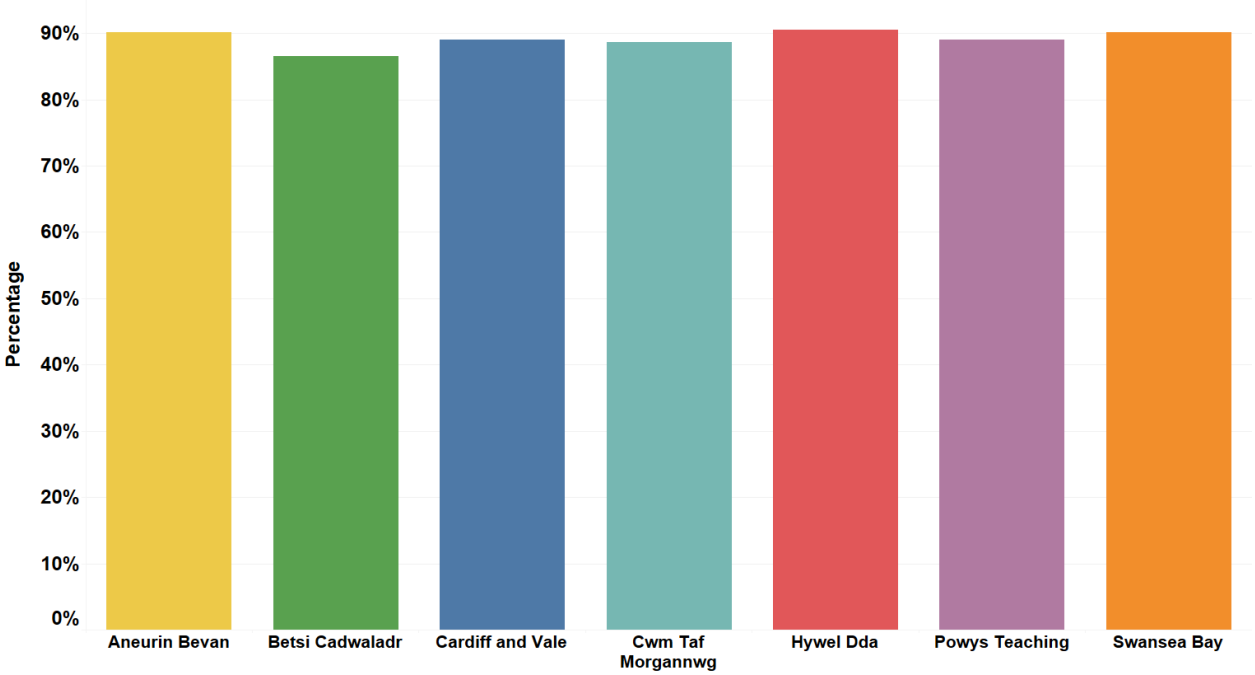


Figure 10. Percentage of patients with AF who are prescribed an anticoagulant and have received an anticoagulant review within the last 12 months – June 2021 vs June 2020[49]

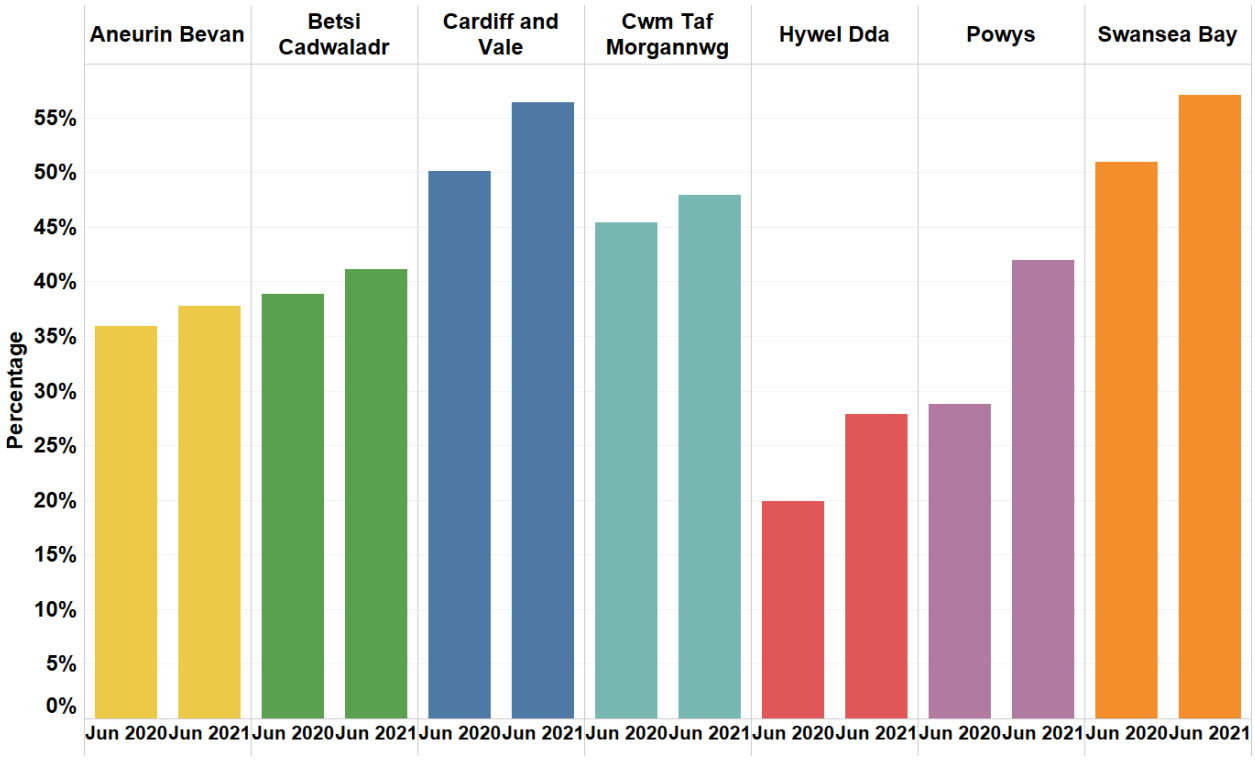
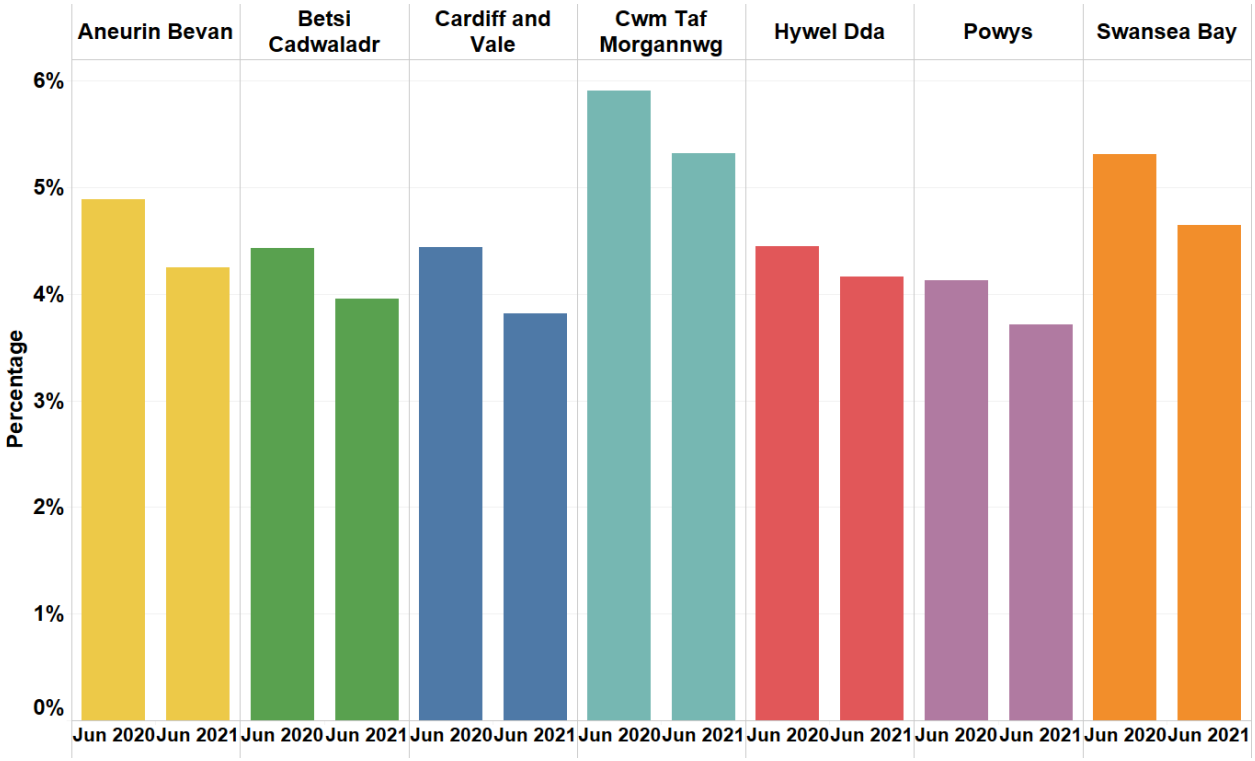


Figure 11. Percentage of patients with AF who are prescribed antiplatelet monotherapy – June 2021 vs June 2020[49]



Background and evidence

This priority area contains a number of measures looking at the use of anticoagulants and antiplatelets in patients with a diagnosis of AF, with the aim of ensuring that patients are appropriately treated and receive a review of their anticoagulant medication. These indicators support the implementation of a number of the quality statements produced by NICE in relation to AF. In addition, the indicators align with the Stop a Stroke project aim to support health boards in Wales in the initiation of a sustainable approach to reviewing the treatment of patients with AF to reduce the risk of having a stroke.

AF is a supraventricular tachyarrhythmia resulting from irregular, disorganised electrical activity and ineffective contraction of the atria[50]. AF is the most common sustained cardiac arrhythmia[50] with over 1 million people in the UK diagnosed with the condition, and it is estimated that a further half a million people in the UK with undiagnosed AF[51]. GP practice data for June 2021 demonstrates that there are over 77,800 patients with AF in Wales[49], with estimates suggesting another third as many people may be undiagnosed[52].

Anticoagulation

AF causes around 20% of strokes, however this can be reduced by about two thirds if people are anticoagulated[53]. The NICE guideline *Atrial fibrillation: diagnosis and management* recommends that patients with paroxysmal, persistent or permanent AF are assessed for stroke risk using the CHA_2DS_2VASc score[54], which takes into account risk factors including age, gender and co-morbidities. Adults with non-valvular AF and a CHA_2DS_2VASc score of 2 or above are at a much higher risk of having a stroke than the general population, however anticoagulation therapy can help to prevent strokes by reducing the likelihood of a blood clot forming.

For patients with a CHA_2DS_2VASc of 2 or above, NICE recommends that anticoagulation should be offered[54]. The patient's bleeding risk should be taken into account in reaching a decision about anticoagulation, however for most people, the benefit of anticoagulation outweighs the bleeding risk[55]. NICE guidance recommends anticoagulation with a direct-acting oral anticoagulant (DOAC), either apixaban, dabigatran, edoxaban or rivaroxaban[54]. If a DOAC is contraindicated, not tolerated or not suitable, a vitamin K antagonist should be offered instead[54].

The Sentinel Stroke National Audit Programme (SSNAP) measures the quality and organisation of stroke care in the NHS and includes a range of measures which can be used to improve the quality of care that is provided to patients. The audit programme captures data from secondary care regarding patients admitted with a stroke[53]. Data from January – March 2021 highlights that 68% of patients across Wales, England and Northern Ireland with known AF prior to admission to hospital with a stroke, were on anticoagulant medication[53], however for Wales alone, the figure was 64.7%. This demonstrates that work still needs to be done to ensure that all patients who would benefit from anticoagulants are prescribed them, as increasing the proportion of people with AF on anticoagulants will reduce the number of people having a stroke.

Anticoagulation review

The review of patients with AF who are taking an anticoagulant is vital. The use of any anticoagulant is associated with some drug-drug interactions which may increase the risk of serious bleeding or diminish stroke prevention[56]. Warfarin has well known food and drug interactions, and treatment with DOACs and warfarin requires vigilance due to potentially severe complications, particularly as the target population tends to be of an

older age and with increased frailty[56]. The NICE guideline *Atrial fibrillation: diagnosis and management* highlights the need to review anticoagulation and the quality of anticoagulation at least annually, or more frequently if clinically relevant events occur affecting anticoagulation or bleeding risk[54]. Quality Statement 3 within the NICE Quality Standard for *Atrial fibrillation* states that adults with AF who are prescribed anticoagulation should discuss the options with their healthcare professional at least once a year[55]. Patients should have the opportunity to discuss the choice of suitable anticoagulants with their healthcare professional, in order to improve adherence to treatment. Adherence to anticoagulation can help to prevent stroke by reducing the likelihood of a blood clot forming[55].

Antiplatelet monotherapy

Antiplatelet medication, i.e. aspirin or clopidogrel, is no longer recommended in patients with AF. Despite this, data from the SSNAP audit, January 2021 – March 2021 highlights that 9% of stroke patients across Wales, England and Northern Ireland with AF were still prescribed an antiplatelet drug prior to their stroke. In Wales this figure was 15%[53]. Quality Statement 2 within the NICE Quality Standard for *Atrial fibrillation* states that adults with AF should not be prescribed aspirin as monotherapy, as the risks of taking aspirin outweigh any benefits[55]. However, prescribers should be aware that adults with AF may need to take aspirin for other indications[55].

Useful resources

- NICE (2021) NG196: Atrial fibrillation: diagnosis and management
- AWMSG (2022) All Wales Advice on Oral Anticoagulation for Non-valvular Atrial Fibrillation
- NICE (2018) Quality Standard Atrial fibrillation
- All Wales Cardiac Network Sharepoint (registration required)

1.3 Antimicrobial stewardship

Antimicrobial resistance (AMR) is a growing threat to global health, and sporadic outbreaks of untreatable 'super-bugs' is now a reality in hospitals across the UK. It is currently estimated that approximately 700,000 people a year die from infection caused by these organisms globally, and without intervention, that figure could rise to 10 million by 2050, eclipsing the number of deaths caused by cancer and malaria. The financial impact on the global economy would be extreme, at an estimated cost of $100 trillion[57].

In 2015, member states of the World Health Organisation endorsed a Global Action Plan (GAP) on Antimicrobial Resistance, encompassing five key strategic objectives[58]. This provides a framework from which National Action Plans (NAP) can be developed and delivered by individual member states. The GAP was adopted a year later at the 71st session of the United Nations General Assembly, and an Intra-Agency Coordination Group was put in place by the UN Secretary General to develop a framework for action and monitor progress[59].

The UK was one of the first countries to establish a National Action Plan, with strategies and action plans in place since 2000, pre-dating the UN GAP. The previous UK NAP, the 2013-2018 AMR Strategy, focused on seven key areas including infection prevention and control; antimicrobial prescribing; education, training and public engagement; and better access to and use of surveillance data[60]. In Wales, this plan was reflected in the Antimicrobial Resistance (AMR) Delivery Plan for NHS Wales, which ran from 2016 – 2019[61].

In 2018, the four devolved administrations of the UK worked together to produce a new 20 year vision, designed to deliver the key strategies of the UN GAP. The vision was published in January 2019[62] along with the first of four 5-year National Action Plans (NAP)[63]. The 20-year vision aims to contain, control and mitigate AMR by 2040 through lowering the burden of infection, optimising the use of antimicrobials and developing new diagnostics, therapies and vaccines. These documents are 'one-health', reflecting a need for coordinated action across human health, animal health, agriculture and the environment.

The UK 2019–2024 NAP contains four overarching targets aimed at human health:

- To halve the number of healthcare associated Gram-negative blood stream infections
- To reduce the number of specific drug-resistant infections by 10% by 2025
- To reduce the UK antimicrobial use in humans by 15% by 2024
- To be able to report on the percentage of antimicrobial prescriptions supported by an appropriate diagnostic test or decision support tool by 2024

In support of the new UK 5-year NAP, Welsh Government have published annual Welsh Health Circulars (WHCs), designed to provide sequential targets to the NHS in Wales, enabling them to meet the overall UK targets. Each of the four devolved administrations will align their targets and metrics, allowing each devolved administration to adjust their targets to reflect local need. An updated WHC was issued in September 2021. It includes a number of improvement goals for primary and secondary care, and states that the antimicrobial stewardship indicators may be used to underpin further improvements in antimicrobial prescribing[64].

1.3.1 Total antibacterial items

Purpose:
To encourage the appropriate prescribing of all antibiotics in primary care.
Unit of measure:
Total antibacterial items per 1,000 STAR-PUs.
Target for 2022–2025:
2022–2023 • Health board target: a quarterly reduction of 5% against a baseline of data from April 2019–March 2020**. • GP practice target: maintain performance levels within lower quartile, or show a reduction towards the quartile below. **2023–2024** • Health board target: a quarterly reduction of 10% against a baseline of data from April 2019–March 2020. • GP practice target: maintain performance levels within lower quartile, or show a reduction towards the quartile below.

Note
Comparative trends for antimicrobial NPIs should be interpreted with caution, with particular respect to seasonal variation.

Table 3. Health board baseline data: total primary care antibacterial items per 1,000 STAR-PUs 2019–2020[65]

Health board	June 2019	September 2019	December 2019	March 2020
Aneurin Bevan	272	259	315	315
Betsi Cadwaladr	260	255	305	293
Cardiff and Vale	243	239	287	279
Cwm Taf Morgannwg	303	290	345	348
Hywel Dda	274	263	313	310
Powys	227	227	262	261
Swansea Bay	294	279	337	324

** Due to the impact of COVID-19 on antimicrobial prescribing, members of the NPI Task and Finish Group (a sub-group of AWPAG), agreed that the baseline year should be set at 2019–2020.

Figure 12. Trend in total primary care antibacterial items per 1,000 STAR-PUs to quarter ending June 2021

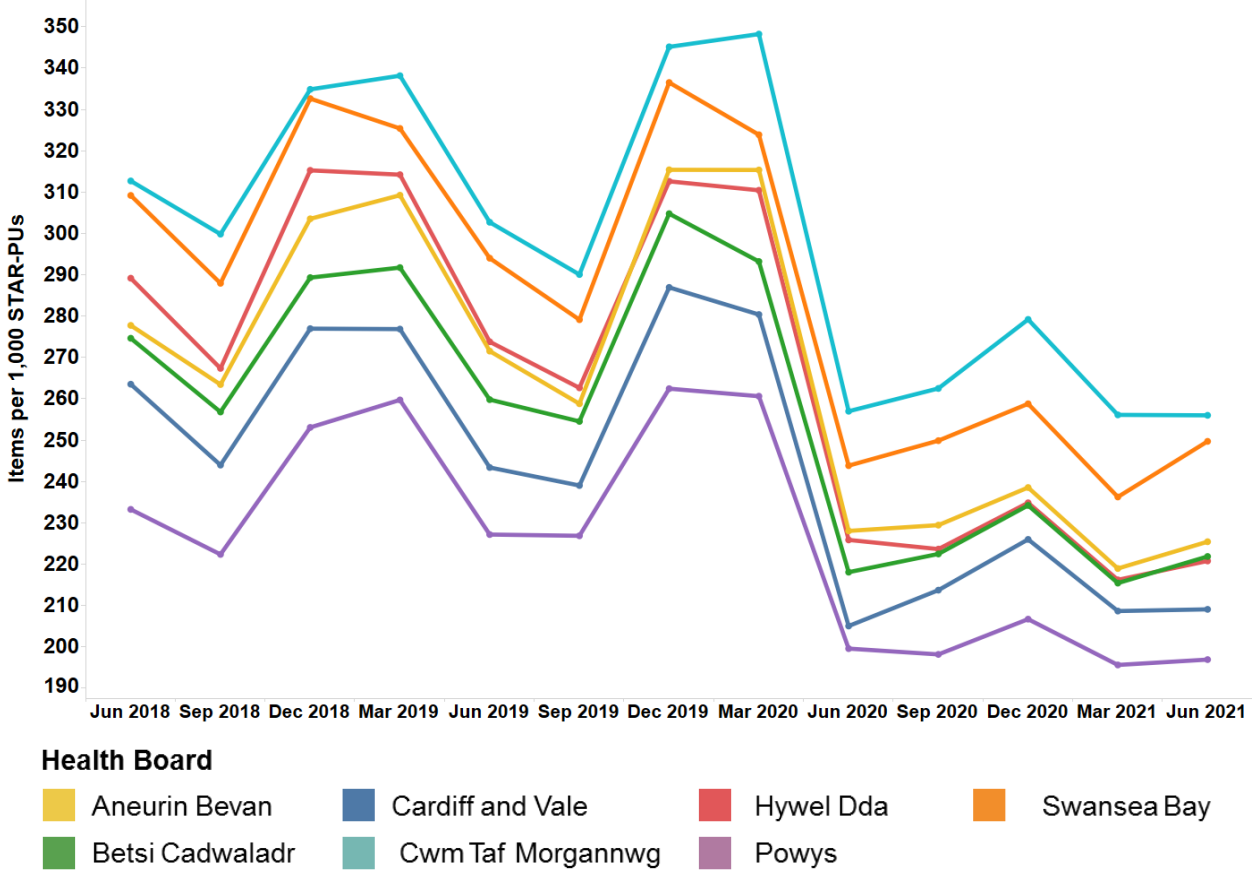
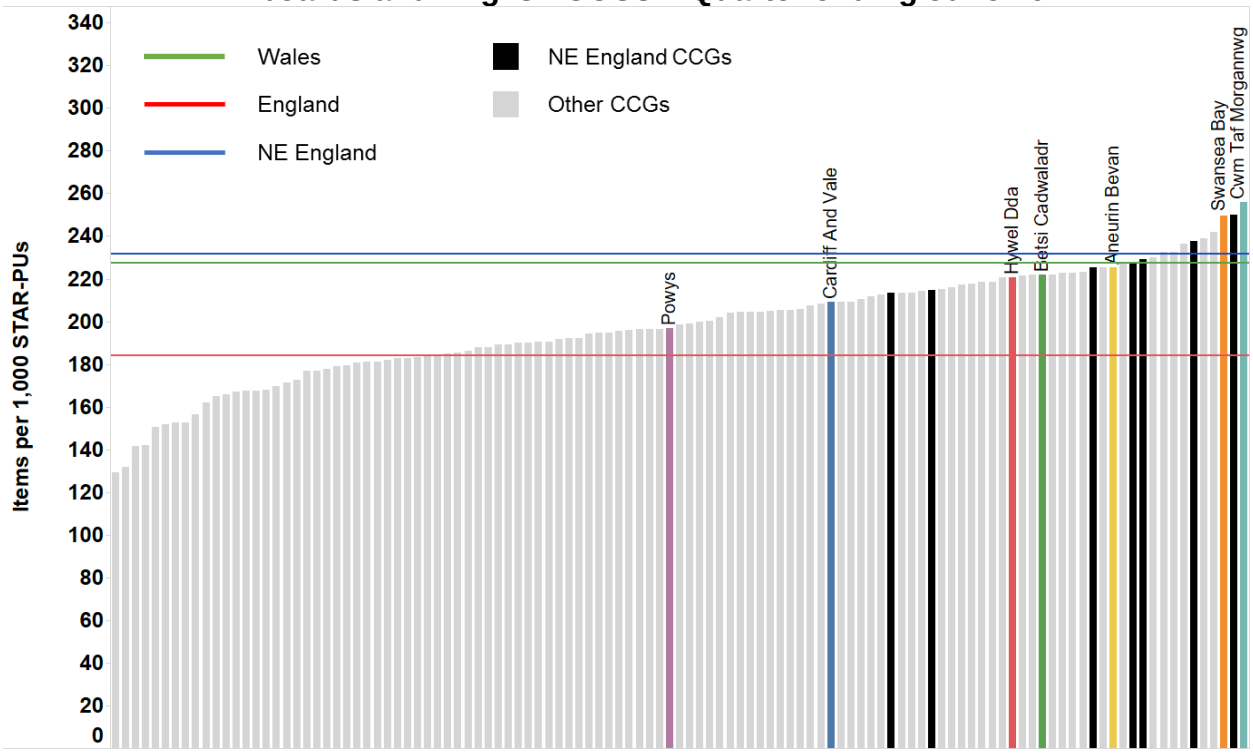


Figure 13. Total primary care antibacterial items per 1,000 STAR-PUs Welsh health boards and English CCGs – Quarter ending June 2021



Background and evidence

The widespread and often excessive use of antimicrobials is one of the main factors contributing to the increasing emergence of AMR. Within Wales, antimicrobial usage in primary care has decreased over recent years, however, variation still exists. For the quarter ending March 2021, primary care prescribing rates varied from 196 to 256 items per 1,000 STAR-PUs across Welsh health boards[65].

The Public Health Wales report *Antibacterial Resistance in Wales 2008–2017* presents the different AMR patterns across Wales[66]. The report shows resistance trends in Wales for drug-bug combinations compared with UK aggregate rates, and finds that while there are small differences, generally the trends are comparable. However, in some cases there is considerable variability in resistance rates between different areas and hospitals[66].

NICE Guideline 15 – *Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use* – makes recommendations for organisations on antimicrobial stewardship programmes, antimicrobial stewardship interventions and communication strategies[67]. In addition it makes recommendations for individual prescribers in both primary and secondary care. Key recommendations include:

- Follow local or national guidelines, prescribing antibiotics for the shortest effective course at the most appropriate dose;
- Consider the risk of antimicrobial resistance for individual patients and the population as a whole;
- Document the clinical diagnosis in the patient's record and the reason for prescribing, or not prescribing, an antimicrobial[67].

Ultimately, indiscriminate or inappropriate use of antibiotics is a key driver in the spread of antibiotic resistance[60]. Therefore, the ultimate aim has to be the reduction in inappropriate prescribing, measured as volume of antimicrobials.

1.3.2 4C antimicrobials

Purpose:
To reduce the prevalence of healthcare associated infection (HCAI), including *Clostridioides difficile* infection and *Staphylococcus aureus* bacteraemia caused by MRSA, by encouraging a reduction in variation and reduce overall prescribing of the 4C antimicrobials (co-amoxiclav, cephalosporins, fluoroquinolones and clindamycin) in primary care.
Unit of measure:
Co-amoxiclav, cephalosporin, fluoroquinolone and clindamycin items combined, per 1,000 patients.
Target for 2022–2025:
2022–2023: • Health board target: a quarterly reduction of 10% against a baseline of data from April 2019–March 2020††. • GP practice target: maintain performance levels within lower quartile, or show a reduction towards the quartile below. **2023–2024:** • GP practice target: maintain performance levels within lower quartile, or show a reduction towards the quartile below.

Note
Comparative trends for antimicrobial NPIs should be interpreted with caution, with particular respect to seasonal variation.

Table 4. Health board baseline data: 4C antimicrobials per 1,000 patients 2019–2020[65]

Health board	June 2019	September 2019	December 2019	March 2020
Aneurin Bevan	9.62	9.26	9.96	10.1
Betsi Cadwaladr	12.7	12.9	12.5	12.7
Cardiff and Vale	8.81	8.83	8.98	9.31
Cwm Taf Morgannwg	15.9	15.6	15.8	15.2
Hywel Dda	14.3	13.7	13.5	13.3
Powys	11.1	11.5	11.4	11.8
Swansea Bay	13.9	13.3	13.6	12.8

†† Due to the impact of COVID-19 on antimicrobial prescribing, members of the NPI Task and Finish Group (a sub-group of AWPAG), agreed that the baseline year should be set at 2019–2020.

Figure 14. Trend in 4C antimicrobial items per 1,000 patients to quarter ending June 2021

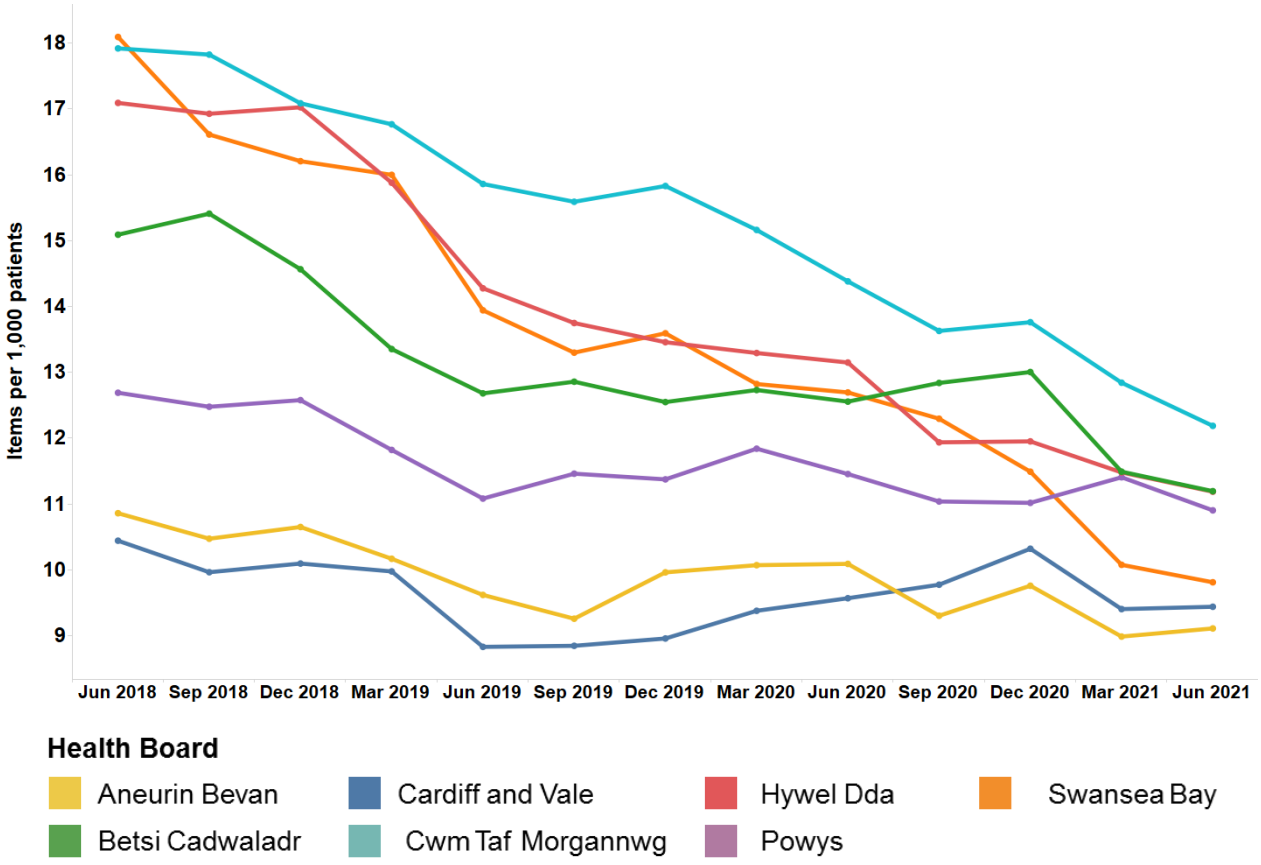
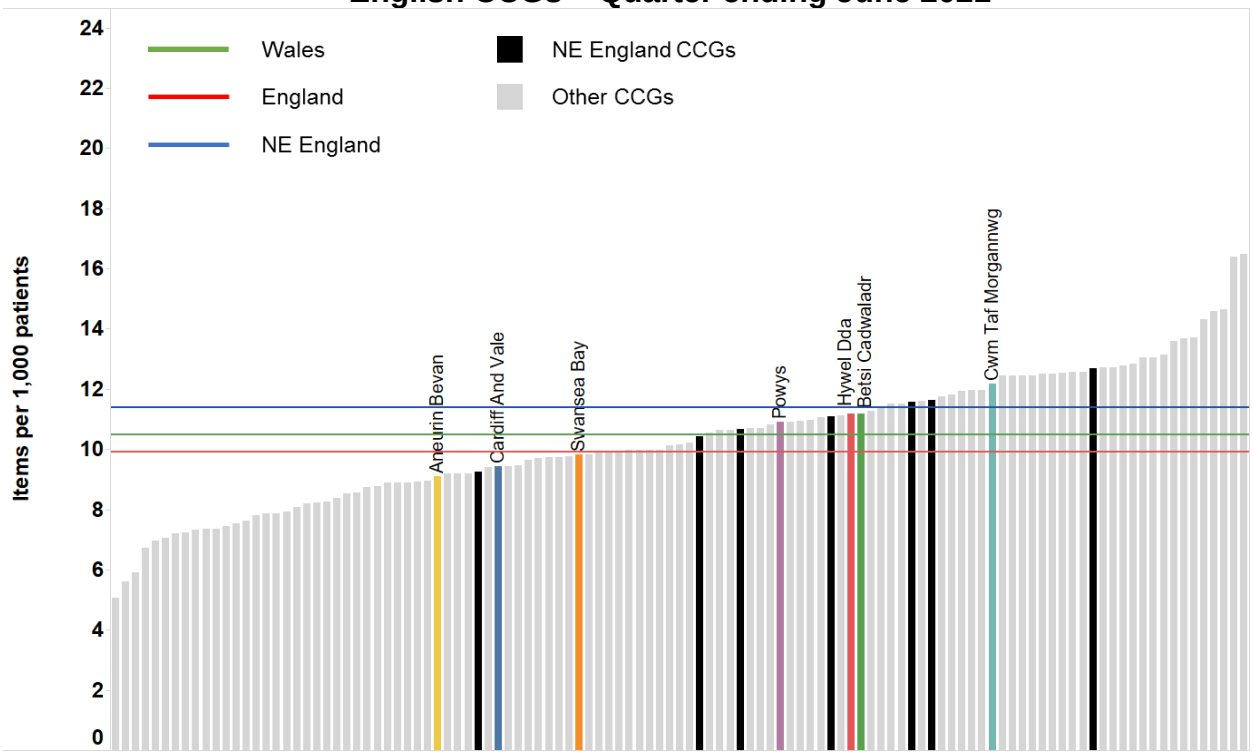


Figure 15. 4C antimicrobial items per 1,000 patients Welsh health boards and English CCGs – Quarter ending June 2021



Background and evidence

AWMSG Primary Care Antimicrobial Guidelines state “Use simple generic antibiotics if possible. Avoid broad spectrum antibiotics (e.g. co-amoxiclav, quinolones and cephalosporins) when narrow spectrum antibiotics remain effective, as they increase the risk of *C. difficile*, methicillin-resistant *Staphylococcus aureus* (MRSA) and resistant urinary tract infections”. The guidelines are currently being updated, however the principles still apply.

The term ‘4C antimicrobials’ refers collectively to four broad-spectrum antibiotics, or groups of antibiotics: co-amoxiclav, cephalosporins, fluoroquinolones and clindamycin. The use of simple generic antibiotics and the avoidance of these broad-spectrum antibiotics preserve them from resistance and reduce the risk of *C. difficile*, MRSA and resistant UTIs. Compared with narrow-spectrum antibiotics, broad-spectrum antibiotics are more likely to significantly change the gut flora, potentially allowing other bacteria, such as *C. difficile,* to become established[68]. *C. difficile* may be found in the gut of people with no symptoms. When the normal bacteria in the gut are disrupted (for example, by antibiotics) the numbers of *C. difficile* bacteria may increase to unusually high levels, particularly in people whose immune system is compromised. Symptoms of *C. difficile* infections vary from mild, self-limiting diarrhoea to severe complications, including pseudomembranous colitis, toxic megacolon, perforation of the colon, sepsis and death[68]. The most commonly implicated antibiotics in *C. difficile* infection include clindamycin, cephalosporins (in particular second and third generation cephalosporins), fluoroquinolones and co-amoxiclav[68]. However, these antimicrobials have a very useful role in specific clinical situations, so should be reserved for use as per local guidelines.

There have been a number of Drug Safety Updates from the MHRA in recent years regarding risk of adverse events related to the use of fluoroquinolones. A 2018 Drug Safety Update highlighted the small increased risk of aortic aneurysm and dissection, particularly in older patients[69]. A further update in March 2019 informed prescribers of new restrictions and precautions for use of fluoroquinolones due to very rare reports of disabling and potentially long-lasting or irreversible side effects mainly affecting musculoskeletal and nervous systems[70]. Following an EU-wide review of safety, new restricted indications were introduced for ciprofloxacin; levofloxacin; moxifloxacin and olfloxacin[70], in addition the marketing authorisation for the quinolone nalidixic acid, licensed for UTIs, was suspended[71]. A December 2020 Drug Safety Update highlighted that systemic and inhaled fluoroquinolones have been associated with a small increased risk of heart valve regurgitation[72]. Fluoroquinolones should not be prescribed for treatment of mild to moderate infections unless other antibiotics that are commonly recommended for such infections are considered inappropriate. Prescribers should be aware of the potential for adverse events, and should only prescribe fluoroquinolones after careful benefit-risk assessment and after consideration of other therapeutic options in at risk patients.

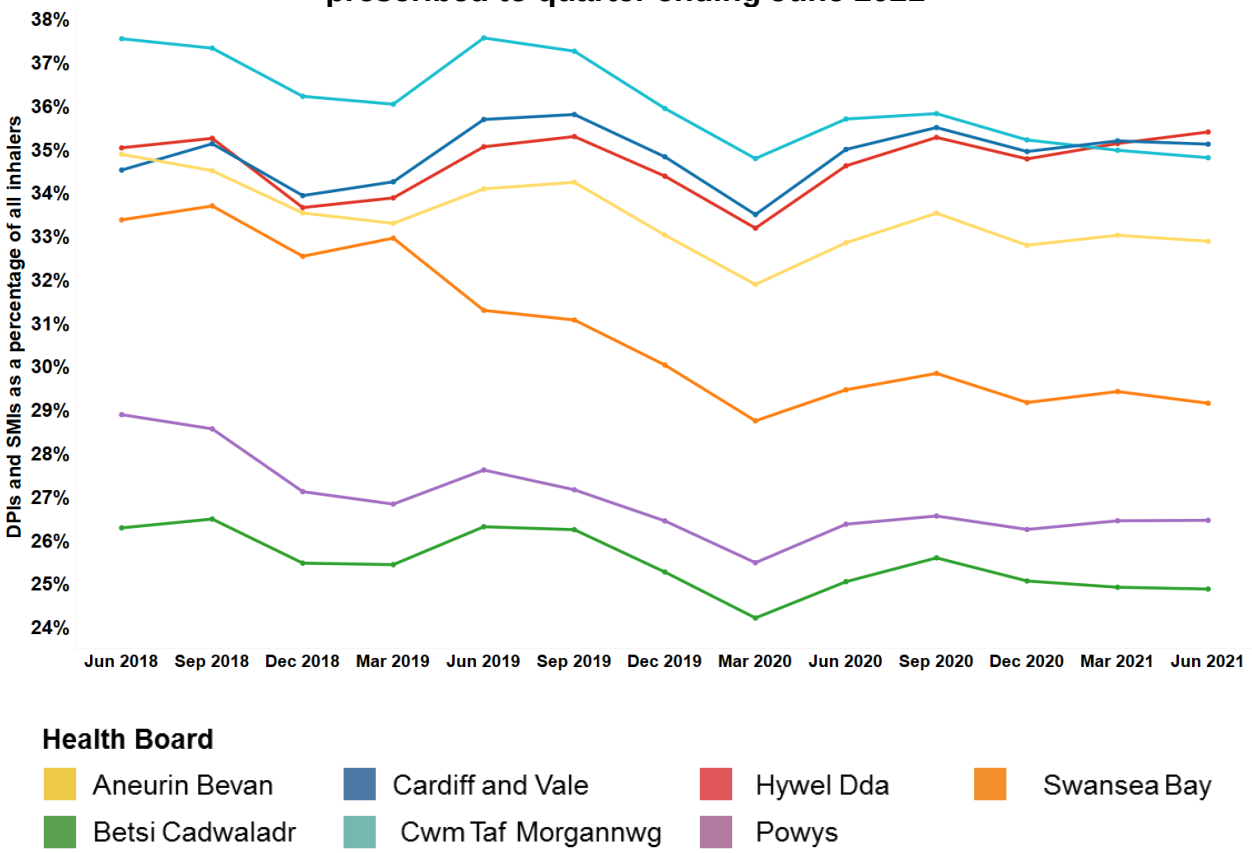
Useful resources

- AWMSG (2022) Primary care antimicrobial guidelines
- AWMSG (2022) CEPP National Audit: Focus on Antibiotic Prescribing
- RCGP TARGET Antibiotics toolkit

1.4 Decarbonisation of inhalers

Purpose:
To encourage an increase in the use of low Global Warming Potential (GWP) inhalers (dry powder inhalers (DPI) and soft mist inhalers (SMI)), to reduce the carbon footprint of inhaler prescribing in Wales.
Unit of measure:
The number of DPIs and SMIs as a percentage of all inhalers prescribed.
Target for 2022–2025:
Maintain performance levels within the upper quartile, or show an increase towards the quartile above.

Figure 16. Trend in the percentage of DPI and SMI as a percentage of all inhalers prescribed to quarter ending June 2021



The NHS Wales Decarbonisation Strategic Delivery Plan, launched in March 2021, sets out NHS Wales' plan for addressing the climate emergency declared by Welsh Government in 2019. The plan contains a number of initiatives and targets for the decarbonisation of NHS Wales that will be assessed and reviewed in 2025 and 2030, and includes several key actions related to inhalers[73].

Metered dose inhalers (MDIs) contain hydrofluorocarbons (HFC) which are powerful greenhouse gases, with a global warming effect several thousand times that of carbon dioxide. These gases are used as the propellant in MDIs[73] and the impact that they have on global warming is known as the carbon footprint. In 2018, these propellants were estimated to be responsible for 4% of the NHS's entire carbon footprint[74]. Dry powder inhalers (DPIs) have a carbon footprint 18 times lower than MDIs, and clinical studies

have shown them to be equally effective and cost effective as MDIs[74]. Soft mist inhalers do not contain a propellant, therefore have a lower carbon footprint that MDIs[75]. Currently, MDI use in Wales accounts for 68%[31] of all inhalers prescribed, whereas MDIs accounted for only 13% of inhalers prescribed in Sweden in 2017[76]. There is clearly scope to increase the proportion of lower global warming potential inhalers prescribed in Wales.

In 2020, the British Thoracic Society (BTS) updated its position statement regarding the environment and lung health, and made a number of recommendations by which the environmental impact of inhaler prescribing can be reduced. The recommendations include prescribing a DPI when a new class of inhaler is commenced; during respiratory reviews, recommending low carbon alternatives to patients currently using MDIs; and where patients are using several classes of inhalers and poor technique is identified with one device, that a DPI is prioritised. It is noted that these changes should only take place where the patient is able to use the device safely[74].

One of the key actions within the NHS Wales Decarbonisation Strategic Delivery Plan is to transition patients to low GWP inhalers, but only where patient care will not be impacted. The target is a shift to 80% of inhalers being low GWP alternatives by 2025[73]. This is an ambitious target, but one that will ensure Wales is moving towards a lower carbon future. It is crucial that while efforts are made to reduce the emissions associated with inhalers, patient choice is maintained and that changes are only made where clinically appropriate[74]. The NICE Asthma Patient Decision Aid can support shared decision making between patients and prescribers and enable the patient to consider a range of factors when considering the best type of inhaler for them, including how important it is for their inhaler to have a low carbon footprint[75]. The 2021 AWMSG asthma and COPD guidelines, developed by the Respiratory Health Implementation Group (RHIG), can aid prescribers to easily identify inhalers with a low GWP.

Useful resources

- AWTTC (2022) SPIRA - Decarbonisation Dashboard (NHS Wales network connection required)
- AWMSG (2021) All Wales Asthma Diagnosis and Management Guidelines
- AWMSG (2021) All Wales COPD Management and Prescribing Guidelines
- NICE (2020) Patient decision aid: Inhalers for asthma

2.0 Supporting domains

2.1 Safety

2.1.1 Prescribing Safety Indicators

Purpose:

To identify patients at high risk of adverse drug reactions and medicines-related harm in primary care.

Units of measure:

Prescribing Safety Indicators related to acute kidney injury (AKI)

- Number of patients on the CKD register (CKD stage 3–5) who have received a repeat prescription for an NSAID within the last 3 months.
- Number of patients who are not on the CKD register but have an eGFR of < 59 ml/min and have received a repeat prescription for an NSAID within the last 3 months.
- Number of patients with concurrent prescriptions of an NSAID, renin-angiotensin system (RAS) drug and a diuretic.
- Number of patients aged 75 and over with a current prescription for an ACE Inhibitor or loop diuretic without a check of renal function and electrolytes in the previous 15 months.

Prescribing Safety Indicators related to bleeds

- Number of patients with a peptic ulcer who have been prescribed NSAIDs without a PPI.
- Number of patients with concurrent prescriptions of warfarin and an oral NSAID.
- Number of patients with concurrent prescriptions for a DOAC and an oral NSAID.
- Number of patients aged 65 years or over prescribed an NSAID plus aspirin and/or clopidogrel but without gastroprotection (PPI or H_2-receptor antagonist).
- Number of patients with concurrent prescriptions of an oral anticoagulant (warfarin or DOAC) and an SSRI.

Prescribing Safety Indicators related to cognition

- Number of patients aged 65 years or over prescribed an antipsychotic.
- Number of patients aged 75 and over with an Anticholinergic Effect on Cognition (AEC) score of 3 or more for items on active repeat.

Prescribing Safety Indicators specific to females

- Number of female patients with a current prescription of oestrogen-only hormone replacement therapy (HRT) without any hysterectomy READ/SNOMED codes.
- Number of female patients with a past medical history of venous or arterial thrombosis who have been prescribed combined hormonal contraceptives.
- Number of female patients aged 14–55 with a prescription for sodium valproate.
- Number of female patients aged 14–55 with a prescription for oral retinoids.

Prescribing Safety Indicators related to 'other'

- Number of patients under 16 with a current prescription of aspirin.
- Number of patients with asthma who have been prescribed a beta-blocker.
- Number of patients with concurrent prescriptions of verapamil and a beta-blocker.

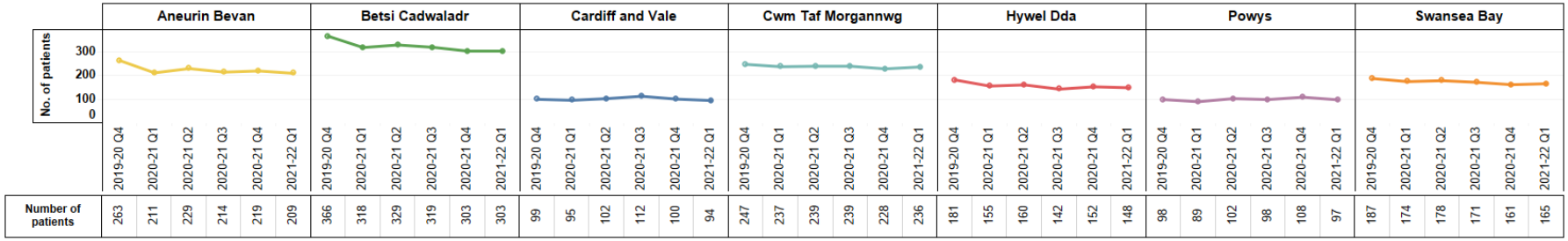
Target for 2022–2025:

No target set

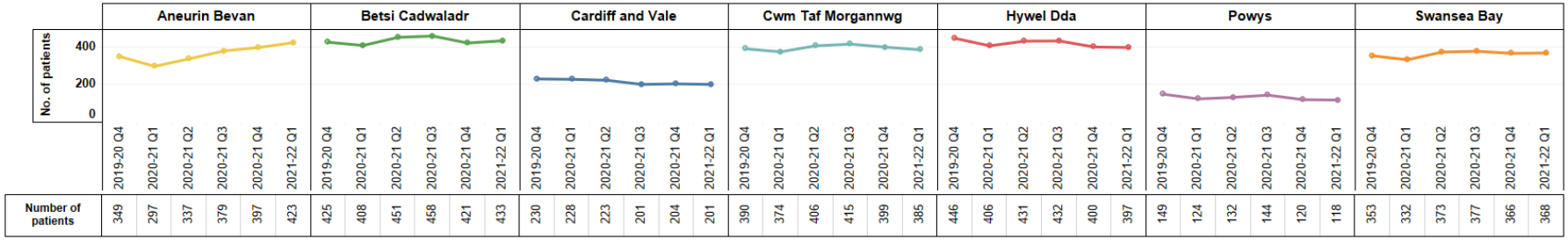
Figure 17. Prescribing Safety Indicators

Prescribing Safety Indicators related to acute kidney injury (AKI)

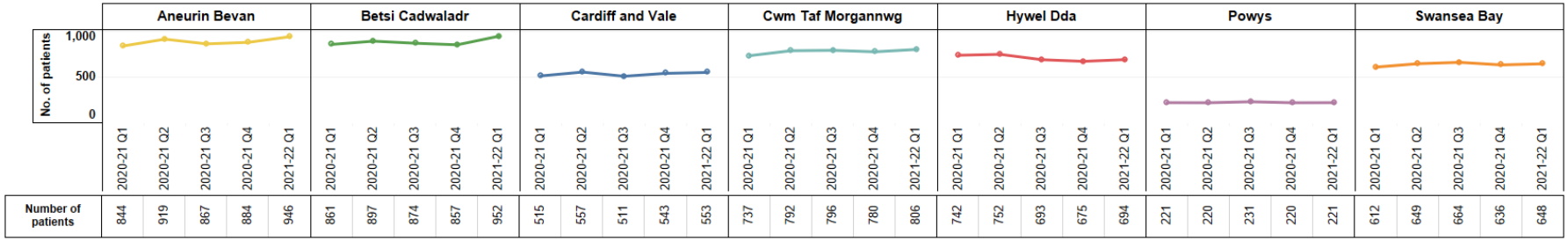
01. Number of patients on the CKD register (CKD stage 3–5) who have received a repeat prescription for an NSAID within the last 3 months*.



02. Number of patients who are not on the CKD register but have an eGFR of < 59 ml/min and have received a repeat prescription for an NSAID within the last 3 months.

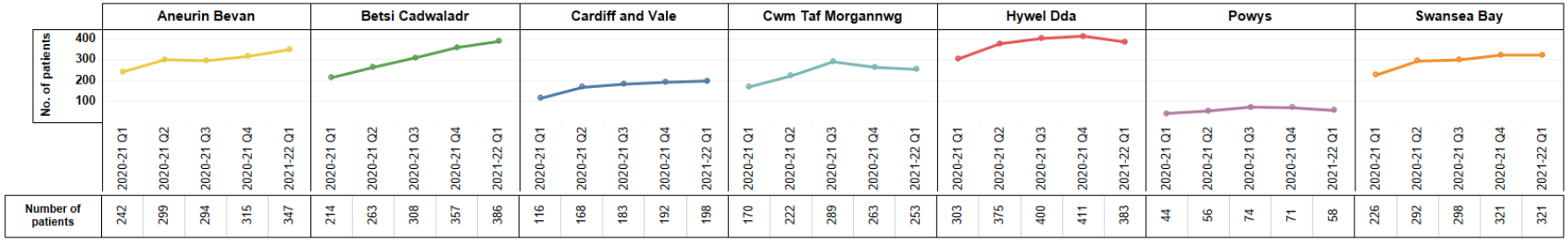


03. Number of patients with concurrent prescriptions of an NSAID, renin-angiotensin system (RAS) drug and a diuretic†.



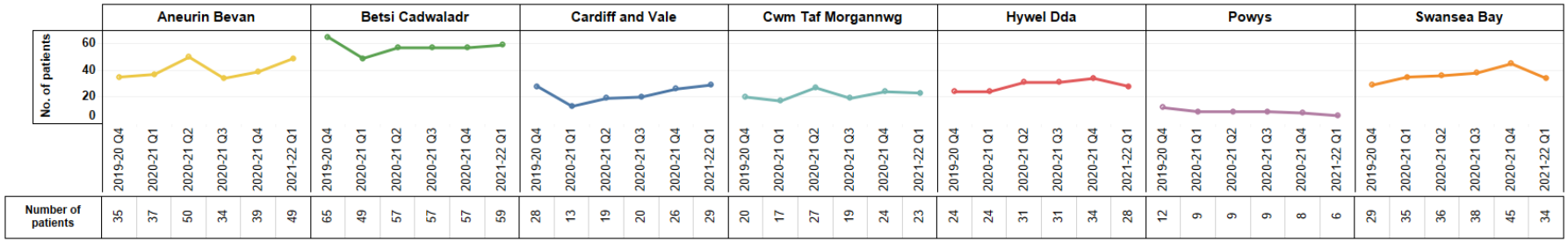
* Audit+ searches for this Prescribing Safety Indicator were amended for the quarter ending March 2020. Therefore there are no data before 2019–2020 Q4.
† This Prescribing Safety Indicator was new for 2020–2021. Therefore, there are no data before 2020–2021 Q1.

04. Number of patients aged 75 years and over with a current prescription for an ACE Inhibitor or loop diuretic without a check of renal function and electrolytes in the previous 15 months*.

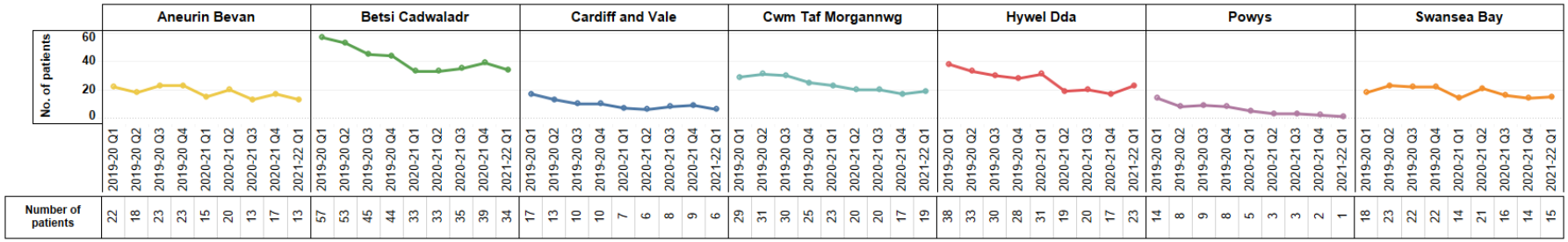


Prescribing Safety Indicators related to bleeds

05. Number of patients with a peptic ulcer who have been prescribed NSAIDs without a PPI.

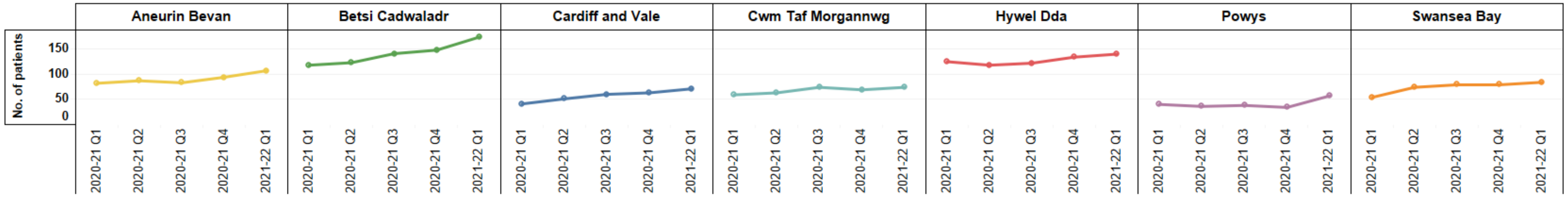


06. Number of patients with concurrent prescriptions of warfarin and an oral NSAID.



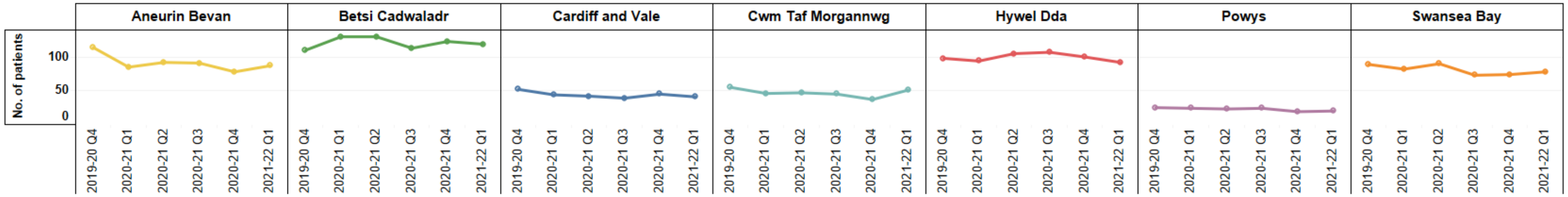
* This Prescribing Safety Indicator was new for 2020–2021. Therefore, there are no data before 2020–2021 Q1.

07. Number of patients with concurrent prescriptions for a DOAC and an oral NSAID*.



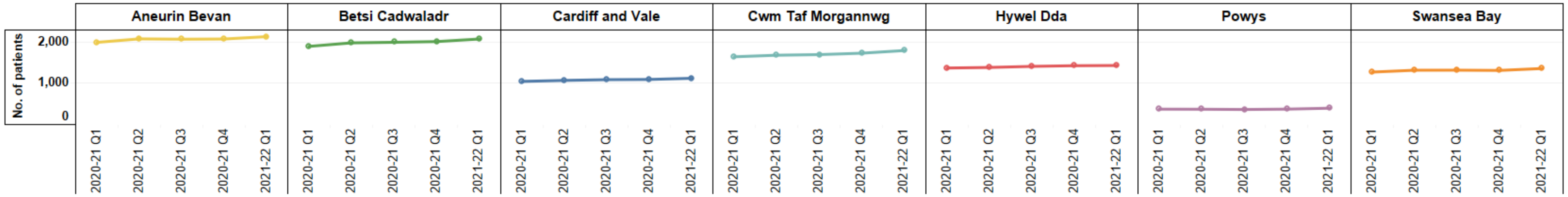
Number of patients	2020-21 Q1	2020-21 Q2	2020-21 Q3	2020-21 Q4	2021-22 Q1
Aneurin Bevan	82	87	83	94	107
Betsi Cadwaladr	118	123	141	148	174
Cardiff and Vale	41	51	60	63	71
Cwm Taf Morgannwg	59	63	74	69	74
Hywel Dda	125	118	122	134	140
Powys	40	36	38	34	57
Swansea Bay	54	74	79	79	84

08. Number of patients aged 65 years or over prescribed an NSAID plus aspirin and/or clopidogrel but without gastroprotection (PPI or H_2 receptor antagonist)†.



Number of patients	2019-20 Q4	2020-21 Q1	2020-21 Q2	2020-21 Q3	2020-21 Q4	2021-22 Q1
Aneurin Bevan	114	85	92	91	78	87
Betsi Cadwaladr	110	130	130	113	123	119
Cardiff and Vale	52	44	42	39	45	41
Cwm Taf Morgannwg	55	46	47	45	37	51
Hywel Dda	98	94	105	107	100	92
Powys	25	24	23	24	19	20
Swansea Bay	89	82	90	73	74	78

09. Number of patients with concurrent prescriptions of an oral anticoagulant (warfarin or DOAC) and an SSRI†.



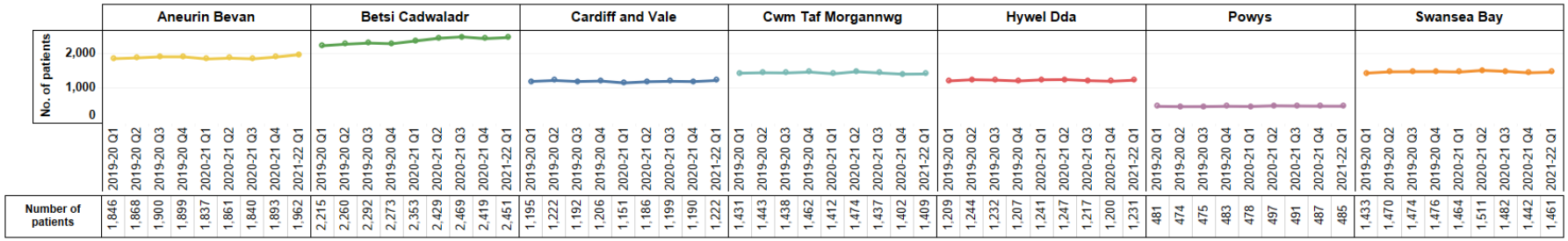
Number of patients	2020-21 Q1	2020-21 Q2	2020-21 Q3	2020-21 Q4	2021-22 Q1
Aneurin Bevan	1,989	2,073	2,065	2,070	2,127
Betsi Cadwaladr	1,892	1,977	1,991	2,008	2,070
Cardiff and Vale	1,044	1,068	1,086	1,091	1,119
Cwm Taf Morgannwg	1,640	1,678	1,693	1,727	1,792
Hywel Dda	1,368	1,382	1,408	1,424	1,429
Powys	372	370	364	373	395
Swansea Bay	1,270	1,315	1,316	1,310	1,356

* This Prescribing Safety Indicator was new for 2020–2021. Therefore, there are no data before 2020–2021 Q1.

† Audit+ searches for this Prescribing Safety Indicator were amended for the quarter ending March 2020. Therefore there are no data before 2019–2020 Q4.

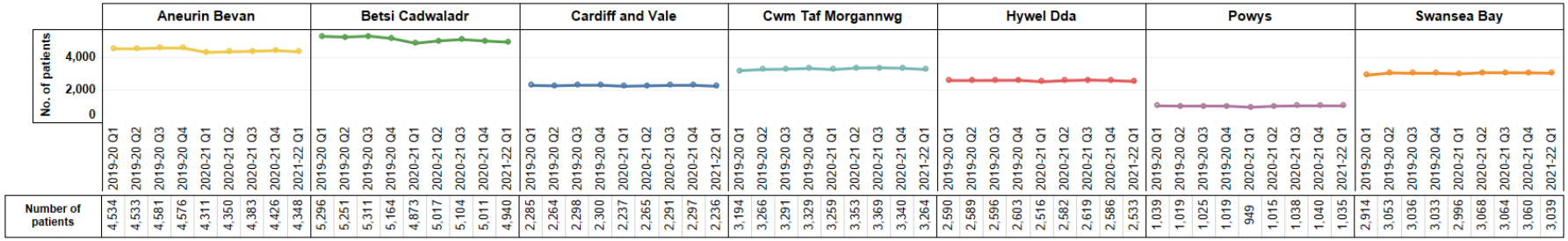
Prescribing Safety Indicators related to cognition

10. Number of patients aged 65 years or over prescribed an antipsychotic.



Number of patients	2019-20 Q1	2019-20 Q2	2019-20 Q3	2019-20 Q4	2020-21 Q1	2020-21 Q2	2020-21 Q3	2020-21 Q4	2021-22 Q1
Aneurin Bevan	1,846	1,868	1,900	1,899	1,837	1,861	1,840	1,893	1,962
Betsi Cadwaladr	2,215	2,260	2,292	2,273	2,353	2,429	2,469	2,419	2,451
Cardiff and Vale	1,195	1,222	1,192	1,206	1,151	1,186	1,199	1,190	1,222
Cwm Taf Morgannwg	1,431	1,443	1,438	1,462	1,412	1,474	1,437	1,402	1,409
Hywel Dda	1,209	1,244	1,232	1,207	1,241	1,247	1,217	1,200	1,231
Powys	481	474	475	483	478	497	491	487	485
Swansea Bay	1,433	1,470	1,474	1,476	1,464	1,511	1,482	1,442	1,461

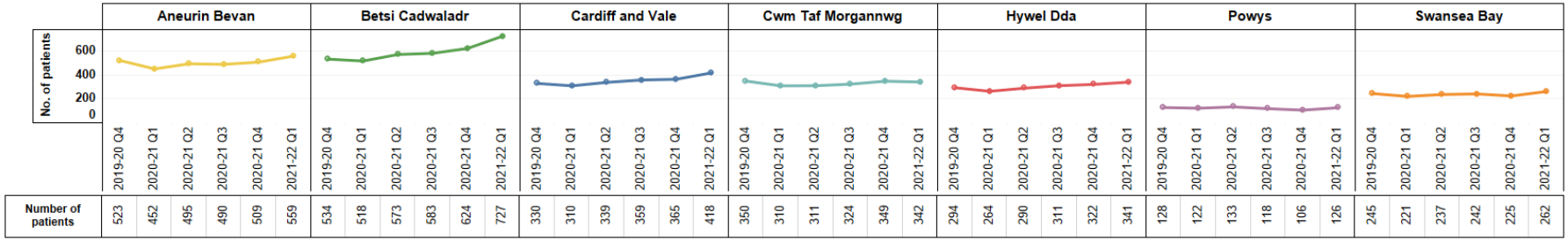
11. Number of patients aged 75 years and over with an Anticholinergic Effect on Cognition (AEC) score of 3 or more for items on active repeat.



Number of patients	2019-20 Q1	2019-20 Q2	2019-20 Q3	2019-20 Q4	2020-21 Q1	2020-21 Q2	2020-21 Q3	2020-21 Q4	2021-22 Q1
Aneurin Bevan	4,534	4,533	4,581	4,576	4,311	4,350	4,383	4,426	4,348
Betsi Cadwaladr	5,296	5,251	5,311	5,164	4,873	5,017	5,104	5,011	4,940
Cardiff and Vale	2,285	2,264	2,298	2,300	2,237	2,265	2,291	2,297	2,236
Cwm Taf Morgannwg	3,194	3,266	3,291	3,329	3,259	3,353	3,369	3,340	3,264
Hywel Dda	2,590	2,589	2,596	2,603	2,516	2,582	2,619	2,586	2,533
Powys	1,039	1,019	1,025	1,019	949	1,015	1,038	1,040	1,035
Swansea Bay	2,914	3,053	3,036	3,033	2,996	3,068	3,064	3,060	3,039

Prescribing Safety Indicators specific to females

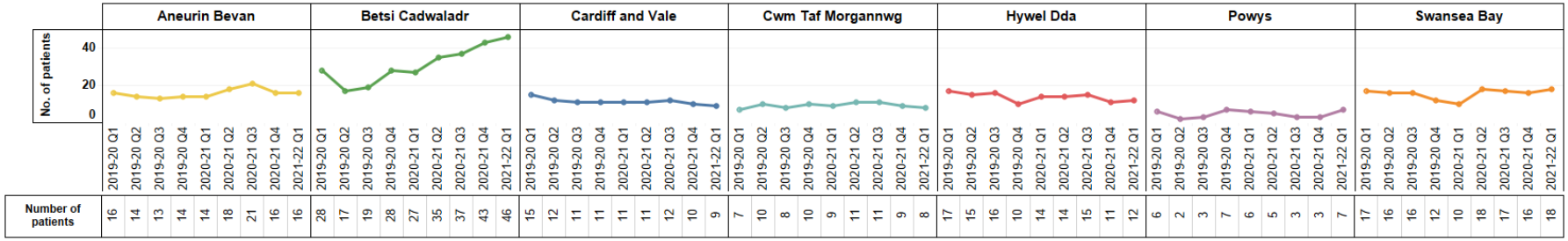
12. Number of female patients with a current prescription of oestrogen-only hormone replacement therapy without any hysterectomy READ/SNOMED codes*.



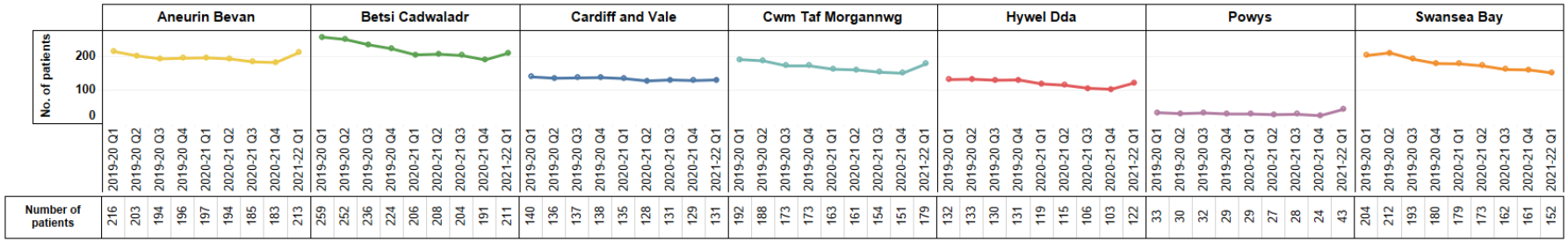
Number of patients	2019-20 Q4	2020-21 Q1	2020-21 Q2	2020-21 Q3	2020-21 Q4	2021-22 Q1
Aneurin Bevan	523	452	495	490	509	559
Betsi Cadwaladr	534	518	573	583	624	727
Cardiff and Vale	330	310	339	359	365	418
Cwm Taf Morgannwg	350	310	311	324	349	342
Hywel Dda	294	264	290	311	322	341
Powys	128	122	133	118	106	126
Swansea Bay	245	221	237	242	225	262

* Audit+ searches for this Prescribing Safety Indicator were amended for the quarter ending March 2020. Therefore there are no data before 2019–2020 Q4.

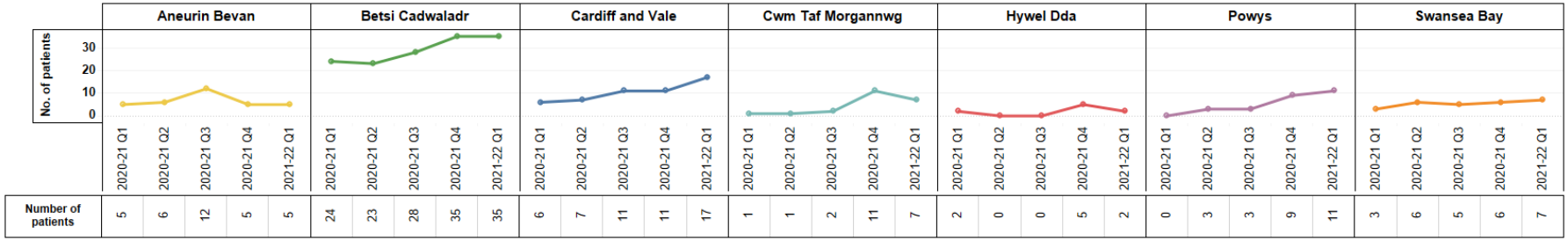
13. Number of female patients with a past medical history of venous or arterial thrombosis who have been prescribed combined hormonal contraceptives.



14. Number of female patients aged 14–45 years with a prescription for sodium valproate*.



15. Number of female patients aged 14–45 years with a prescription for oral retinoids†.

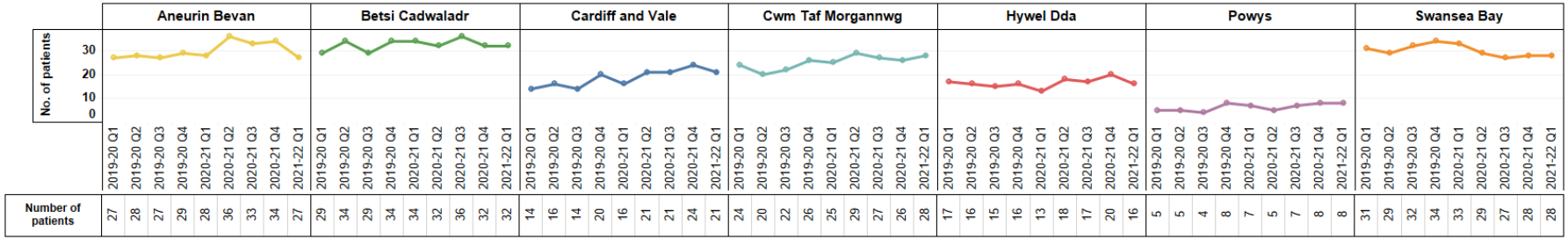


* Please note that, for 2022–2025, this indicator will be looking at female patients aged 14–55 years.

† This Prescribing Safety Indicator was new for 2020–2021, therefore there are no data before 2020–2021 Q1. Please note that, for 2022-2025, this indicator will be looking at female patients aged 14-55 years.

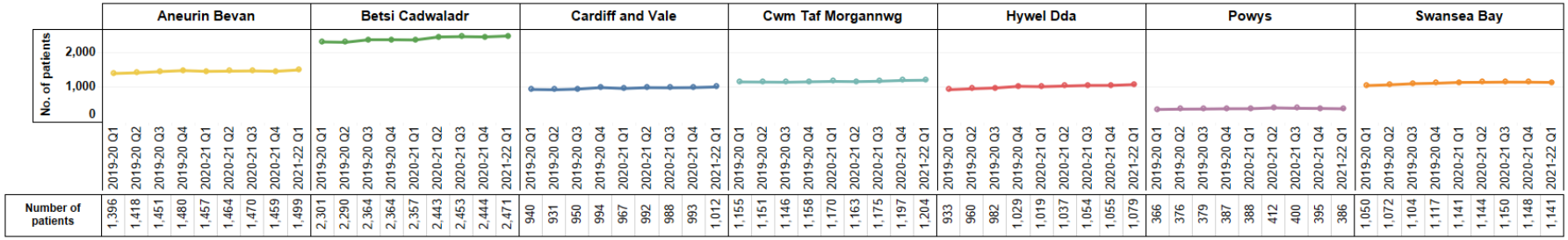
Prescribing Safety Indicators related to 'other'

16. Number of patients aged under 16 years with a current prescription of aspirin.



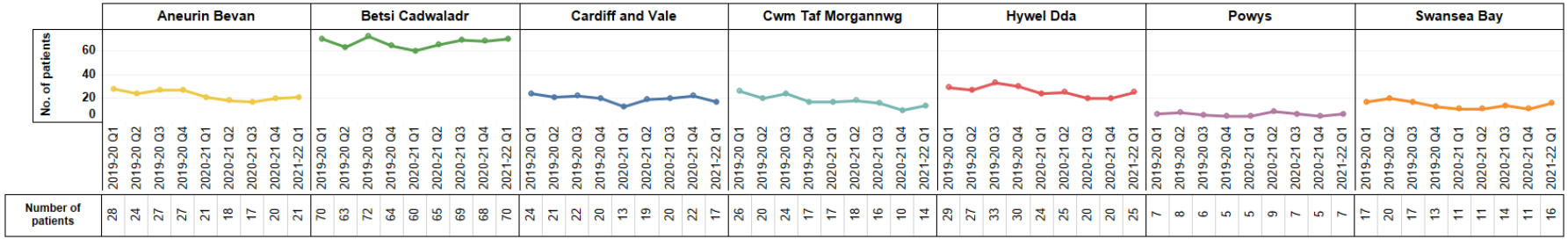
Number of patients	2019-20 Q1	2019-20 Q2	2019-20 Q3	2019-20 Q4	2020-21 Q1	2020-21 Q2	2020-21 Q3	2020-21 Q4	2021-22 Q1
Aneurin Bevan	27	28	27	29	28	36	33	34	27
Betsi Cadwaladr	29	34	29	34	34	32	36	32	32
Cardiff and Vale	14	16	14	20	16	21	21	24	21
Cwm Taf Morgannwg	24	20	22	26	25	29	27	26	28
Hywel Dda	17	16	15	16	13	18	17	20	16
Powys	5	5	4	8	7	5	7	8	8
Swansea Bay	31	29	32	34	33	29	27	28	28

17. Number of patients with asthma who have been prescribed a beta-blocker.



Number of patients	2019-20 Q1	2019-20 Q2	2019-20 Q3	2019-20 Q4	2020-21 Q1	2020-21 Q2	2020-21 Q3	2020-21 Q4	2021-22 Q1
Aneurin Bevan	1,396	1,418	1,451	1,480	1,457	1,464	1,470	1,459	1,499
Betsi Cadwaladr	2,301	2,290	2,364	2,364	2,357	2,443	2,453	2,444	2,471
Cardiff and Vale	940	931	950	994	967	992	988	993	1,012
Cwm Taf Morgannwg	1,155	1,151	1,146	1,158	1,170	1,163	1,175	1,197	1,204
Hywel Dda	933	960	982	1,029	1,019	1,037	1,054	1,055	1,079
Powys	366	376	379	387	388	412	400	395	386
Swansea Bay	1,050	1,072	1,104	1,117	1,141	1,144	1,150	1,148	1,141

18. Number of patients with concurrent prescriptions of verapamil and a beta-blocker.



Number of patients	2019-20 Q1	2019-20 Q2	2019-20 Q3	2019-20 Q4	2020-21 Q1	2020-21 Q2	2020-21 Q3	2020-21 Q4	2021-22 Q1
Aneurin Bevan	28	24	27	27	21	18	17	20	21
Betsi Cadwaladr	70	63	72	64	60	65	69	68	70
Cardiff and Vale	24	21	22	20	13	19	20	22	17
Cwm Taf Morgannwg	26	20	24	17	17	18	16	10	14
Hywel Dda	29	27	33	30	24	25	20	20	25
Powys	7	8	6	5	5	9	7	5	7
Swansea Bay	17	20	17	13	11	11	14	11	16

Background and evidence

As adverse drug reactions can often be predictable, a system to identify patients at risk can enable potential problems to be identified and addressed before actual patient harm occurs[77]. The Prescribing Safety Indicators (PSIs) identify groups of patients within the GP practice, enabling intervention and avoidance of harm. Patients identified via the PSIs should be reviewed and/or monitored as appropriate.

These indicators support the third WHO Global Patient Safety Challenge: *Medication Without Harm*, launched in 2017, which aims to reduce severe avoidable medication-related harm by 50% globally, within 5 years[78].

PSIs related to Acute Kidney Injury (AKI)

AKI is a term covering a range of injury to the kidneys, resulting from a number of different causes. It is characterised by a decline in renal excretory function over hours or days that can result in failure to maintain fluid, electrolyte and acid based homeostasis[79].

One of the most common causes of AKI is reduced perfusion of the kidneys leading to decreased glomerular filtration rate (GFR). This can be caused by drugs that reduce blood pressure, circulating volume or renal blood flow, for example ACE inhibitors, ARBs, NSAIDs and loop diuretics[79]. AWMSG *Polypharmacy Guidance* notes that use of an ACE inhibitor or ARB and diuretic, in conjunction with an NSAID is a high risk drug combination[80]. Groups of patients most at risk of developing AKI include those aged over 65 years; patients with CKD; use of nephrotoxic drugs within the last week and people with a history of AKI[79]. NICE guidance *Chronic kidney disease in adults: assessment and management* highlights that in patients with CKD, the long-term use of NSAIDs may be associated with disease progression. The guideline recommends caution and monitoring of the effects on GFR, when using NSAIDs in people with CKD over prolonged periods of time[81].

Regular review of the ongoing need for treatment with drugs which may contribute to AKI, ensuring systems are in place for regular monitoring of renal function, in addition to reassessment of the risk versus benefit is appropriate, and processes for this should be in place.

PSIs related to bleeds

NSAIDs have been shown to be the medicine group most likely to cause an adverse drug reaction requiring hospital admission due to events such as gastrointestinal bleeding and peptic ulceration[77]. A PPI can be considered for gastroprotection in patients at high risk of gastrointestinal complications with an NSAID[11].

NSAIDs can reduce platelet aggregation which can worsen any bleeding event in patients on an anticoagulant[11]. Wherever possible, patients taking anticoagulants should avoid concomitant use of NSAIDs[82]. AWMSG *Polypharmacy Guidance* notes that NSAIDs plus an oral anticoagulant is a potential high risk drug combination[80] which should be avoided.

Hospital admission due to gastrointestinal bleeding has been associated with aspirin and clopidogrel, as well as NSAIDs[77]. The harmful consequences of bleeds due to antiplatelet therapy increase with age[83] and PPIs are recommended in older patients undergoing antiplatelet treatment[83,84]. PPIs are the preferred option to reduce GI adverse effects in people taking low dose aspirin, as the level of suppression provided by traditional doses of H_2-receptor antagonists may not prevent NSAID related ulcers[85].

SSRIs are associated with increased risk of bleeding, especially in the elderly, or those taking drugs which damage the GI mucosa/interfere with clotting such as aspirin, NSAIDs and warfarin[80]. Anticoagulants are likely to increase the risk of bleeding events used in conjunction with SSRIs[11].

PSIs related to cognition

Use of antipsychotics in patients with dementia have a significant risk of harm, with only a limited benefit in treating behavioural and psychological symptoms of dementia[86]. The Welsh Government *Dementia Action Plan for Wales 2018–2022* calls for health boards to demonstrate a reduction in the percentage of people with a diagnosis of dementia prescribed an antipsychotic medication, and a reduction in the duration of treatment[87].

The harms associated with antipsychotic use in patients with dementia include a clear increased risk of stroke and a small increase in risk of death[88]; falls; gait disturbances; dehydration; chest infection and cognitive decline[80]. Antipsychotics should be avoided in patients with dementia unless the person is at risk of harming themselves or others, or experiencing agitation, hallucinations or delusions that are causing them severe distress[89]. Completion of the AWMSG National Audit *Antipsychotics in Dementia* can help to ensure appropriate prescribing.

An increasing number of studies report that medicines with anticholinergic effects are associated with an increased risk of cognitive impairment, dementia and falls in older people, with research also suggesting a link to increased mortality with the number and potency of anticholinergic agents prescribed. Anticholinergic medicines are used for a variety of conditions, including Parkinson's disease, overactive bladder, COPD and depression. Risk of adverse clinical outcomes in older people prescribed anticholinergic medications increases with increasing anticholinergic exposure[90], and a number of rating scales are available to asses overall anticholinergic burden. The Anticholinergic Effect on Cognition (AEC)[91] scale is used for this indicator and it is good practice, where possible, to use drugs with AEC scores of zero and to avoid those scored 1, 2 or 3 (Appendix 2). Encouraging timely review to reduce the anticholinergic burden in older people by avoiding or reducing doses and deprescribing medicines with anticholinergic activity where clinically possible will help minimise potential medication-related risks.

PSIs specific to females

Oestrogen-only hormone replacement therapy without a record of hysterectomy

Where hormone replacement therapy is indicated, hysterectomy status of the woman will determine which type is appropriate. All women with an intact uterus require a progestogen component in their hormone replacement therapy to prevent endometrial hyperplasia, which can occur after as little as six months of unopposed oestrogen therapy[92], however there may be instances where patients with an intact uterus may be prescribed oestrogen-only HRT in conjunction with a separate progestogen for progestogenic opposition of oestrogen HRT. Conversely, women who have undergone a hysterectomy should not receive a progestogen component[92].

Combined hormonal contraceptives in thrombosis patients

There is an increased risk of venous thromboembolic disease and a slight increase in the risk of arterial thromboembolism in people using combined hormonal contraceptives[11]. Any patients with a history of venous or arterial thrombosis who have been prescribed combined hormonal contraceptives are therefore at an increased risk[11].

Sodium valproate in females of child bearing age
In March 2018, the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh)[15] endorsed new measures to avoid exposure of babies to valproate medicines in the womb, because exposed babies are at high risk of malformations and developmental problems[93]. The MHRA have published a Drug Safety Update stating that valproate must no longer be used in any women or girl able to have children unless she has a Pregnancy Prevention Programme in place[94] to ensure that patients are fully aware of the risks and the need to avoid becoming pregnant[95]. An annual risk acknowledgement form is available to support the valproate Pregnancy Prevention Programme[96].

Oral retinoids in females of child bearing age
Oral retinoids are highly teratogenic and there is an extremely high risk that foetal exposure to isotretinoin will result in life-threatening congenital abnormalities. Any use of oral acitretin, alitretinoin, and isotretinoin in women and girls of childbearing potential must be in accordance with the conditions of a Pregnancy Prevention Programme[97].

PSIs related to 'other'

Aspirin in under 16s
Reye's syndrome is a very rare disorder that can cause serious liver and brain damage. If it is not treated promptly, it may lead to permanent brain injury or death. Reye's syndrome mainly affects children and young adults under 20 years of age[98]. Owing to an association with Reye's syndrome, aspirin should not be given to children under the age of 16, unless specifically indicated e.g. for Kawasaki disease[11,99].

Beta-blockers in asthma patients
Beta-blockers should be avoided in patients with asthma due to the potential to precipitate bronchospasm[11]. If the benefits of using a beta-blocker in an asthma patient are justified the patient should be monitored closely[11].

Verapamil in combination with beta-blockers
Beta-blockers are associated with adverse drug reactions such as bradycardia and atrio-ventricular conduction disturbances[11]. A co-prescription of a calcium channel blocker, such as verapamil, with a beta-blocker is generally not recommended due to an increased negative effect on heart function compared with beta-blocker therapy alone[11].

Useful resources
- AWMSG (2023) Polypharmacy in older people: A guide for healthcare professionals
- AWMSG (2017) CEPP National Audit: Medicines Management for CKD
- AWMSG (2015) CEPP All Wales Audit: Towards Appropriate NSAID Prescribing
- MHRA (2014) Antipsychotics e-learning module
- AWMSG (2018) CEPP National Audit: Antipsychotics in dementia
- PrescQIPP (2020) Bulletin 253: Anticholinergic burden (log in required)
- South London and Maudsley NHS Foundation Trust (2017) Medichec: The Anticholinergic Effect on Cognition Tool (Android and iOS Medichec apps available)
- Sanofi (2020) Guide for healthcare professionals: Information on the risks of valproate▼ use in girls (of any age) and women of childbearing potential

[15]The CMDh is a medicines regulatory body representing the European Union (EU) Member States, Iceland, Liechtenstein and Norway.

2.1.2 Hypnotics and anxiolytics

Purpose:
To encourage a reduction in the inappropriate prescribing of hypnotics and anxiolytics in primary care.
Unit of measure:
Hypnotic and anxiolytic UDG ADQs per 1,000 STAR-PUs.
Target for 2022–2025:
Maintain performance levels within the lower quartile, or show a reduction towards the quartile below.

Figure 18. Trend in hypnotic and anxiolytic ADQs per 1,000 STAR-PUs to quarter ending June 2021

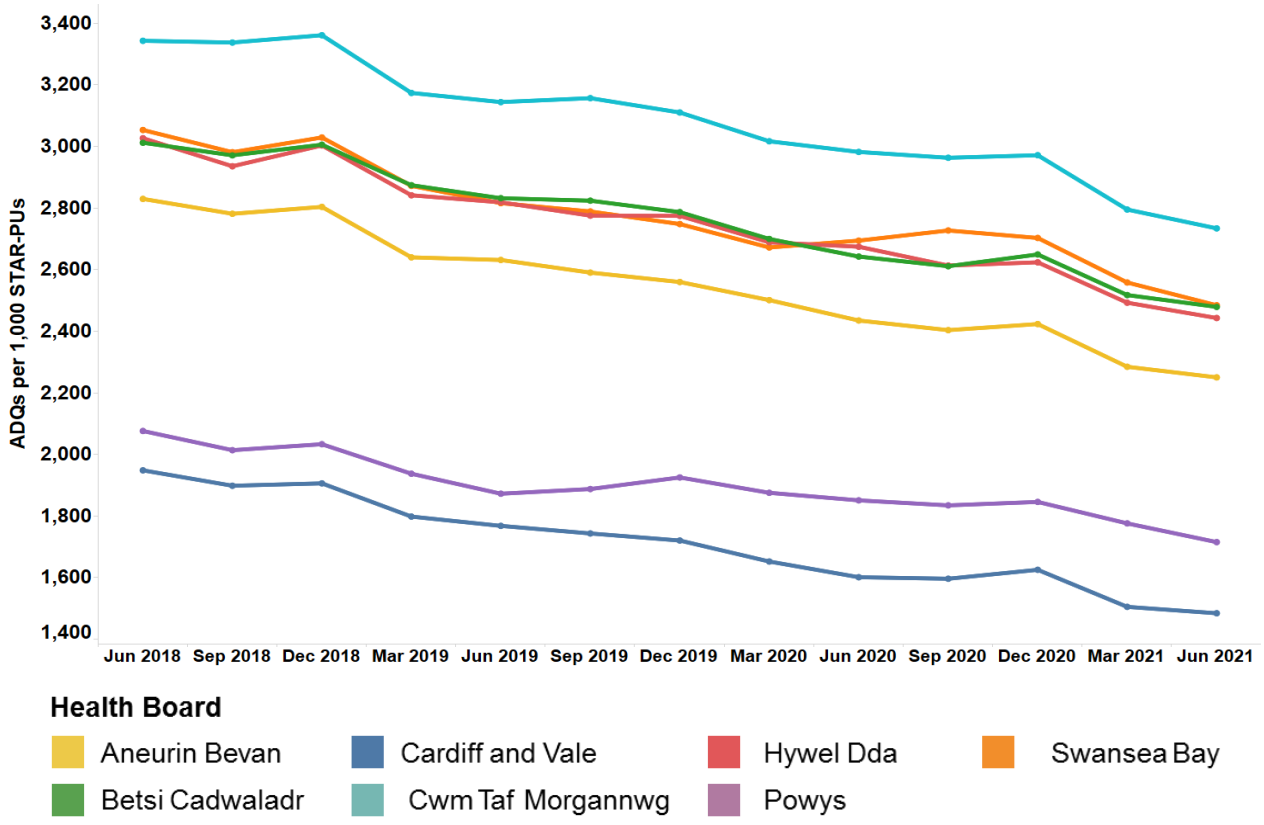
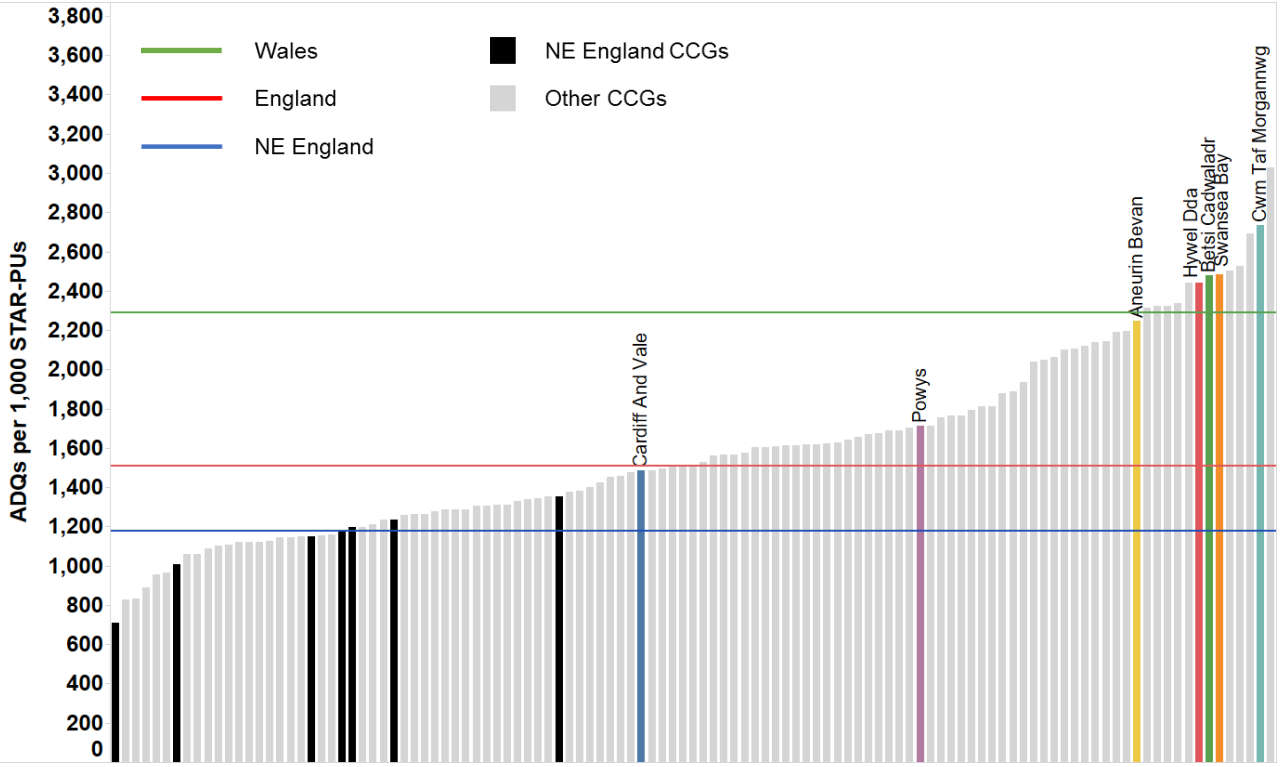


Figure 19. Hypnotic and anxiolytic ADQs per 1,000 STAR-PUs Welsh health boards and English CCGs – Quarter ending June 2021



Background and evidence

There has been concern with regard to the high level of hypnotic and anxiolytic prescribing in NHS Wales, with the substance misuse strategy of the Welsh Government, *Working together to reduce harm*, calling for the reduction of inappropriately prescribed benzodiazepines[100]. Although the prescribing volume of hypnotics and anxiolytics in Wales has declined over recent years, there is considerable variation in prescribing rates across health boards and between GP practices. Prescribing in Wales is still high in comparison to England, with five out of seven health boards in Wales within the highest prescribing quartile when compared with CCGs in England[31,32]. Across Wales, 35 deaths were recorded where any benzodiazepine was mentioned on the death certificate in 2020. This is a reduction of 37% compared with 2019[15]. In England, deaths continue to rise with 437 deaths recorded in 2020. This is the highest number recorded since records began in 1993[15].

The problems associated with benzodiazepines (such as development of tolerance and dependence, and falls) are well known. It is recommended that benzodiazepines should not be used for more than two to four weeks for insomnia and anxiety, and only if it is severe, disabling, or subjecting the individual to unacceptable distress[101]. NICE guidance on the management of insomnia advises that if, after non-drug therapies have been explored, hypnotics are considered appropriate, they should be used in the lowest effective dose possible for the shortest duration possible in strict accordance with their licensed indications[102,103]:

AWMSG has developed an *Educational Pack: Material to Support Appropriate Prescribing of Hypnotics and Anxiolytics across Wales*, which provides examples of practice protocols to allow clinicians to agree a consistent approach for the prescribing and review of hypnotics and anxiolytics. The pack also provides materials to support the review and discontinuation of hypnotic and anxiolytic treatment.

Useful resources

- AWMSG (2021) Material to Support Appropriate Prescribing of Hypnotics and Anxiolytics across Wales
- Bruyère Research Institute (2019) Benzodiazepine & Z-Drug (BZRA) Deprescribing Algorithm
- AWMSG (2023) Polypharmacy in older people: A guide for healthcare professionals

2.1.3 Yellow Cards

Purpose:
To encourage an increase in the number of Yellow Cards submitted in Wales.
Unit of measure:
Number of Yellow Cards submitted, per GP practice, per health board and per hospital. Number of Yellow Cards submitted by Community Pharmacies, per health board.
Target for 2022–2025:
GP practices: Submit one Yellow Card per 2,000 practice population. Health boards: • Submit one Yellow Card per 2,000 health board population • Demonstrate a 10%, or greater, increase from baseline (previous financial year), for Yellow Cards submitted by secondary care • Demonstrate a 25%, or greater, increase from baseline (previous financial year), for Yellow Cards submitted by members of the public Community pharmacy: no target set

Figure 20. Percentage of GP practices meeting the target of one Yellow Card per 2,000 practice population 2020–2021

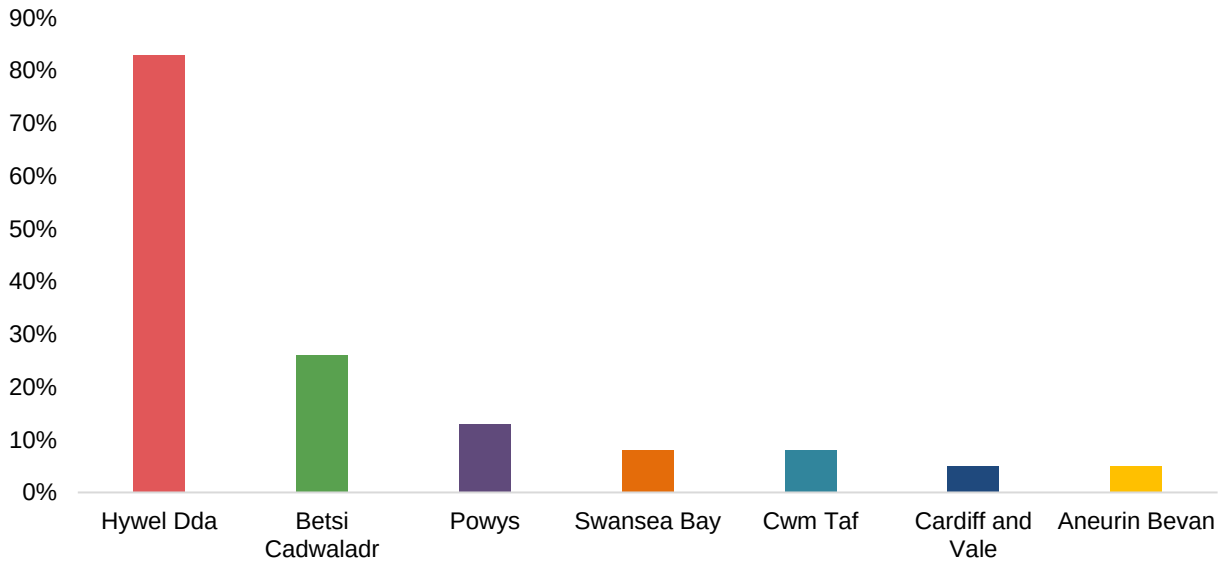


Table 5. Yellow Card data showing total number of reports, number of secondary care reports and number of member of public reports in 2020–2021

Health board/ NHS Trust	Total number of reports	General Practice reports	Secondary care reports	Member of public reports
Aneurin Bevan	186	71	35	60
Betsi Cadwaladr	498	261	128	85
Cardiff and Vale	220	54	87	61
Cwm Taf Morgannwg	207	10	37	40
Hywel Dda	590	475	56	50
Powys	44	22	5	17
Swansea Bay	147	54	47	36
Velindre	86	N/A	86	N/A

Background and evidence

Adverse drug reactions (ADRs) are a significant clinical problem, increasing morbidity and mortality. Studies have shown that ADRs are the cause of up to around 6.5% of hospital admissions in adults and 2.1% in children[77,104]. An ADR has been defined as *"a response to a medicinal product that is noxious and unintended resulting not only from the authorised use of a medicinal product at normal doses but also from medication errors and uses outside the terms of the marketing authorisation, including the misuse and abuse of the medicinal product"*[105]. The Yellow Card Scheme is vital in helping the MHRA monitor the safety of all healthcare products in the UK, to ensure they are acceptably safe for those that use them.

Prior to April 2013, the number of reports from GPs across Wales had been in decline. In April 2013, Yellow Card reporting was included as a Clinical Effectiveness Prescribing Programme (CEPP) Local Comparator and in April 2014 it became an NPI. In 2020–2021, the number of Yellow Cards submitted by GP practices in Wales increased by 8.5% compared with the previous year, to 2,149. This NPI also monitors the number of Yellow Cards submitted by all reporters per health board population. In 2018–2019, the number of Yellow Cards submitted by health boards in Wales increased by 6% compared with the previous year, to 3,221. It is anticipated that continuing to monitor Yellow Card reporting as an NPI for 2022–2025 will further increase reporting rates.

In 2020–2021, 597 Yellow Card reports were submitted across Wales from secondary care settings. This represents an 8% decrease on the number reported in the previous year. The purpose of this measure is for health boards to compare how their secondary care sites are progressing each quarter, it is not intended to measure performance between health boards due to the varying size and nature of the services provided.

Yellow Cards submitted by patients have been shown to provide greater descriptions of reactions than those from healthcare professionals, and more often noted the effects of ADRs on their lives. Patient reporting of suspected ADRs has the potential to add value to pharmacovigilance by reporting types of drugs and reactions different from those reported by healthcare professionals, therefore generating new potential signals[106]. In 2020–2021, 354 Yellow Card reports were submitted across Wales by members of the public. Continued monitoring of the number of Yellow Cards submitted by patients, their carers and/or parents will aim to ensure that reporting continues to increase.

Community pharmacists are required to ask patients about ADRs as part of the essential (batch repeat dispensing) and advanced (medicines use review [MUR] and discharge medicines review [DMR]) elements of the community pharmacy contract[107,108]. As a result, community pharmacists are ideally placed to make a significant contribution to the number of Yellow Cards submitted. In 2020–2021, a total of 68 Yellow Card reports were submitted from community pharmacies across Wales. This NPI will measure the total number of reports submitted from community pharmacies in each health board.

Useful resources

- Yellow Card champions are available in each health board to provide training. Contact YCCWales@wales.nhs.uk for more information
- Yellow Card reports can be completed online – Yellow Card website
- Health Professional Guidance on Reporting
- MHRA website
- YCC Wales website
- NHS Education for Scotland e-learning modules on ADRs
- Health Education and Improvement Wales (HEIW) e-Learning module on the Yellow Card Scheme

Download the Yellow Card App:

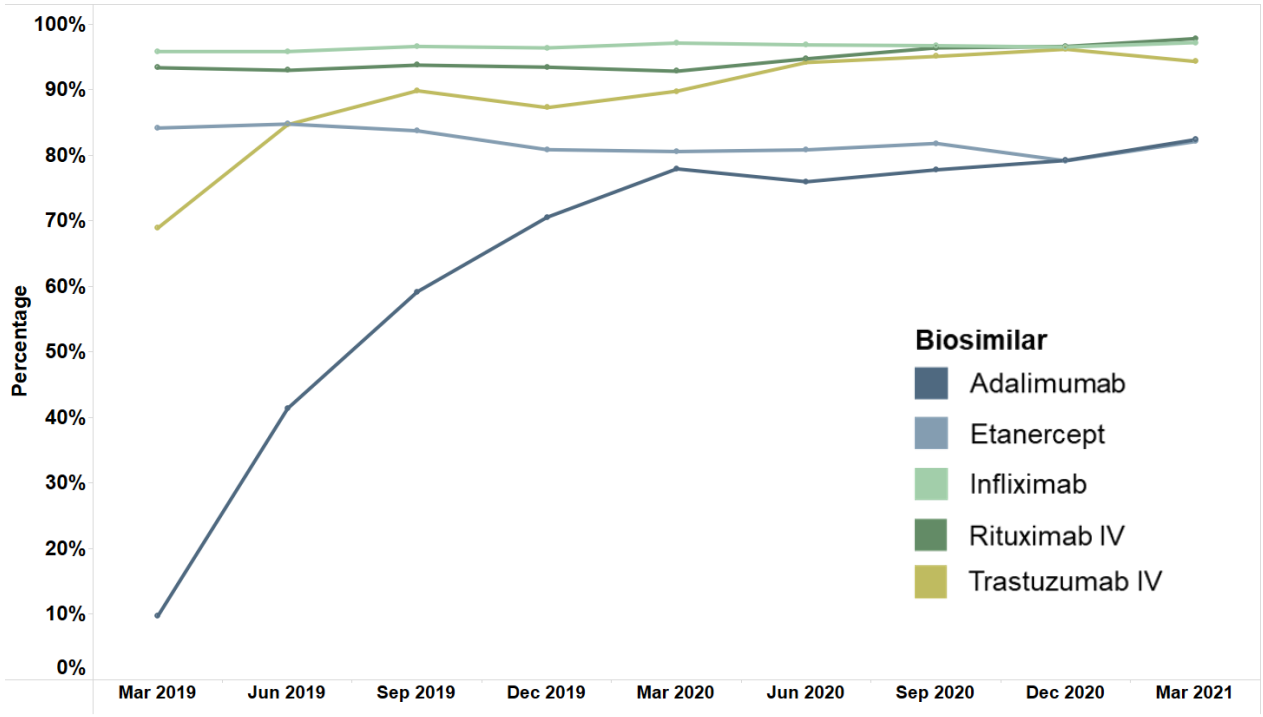
- Android
- Apple

2.2 Efficiencies

2.2.1 Best value biological medicines

Purpose:
To ensure prescribing of best value biological medicines supports cost-efficient prescribing in primary and secondary care in Wales.
Unit of measure:
Quantity of best value biological medicines prescribed as a percentage of total ‘biosimilar’ plus ‘reference’ product.
Target for 2022–2025:
Increase the appropriate use of cost-efficient biological medicines, including biosimilar medicines.

Figure 21. Trend in biosimilar percentage to quarter ending March 2021



Background and evidence

Biological medicines account for a significant expenditure within the NHS. Continuing development of biological medicines, including biosimilar medicines, creates increased choice for patients and clinicians, increased commercial competition and possible enhanced value propositions for individual medicines. This indicator supports the ongoing work within NHS Wales to increase the use of the best value intervention wherever possible within healthcare.

The list of biological medicines being reported on will be determined by the requirements of the service. For 2022–2025 this will be focused on the biological medicines where a biosimilar version has recently become available. However, there will continue to be monitoring of an overall basket of biological medicines which will include:

- Infliximab – Flixabi®, Inflectra®, Remsima®, Zessly®▼
- Etanercept – Benepali®, Erelzi®▼

- Rituximab – Rixathon®▼, Ruxience®▼, Truxima®▼
- Trastuzumab – Herzuma®▼, Ontruzant®▼, Trazimera®▼, Zercepac®▼
- Adalimumab – Amgevita®▼, Hyrimoz®▼, Idacio®▼, Imraldi®▼, Yuflyma®▼
- Ranibizumab – Ongavia®▼

Within this efficiency indicator, 'best value' is primarily derived from cost data as any meaningful outcome data is not retrievable from within the current prescribing systems. Currently, for all of the biological medicines being reported on, the 'best value' option is the biosimilar version.

It is the responsibility of the clinician, in consultation with the patient, to make the decision about whether to prescribe a biological medicine and whether that should be the original reference medicine or a biosimilar medicine. Switching between a reference product and its biosimilar (and indeed amongst biosimilar medicines) should be managed at the discretion of the individual prescriber in partnership with the patient, and with appropriate monitoring in place. The NHS England publication *What is a biosimilar medicine?* provides supportive information for the use of biosimilar medicines[109].

Where AWMSG or NICE has already recommended the reference biological medicine, the same guidance will normally apply to any biosimilars[110,111]. However, where a review of the evidence for a biosimilar medicine is considered necessary, NICE will consider producing a further evidence summary[110].

Useful resources

- AWMSG (2023) Maximising the opportunity presented by biosimilar medicines – A national strategy for Wales
- AWTTC (2019) Biosimilar Best Practice Day
- AWTTC (2021) SPIRA – Biosimilar Efficiencies (NHS network connection required)
- NHS England (2019) What is a Biosimilar Medicine?
- The Cancer Vanguard (2017) Biosimilars frequently asked questions for healthcare professionals
- AWMSG (2019) Position statement for biosimilar medicines
- NICE Position statement for biosimilar medicines
- NICE (2018) Key Therapeutic Topic 15: Biosimilar medicines
- MHRA (2008) Drug safety update. Biosimilar products
- European Medicines Agency (2018) European public assessment reports
- The Cancer Vanguard (2018) Biosimilars adoption

2.2.2 Low value for prescribing

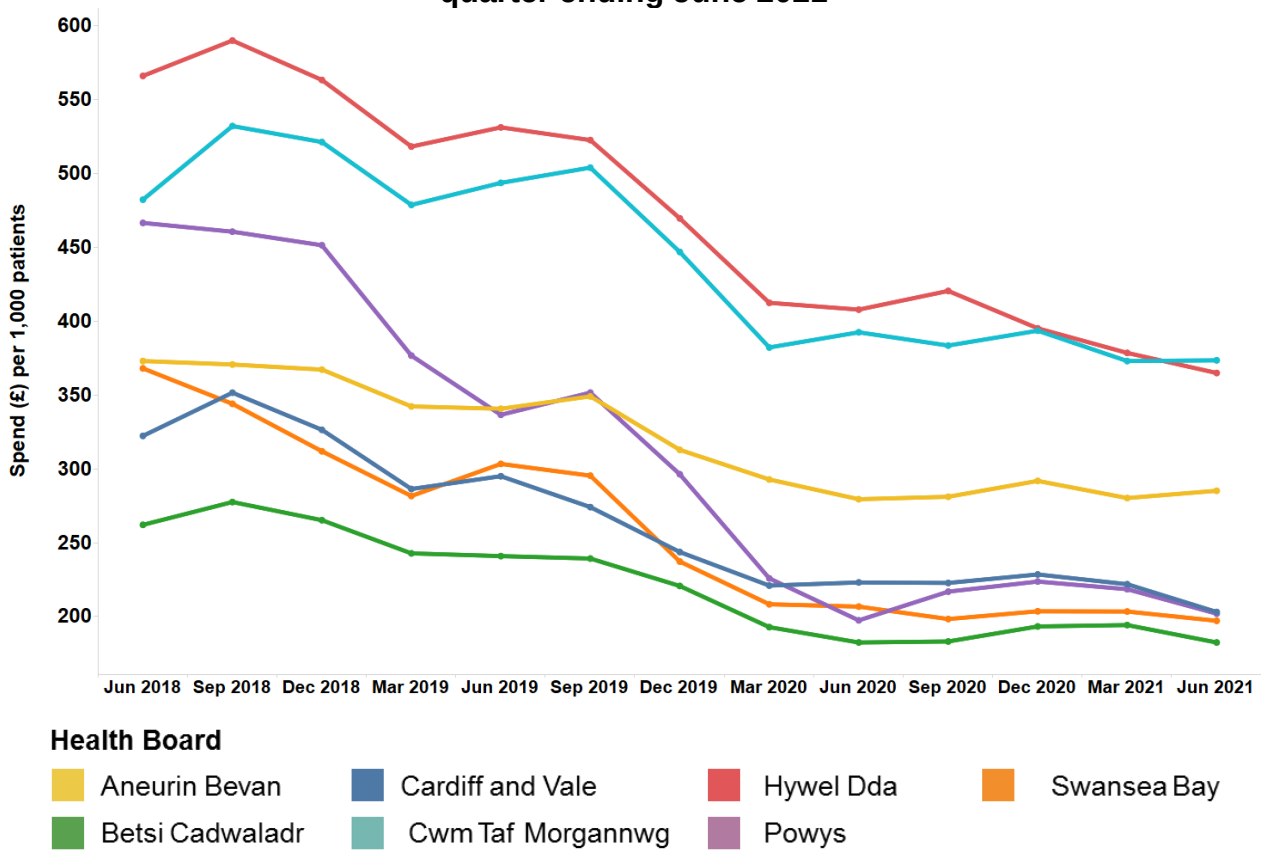
Purpose:
To drive a reduction in the prescribing of items considered as not suitable for routine prescribing in Wales
Unit of measure:
Low value for prescribing UDG spend per 1,000 patients
Target for 2022–2025:
Maintain performance levels within the lower quartile or show a reduction towards the quartile below

The aim of the *Low Value for Prescribing in NHS Wales* initiative is to minimise the prescribing of items that offer a limited clinical benefit to patients and where more cost-effective treatments *may be* available. The first paper in the initiative, entitled *Medicines Identified as Low Priority for Funding in NHS Wales* was endorsed by AWMSG in 2017, and the second paper was endorsed in 2018[112,113]. Five items/item groups were identified for the purposes of the first phase of this initiative, with an additional four included in the second phase. The paper detailing the items included in the third phase of this initiative was endorsed and published in February 2020. However, these items are not considered within the 2022–2025 NPI.

Within 2020–2021 there has been a decrease achieved in the overall spend on the items/item groups included in phases 1 and 2 of the low value for prescribing initiative of £0.63m. Although this cannot be taken as a direct overall saving to the NHS in Wales it does confirm a continuing decreased spend on the items identified as not suitable for routine prescribing.

Figure 22 illustrates the differences in spend between March 2018 and March 2021 for the nine items/item groups within phases 1 and 2 of the low value for prescribing initiative by health board.

Figure 22. Trend in low value for prescribing UDG spend per 1,000 patients to quarter ending June 2021



Useful resources

- AWMSG (2017) Medicines Identified as Low Priority for Funding in NHS Wales – paper 1
- AWMSG (2018) Medicines Identified as Low Priority for Funding in NHS Wales – paper 2
- AWMSG (2020) Items Identified as Low Value for Prescribing in NHS Wales – paper 3
- AWTTC (2021) SPIRA - Low Value for Prescribing Dashboard (NHS network connection required).

References

1. Welsh Government. A Healthier Wales: our Plan for Health and Social Care. 2018. Available at: https://gov.wales/sites/default/files/publications/2019-04/a-healthier-wales-our-plan-for-health-and-social-care.pdf. Accessed August 2021
2. Welsh Government. A Healthier Wales: our Plan for Health and Social Care actions. 2021. Available at: https://gov.wales/sites/default/files/publications/2021-04/a-healthier-wales-actions.pdf. Accessed August 2021
3. Royal College of Anaesthesists, and Faculty of Pain Medicine. About Pain. 2018. Available at: https://fpm.ac.uk/opioids-aware-understanding-pain-medicines-pain/about-pain. Accessed August 2021.
4. National Institute for Health and Care Excellence. NICE Guideline 193. Chronic pain (primary and secondary) in over 16s: assessment of all chronic pain and management of chronic primary pain (NG193). 2021. Available at: https://www.nice.org.uk/guidance/ng193. Accessed August 2021.
5. Scottish Government, and NHS Scotland. Quality Prescribing for Chronic Pain: A Guide for Improvement 2018-2021. 2018. Available at: https://www.therapeutics.scot.nhs.uk/wp-content/uploads/2018/03/Strategy-Chronic-Pain-Quality-Prescribing-for-Chronic-Pain-2018.pdf. Accessed August 2021.
6. Public Health England. Dependence and withdrawal associated with some prescribed medicines. An evidence review. 2019. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/829777/PHE_PMR_report.pdf. Accessed August 2021.
7. Zin CS, Chen L-C, and Knaggs RD. Changes in trends and pattern of strong opioid prescribing in primary care. *European Journal of Pain.* 2014;18(9):1343-1351. Available at: https://onlinelibrary.wiley.com/doi/full/10.1002/j.1532-2149.2014.496.x. Accessed August 2021.
8. World Health Organization. WHO's cancer pain ladder for adults. 2018. Available at: https://www.who.int/publications/i/item/9789241550390. Accessed August 2021.
9. British Medical Association. Chronic pain: supporting safer prescribing of analgesics. 2017. Available at: https://www.bma.org.uk/media/2100/analgesics-chronic-pain.pdf. Accessed August 2021.
10. Ballantyne JC. WHO analgesic ladder: a good concept gone astray. *BMJ.* 2016;352. Available at: https://www.bmj.com/content/bmj/352/bmj.i20.full.pdf. Accessed August 2021.
11. BMJ Group, and Royal Pharmaceutical Society of Great Britain. British National Formulary. 2021. Available at: https://www.medicinescomplete.com/#/. Accessed August 2021.
12. Advisory Council on the Misuse of Drugs. ACMD report on Diversion and Illicit Supply of Medicines. 2016. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/580296/Meds_report-_final_report_15_December_LU__2_.pdf. . Accessed August 2021.
13. Royal College of Anaesthesists, and Faculty of Pain Medicine. Tapering and Stopping. 2019. Available at: https://www.rcoa.ac.uk/faculty-of-pain-medicine/opioids-aware/structured-approach-to-prescribing/tapering-and-stopping. Accessed August 2021.
14. Davies E, Sewell B, Jones M et al. Examining opioid prescribing trends for non-cancer pain using an estimated oral morphine equivalence measure: a retrospective cohort study between 2005 and 2015. *British Journal of General Practice Open.*

2021;5(1). Available at: https://doi.org/10.3399/bjgpopen20X101122. Accessed August 2021.
15. Office for National Statistics. Deaths related to drug poisoning by selected substances. 2021. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/deathsrelatedtodrugpoisoningbyselectedsubstances. Accessed August 2021.
16. Royal College of Anaesthesists, and Faculty of Pain Medicine. Briefing Statement to Health Professionals on the Management of Opioid Medications 2018. Available at: https://fpm.ac.uk/sites/fpm/files/documents/2019-07/FPM%20Opioid%20letter%202018.pdf. Accessed August 2021.
17. National Institute for Health and Care Excellence. Key Therapeutic Topic 21. Medicines optimisation in chronic pain (KTT21). 2018. Available at: https://www.nice.org.uk/advice/ktt21. Accessed August 2021.
18. Advisory Council on the Misuse of Drugs. ACMD consideration of tramadol. 2013. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/144116/advice-tramadol.pdf. Accessed August 2021.
19. Electronic Medicines Compendium. SPC: Tramadol Hydrochloride 50mg Capsules. 2019. Available at: http://www.medicines.org.uk/EMC/medicine/24186/SPC. Accessed August 2021.
20. Senay EC, Adams EH, Geller A et al. Physical dependence on Ultram (tramadol hydrochloride): both opioid-like and atypical withdrawal symptoms occur. *Drug and Alcohol Dependence.* 2003;69(3):233-241. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12633909. Accessed August 2021.
21. All Wales Medicines Strategy Group. Tramadol Educational Resource Materials. Audit Materials. 2014. Available at: https://awmsg.nhs.wales/medicines-appraisals-and-guidance/medicines-optimisation/prescribing-guidance/tramadol-educational-resource-materials/. Accessed August 2021.
22. National Institute for Health and Care Excellence. Clinical Guideline 173. Neuropathic pain in adults: pharmacological management in non-specialist settings (CG173). 2019. Available at: https://www.nice.org.uk/guidance/cg173. Accessed August 2021.
23. Electronic Medicines Compendium. SPC: Gabapentin 300mg capsules. 2019. Available at: https://www.medicines.org.uk/emc/product/2361/smpc. Accessed August 2021.
24. Electronic Medicines Compendium. SPC: Neurontin 100mg Hard Capsules. 2019. Available at: https://www.medicines.org.uk/emc/product/158. Accessed August 2021.
25. Electronic Medicines Compendium. SPC: Gabapentin 100mg capsules. 2019. Available at: https://www.medicines.org.uk/emc/medicine/26529. Accessed August 2021.
26. Electronic Medicines Compendium. SPC: Pregabalin 150mg Capsules. 2017. Available at: https://www.medicines.org.uk/emc/medicine/30924. Accessed August 2021.
27. Electronic Medicines Compendium. SPC: Lyrica Capsules. 2019. Available at: https://www.medicines.org.uk/emc/medicine/14651. Accessed August 2021.
28. Electronic Medicines Compendium. SPC: Alzain 100 mg Capsules, Hard. 2019. Available at: https://www.medicines.org.uk/emc/medicine/30054. Accessed August 2021.
29. National Institute for Health and Care Excellence. Clinical Guideline 113. Generalised anxiety disorder and panic disorder in adults: management (CG113).

2019. Available at: https://www.nice.org.uk/guidance/cg113/resources/generalised-anxiety-disorder-and-panic-disorder-in-adults-management-pdf-35109387756997. Accessed October 2019.
30. Advisory Council on the Misuse of Drugs. Pregabalin and Gabapentin advice. 2016. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/491854/ACMD_Advice_-_Pregabalin_and_gabapentin.pdf. Accessed August 2021.
31. NHS Wales Shared Services Partnership. Comparative Analysis System for Prescribing Audit (CASPA). 2021 Accessed June 2021.
32. NHS Business Services Authority. Electronic Prescribing Analysis and Cost Tool (ePACT). 2021 Accessed June 2021.
33. Pearce C. NI GPs told to stop initiating pregabalin for neuropathic pain amid deaths rise. Pulse. 2021. Available at: https://www.pulsetoday.co.uk/news/clinical-areas/pain/ni-gps-told-to-stop-initiating-pregabalin-for-neuropathic-pain-amid-deaths-rise/. Accessed October 2021
34. Welsh Government. Welsh Health Circular. Advice for prescribers on the risk of the misuse of pregabalin and gabapentin. 2016. Available at: https://gov.wales/prescribing-guidance-pregabalin-and-gabapentin-whc2016030. Accessed August 2021.
35. NHS Scotland. Gabapentinoid Prescribing for Chronic Pain in Primary Care. 2018. Available at: http://www.therapeutics.scot.nhs.uk/wp-content/uploads/2018/12/Gabapentinoid-Guidance-updated-11122018-Final-v12-1.docx. Accessed August 2021.
36. Public Health England, and NHS England. Advice for prescribers on the risk of the misuse of pregabalin and gabapentin. 2014. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/385791/PHE-NHS_England_pregabalin_and_gabapentin_advice_Dec_2014.pdf. Accessed August 2021.
37. Derry S, Bell RF, Straube S et al. Pregabalin for neuropathic pain in adults. *Cochrane Database of Systematic Reviews.* 2019(1). Available at: https://www.cnfbook.org/pregabalin-for-acute-and-chronic-pain-in-adults/#:~:text=This%20review%20updates%20part%20of%20an%20earlier%20Cochrane,drug%20used%20in%20management%20of%20chronic%20pain%20conditions. Accessed August 2021.
38. McManus S, Bebbington P, Jenkins R et al. Mental Health and Wellbeing in England: Adult Psychiatric Morbidity Survey 2014. 2016. Available at: https://files.digital.nhs.uk/pdf/q/3/mental_health_and_wellbeing_in_england_full_report.pdf. Accessed August 2021.
39. Welsh Government, and Statistics for Wales. General Medical Services Contract: Quality and Outcomes Framework Statistics for Wales, 2018-2019. 2019. Available at: https://gov.wales/sites/default/files/statistics-and-research/2019-09/general-medical-services-contract-quality-and-outcomes-framework-april-2018-march-20199-599.pdf. Accessed August 2021.
40. International Association for the Study of Pain. What is neuropathic pain? 2014-2015. Available at: http://s3.amazonaws.com/rdcms-iasp/files/production/public/AM/Images/GYAP/What%20is%20Neuropathic%20Pain.pdf. Accessed August 2021.
41. Scottish Intercollegiate Guidelines Network. Management of chronic pain. 2019. Available at: https://www.sign.ac.uk/our-guidelines/management-of-chronic-pain/. Accessed August 2021.

42. Bennett M. The LANSS Pain Scale: the Leeds assessment of neuropathic symptoms and signs. *Pain.* 2001;92:147-157. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11323136. Accessed August 2021.
43. Freynhagen R, Baron R, Gockel U et al. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. *Current Medical Research and Opinion.* 2006;22(10):1911-1920. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17022849. Accessed August 2021.
44. PrescQIPP. Bulletin 216. Neuropathic pain. 2021. Available at: https://www.prescqipp.info/umbraco/surface/authorisedmediasurface/index?url=%2fmedia%2f5437%2f216-neuropathic-pain-20.pdf. Accessed August 2021.
45. National Institute for Health and Care Excellence. Clinical Knowledge Summaries. Neuropathic pain - drug treatment. 2019. Available at: https://cks.nice.org.uk/neuropathic-pain-drug-treatment#!backgroundSub:3. Accessed August 2021.
46. Finnerup NB, Attal N, Haroutounian S et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *The Lancet Neurology.* 2015;14(2):162-173. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25575710. Accessed August 2021.
47. Shanthanna H, Gilron I, Rajarathinam M et al. Benefits and safety of gabapentinoids in chronic low back pain: A systematic review and meta-analysis of randomized controlled trials. *PLoS Med.* 2017. Available at: http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002369. Accessed August 2021.
48. Royal College of General Practitioners. Prescription and over-the-counter medicines misuse and dependence. Factsheet 3. Identification. 2013. Available at: http://www.rcgp.org.uk/-/media/Files/SMAH/RCGP-Factsheet-3_artwork_v3_28Apr.ashx?la=en. Accessed August 2021.
49. NHS Wales Informatics Service. Primary Care Information Portal. 2021. Available at: http://gig01srvisdlogi.cymru.nhs.uk/pcip/. Accessed August 2021.
50. National Institute for Health and Care Excellence. Clinical Knowledge Summaries: Atrial fibrillation. 2019. Available at: https://cks.nice.org.uk/atrial-fibrillation#!topicSummary. Accessed August 2021.
51. Stroke Association. Atrial Fibrillation: information and resources. Available at: https://www.stroke.org.uk/professionals/atrial-fibrillation-information-and-resources. Accessed October 2021.
52. Cross Party Group on Stroke. The future of Stroke Care in Wales. 2020. Available at: https://business.senedd.wales/documents/s100374/Report%20of%20the%20inquiry%20into%20the%20implementation%20of%20the%20Welsh%20Governments%20Stroke%20Delivery%20Plan.pdf. Accessed September 2021.
53. Kings College London. Sentinel Stroke National Audit Proramme (SSNAP) – Country Results Portfolio 2021. Available at: https://www.strokeaudit.org/results/Clinical-audit/National-Results.aspx. Accessed July 2021.
54. National Institute for Health and Care Excellence. NICE Guideline 196. Atrial fibrillation: diagnosis and management (NG196). 2021. Available at: https://www.nice.org.uk/guidance/ng196. Accessed August 2021.
55. National Institute for Health and Care Excellence. Quality Standard 93. Atrial Fibrillation. 2018. Available at: https://www.nice.org.uk/guidance/qs93/. Accessed August 2021.
56. European Society of Cardiology. The 2018 European Hearth Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in

patients with atrial fibrillation. *European Heart Journal,.* 2018;39:1330-1393. Available at: https://academic.oup.com/eurheartj/article/39/16/1330/4942493. Accessed August 2021.
57. Wellcome Trust and HM Government. Tackling Drug-Resistant Infections Globally: Final Report and Recommendations. 2016. Available at: https://amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf. Accessed August 2021.
58. World Health Organization. Global Action Plan on Antimicrobial Resistance. 2015. Available at: https://apps.who.int/iris/bitstream/handle/10665/193736/9789241509763_eng.pdf?sequence=1. Accessed August 2021.
59. Interagency Coordination Group (IACG) on Antimicrobial Resistance. No Time to Wait: Securing the future from drug-resistant infections. Report to the Secretary-General of the United Nations. 2019. Available at: https://www.who.int/antimicrobial-resistance/interagency-coordination-group/IACG_final_report_EN.pdf?ua=1. Accessed August 2021.
60. Department of Health. UK Five Year Antimicrobial Resistance Strategy 2013 to 2018. 2013. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/244058/20130902_UK_5_year_AMR_strategy.pdf. Accessed August 2021.
61. Welsh Government. Together for Health. Tackling antimicrobial resistance and improving antibiotic prescribing. 2016. Available at: http://www.wales.nhs.uk/sitesplus/documents/888/Antimicrobial%20Resistance%20Delivery%20Plan.pdf. Accessed August 2021.
62. HM Government. Contained and controlled. The UK's 20-year vision for antimicrobial resistance. 2019. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/773065/uk-20-year-vision-for-antimicrobial-resistance.pdf. Accessed August 2021.
63. HM Government. Tackling antimicrobial resistance 2019-2024. The UK's five-year national action plan. 2019. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/784894/UK_AMR_5_year_national_action_plan.pdf. Accessed August 2021.
64. Welsh Government. AMR & HCAI Improvement Goals for 2021-22. 2021;WHC (2021) Number 028. Available at: https://gov.wales/sites/default/files/publications/2021-09/amr-hcai-improvement-goals-for-2021-to-2022.pdf. Accessed September 2021.
65. All Wales Therapeutics and Toxicology Centre. Server for Prescribing Information Reporting and Analysis. National Prescribing Indicators. 2021. Available at: https://www.awttc.org/spira. Accessed August 2021.
66. Public Health Wales. Antibacterial resistance in Wales 2008-2017. 2018. Available at: http://www.wales.nhs.uk/sitesplus/documents/888/Antimicrobial%20Resistance%20in%20Wales%202008-2017%20v1.pdf. Accessed August 2021.
67. National Institute for Health and Care Excellence. NICE Guideline 15. Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (NG15). 2015. Available at: https://www.nice.org.uk/guidance/ng15. Accessed August 2021.
68. National Institute for Health and Care Excellence. Evidence Summary. Clostridium difficile infection: risk with broad-spectrum antibiotics (ESMPB1). 2015. Available at:

https://www.nice.org.uk/advice/esmpb1/chapter/Key-points-from-the-evidence. Accessed August 2021.
69. Medicines and Healthcare products Regulatory Agency. Systemic and inhaled fluoroquinolones: small increased risk of aortic aneurysm and dissection; advice for prescribing in high-risk patients. 2018. Available at: https://www.gov.uk/drug-safety-update/systemic-and-inhaled-fluoroquinolones-small-increased-risk-of-aortic-aneurysm-and-dissection-advice-for-prescribing-in-high-risk-patients. Accessed August 2021.
70. Medicines and Healthcare products Regulatory Agency. Drug Safety Update: Fluoroquinolone antibiotics - new restrictions and precautions for use due to very rare resports of disabling and potantielly long-lasting or irreversible side effects. 2019. Available at: https://www.gov.uk/drug-safety-update/fluoroquinolone-antibiotics-new-restrictions-and-precautions-for-use-due-to-very-rare-reports-of-disabling-and-potentially-long-lasting-or-irreversible-side-effects. Accessed August 2021.
71. European Medicines Agency. Disabling and potentially permanent side effects lead to suspension or restrictions of quinolone and fluoroquinolone antibiotics. 2019. Available at: https://www.ema.europa.eu/en/documents/referral/quinolone-fluoroquinolone-article-31-referral-disabling-potentially-permanent-side-effects-lead_en.pdf. Accessed August 2021.
72. Medicines and Healthcare products Regulatory Agency. Systemic and inhaled fluoroquinolones: small risk of heart valve regurgitation; consider other therapeutic options first in patients at risk. 2020. Available at: https://www.gov.uk/drug-safety-update/systemic-and-inhaled-fluoroquinolones-small-risk-of-heart-valve-regurgitation-consider-other-therapeutic-options-first-in-patients-at-risk. Accessed August 2021.
73. Carbon Trust Wales. NHS Wales Decrbonisation Strategic Delivery Plan 2021-2030. 2021. Available at: https://gov.wales/sites/default/files/publications/2021-03/nhs-wales-decarbonisation-strategic-delivery-plan.pdf#:~:text=This%20NHS%20Wales%20Decarbonisation%20Strategic%20Delivery%20Plan%20has,cover%20emissions%20from%20Scopes%201%2C%202%2C%20and%203. Accessed October 2021.
74. British Thoracic Society. Position Statement: The environment and lung health. 2020. Available at: https://www.brit-thoracic.org.uk/document-library/governance-and-policy-documents/position-statements/environment-and-lung-health-position-statement-2019/. Accessed October 2021.
75. National Institute for Health and Care Excellence. Patient decision aid: Inhalers for asthma. 2020. Available at: https://www.nice.org.uk/guidance/ng80/resources/inhalers-for-asthma-patient-decision-aid-pdf-6727144573. Accessed October 2021.
76. Janson C, Henderson R, Löfdahl M et al. Carbon footprint impact of the choice of inhalers for asthma and COPD. *Thorax.* 2020;75(1):82-84. Available at: https://thorax.bmj.com/content/thoraxjnl/75/1/82.full.pdf.
77. Pirmohamed M, James S, Meakin S et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *BMJ.* 2004;329(7456):15-19. Available at: https://www.bmj.com/content/329/7456/15.long. Accessed August 2021.
78. World Health Organization. WHO Global Patient Safety Challenge: Medication Without Harm. 2017. Available at: https://www.who.int/initiatives/medication-without-harm. Accessed August 2021.

79. National Institute for Health and Care Excellence. Clinical Knowledge Summary: Acute kidney injury. 2018. Available at: https://cks.nice.org.uk/acute-kidney-injury#!backgroundSub:3. Accessed August 2021.
80. All Wales Medicines Strategy Group. Polypharmacy: Guidance for Prescribing. Supplementary Guidance - BNF Sections to Target. 2014. Available at: https://awmsg.nhs.wales/files/guidelines-and-pils/polypharmacy-supplementary-guidance-bnf-sections-to-target-pdf/. Accessed August 2021.
81. National Institute for Health and Care Excellence. Clinical Guideline 182. Chronic kidney disease in adults: assessment and management (CG182). 2015. Available at: http://www.nice.org.uk/guidance/cg182. Accessed August 2021.
82. Electronic Medicines Compendium. SPC: Warfarin 1mg Tablets. 2017. Available at: https://www.medicines.org.uk/emc/product/4442. Accessed August 2021.
83. Li L, Geraghty OC, Mehta Z et al. Age-specific risks, severity, time course, and outcome of bleeding on long-term antiplatelet treatment after vascular events: a population-based cohort study. *The Lancet.* 2017;390(10093):490-499. Available at: http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)30770-5/fulltext Accessed August 2021.
84. Mayor S. Older patients should take PPIs to cut risk of bleed from aspirin, study says. *The BMJ.* 2017;357. Available at: http://www.bmj.com/content/357/bmj.j2865. Accessed August 2021.
85. National Institute for Health and Care Excellence. Clinical Knowledge Summaries. Antiplatelet treatment. 2018. Available at: https://cks.nice.org.uk/antiplatelet-treatment#!scenario:1. Accessed August 2021.
86. Banerjee S. The use of antipsychotic medication for people with dementia: Time for action. *Department of Health.* 2009. Available at: http://psychrights.org/Research/Digest/NLPs/BanerjeeReportOnGeriatricNeuroleptic Use.pdf. Accessed September 2021.
87. Welsh Government. Dementia Action Plan for Wales 2018-2022. 2018. Available at: https://gov.wales/sites/default/files/publications/2019-04/dementia-action-plan-for-wales.pdf. Accessed August 2021.
88. Medicines and Healthcare products Regulatory Agency. Drug Safety Update: Antipsychotics - use in elderly patients with dementia. 2009;2(8). Available at: https://webarchive.nationalarchives.gov.uk/20091114182659/http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/CON041211. Accessed August 2021.
89. National Institute for Health and Care Excellence. NICE Guideline 97. Dementia: assessment, management and support for people living with dementia and their carers (NG 97). 2018. Available at: https://www.nice.org.uk/guidance/ng97. Accessed August 2021.
90. Sumukadas D, McMurdo MET, Mangoni AA et al. Temporal trends in anticholinergic medication prescription in older people: repeated cross-sectional analysis of population prescribing data. *Age and Ageing.* 2013;43(4):515-521. Available at: https://doi.org/10.1093/ageing/aft199. Accessed August 2021.
91. Bishara D, Harwood D, Sauer J et al. Anticholinergic effect on cognition (AEC) of drugs commonly used in older people. *International Journal of Geriatric Psychiatry.* 2016;32(6):650-656. Available at: http://onlinelibrary.wiley.com/doi/10.1002/gps.4507/full. Accessed August 2021.
92. Martin KA, and Barbieri RL. Treatment of menopausal symptoms with hormone therapy. *UpToDate.* 2019. Available at: https://www.uptodate.com/contents/treatment-of-menopausal-symptoms-with-hormone-therapy?source=see_link. Accessed August 2021.

93. European Medicines Agency. New measures to avoid valproate exposure in pregnancy endorsed. 2018. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/03/news_detail_002929.jsp&mid=WC0b01ac058004d5c1. Accessed August 2021.
94. Medicines and Healthcare products Regulatory Agency. Valproate medicines (Epilim, Depakote): contraindicated in women and girls of childbearing potential unless conditions of Pregnancy Prevention Programme are met. 2018. Available at: https://www.gov.uk/drug-safety-update/valproate-medicines-epilim-depakote-contraindicated-in-women-and-girls-of-childbearing-potential-unless-conditions-of-pregnancy-prevention-programme-are-met. Accessed August 2021.
95. Medicines and Healthcare products Regulatory Agency. Drug Safety Update. Valproate Pregnancy Prevention Programme: actions required now from GPs, specialists, and dispensers. 2018. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/743094/Sept-2018-DSU-PDF.pdf. Accessed August 2021.
96. Medicines and Healthcare products Regulatory Agency. Valproate medicines and serious harms in pregnancy: new Annual Risk Acknowledgement Form and clinical guidance from professional bodies to support compliance with the Pregnancy Prevention Programme. 2019. Available at: https://www.gov.uk/drug-safety-update/valproate-medicines-and-serious-harms-in-pregnancy-new-annual-risk-acknowledgement-form-and-clinical-guidance-from-professional-bodies-to-support-compliance-with-the-pregnancy-prevention-programme. Accessed August 2021.
97. Medicines and Healthcare products Regulatory Agency. Direct Healthcare Professional Communication: Retinoids (Acitretin, Adapalene, Alitretinoin, Bexarotone, Isotretinoin, Tretinoin, and Tazarotene): risk of teratogenicity and neuropsychiatric disorders. 2019. Available at: https://assets.publishing.service.gov.uk/media/5d0a2879ed915d095ffdaf84/Retinoids-DHPC-June-19.pdf. Accessed August 2021.
98. NHS Choices. Reye's syndrome. 2016. Available at: http://www.nhs.uk/conditions/Reyes-syndrome/Pages/Introduction.aspx Accessed August 2021.
99. Electronic Medicines Compendium. SPC: Aspirin tablets BP 300mg. 2013. Available at: http://www.medicines.org.uk/emc/medicine/23776. Accessed August 2021.
100. Welsh Government. Working together to reduce harm: The substance misuse strategy for Wales 2008-2018. 2008. Available at: https://gov.wales/review-working-together-reduce-harm-substance-misuse-strategy-2008-2018-0. Accessed August 2021.
101. Committee on Safety of Medicines. Current Problems in Pharmacovigilance: Benzodiazepines, dependence and withdrawal symptoms. 1988;21:1-2. Available at: http://webarchive.nationalarchives.gov.uk/20141205150130/http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con2024428.pdf. Accessed August 2021.
102. National Institute for Health and Care Excellence. Technology Appraisal 77. Guidance on the use of zaleplon, zolpidem and zopiclone for the short-term management of insomnia (TA77). 2004. Available at: https://www.nice.org.uk/guidance/ta77. Accessed August 2021.
103. National Institute for Health and Care Excellence. Clinical Knowledge Summaries. Insomnia. 2015. Available at: https://cks.nice.org.uk/insomnia#!scenario. Accessed August 2021.

104. Impicciatore P, Choonara I, Clarkson A et al. Incidence of adverse drug reactions in paediatric in/out-patients: a systematic review and meta-analysis of prospective studies. *Br J Clin Pharmacol.* 2001;52(1):77-83. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2014499/. Accessed August 2021.
105. European Parliament. Directive 2010/84/EU of the European Parliament and of the Council. *Official Journal of the European Union.* 2010. Available at: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2010_84/dir_2010_84_en.pdf. Accessed August 2021.
106. Avery AJ, Anderson C, Bond CM, Fortnum H, Gifford A, Hannaford PC, Hazell L, Krska J, Lee AJ, McLernon DJ, Murphy E, Shakir S, Watson MC, . Evaluation of patient reporting of adverse drug reactions to the UK 'Yellow Card Scheme': literature review, descriptive and qualitative analyses, and questionnaire surveys. *Health Technol Assessment.* 2011;20. Available at: https://pubmed.ncbi.nlm.nih.gov/21545758/. Accessed September 2021.
107. Community Pharmacy Wales. Batch Repeat Dispensing Operations Manual. For pharmacies in Wales. 2017. Available at: http://www.cpwales.org.uk/getattachment/Contract-support-and-IT/Contractual-Framework/Essentail-Services/Repeat-Dispensing-(1)/Batch-Repeat-Dispensing-Operations-Manual-Pharmacy-FINAL.pdf.aspx?lang=en-GB. Accessed August 2021.
108. NHS Business Services Authority. NHS Electronic Drug Tariff. 2017. Available at: http://www.drugtariff.nhsbsa.nhs.uk/#/00475250-DA_1/DA00474640/Part%20VID%20-%20Advanced%20Services%20(Pharmacy%20and%20Appliance%20Contractors)(Wales). Accessed August 2021.
109. NHS England. What is a Biosimilar Medicine? 2019. Available at: https://www.england.nhs.uk/wp-content/uploads/2019/05/what-is-a-biosimilar-medicine-guide-v2.pdf. Accessed December 2019.
110. National Institute for Health and Care Excellence. Key Therapeutic Topic 15. Biosimilar medicines (KTT15). 2018. Available at: https://www.nice.org.uk/guidance/ktt15/resources/biosimilar-medicines-58757954414533. Accessed August 2021.
111. All Wales Medicines Strategy Group. Position statement for biosimilar medicines. Available at: https://awmsg.nhs.wales/make-a-submission/make-a-submission-pharmaceutical-industry/submit-for-awmsg-appraisal/invisible/appraisal-of-biosimilar-medicines-cell-therapies-and-gene-therapies/. Accessed August 2021.
112. All Wales Medicines Strategy Group. Medicines Identified as Low Priority for Funding in NHS Wales. 2018. Available at: https://awmsg.nhs.wales/files/guidelines-and-pils/medicines-identified-as-low-priority-for-funding-in-nhs-wales-paper-2/. Accessed August 2021.
113. All Wales Medicines Strategy Group. Medicines Identified as Low Priority for Funding in NHS Wales - Paper 2. 2018. Available at: https://awmsg.nhs.wales/medicines-appraisals-and-guidance/medicines-optimisation/prescribing-guidance/items-identified-as-low-value-for-prescribing-in-nhs-wales/. Accessed August 2021.

Appendix 1. Opioid equivalence table

(Values are approximate – see notes below)

Reproduced with kind permission from a resource developed by Emma Davies, Advanced Pharmacist Practitioner in Pain Management, Swansea Bay University Health Board.

<table>
<tr><th>Morphine</th><th>Oxycodone</th><th>Fentanyl</th><th>Buprenorphine</th><th>Codeine phosphate/ Dihydrocodeine</th><th>Tramadol</th><th>Tapentadol (Palexia® SR)</th></tr>
<tr><th>Oral (mg)</th><th>Oral (mg)</th><th>Transdermal patch (mcg/hr)</th><th>Transdermal patch (mcg/hr)</th><th>Oral (mg)</th><th>Oral (mg)</th><th>Oral (mg)</th></tr>
<tr><td>24hr total dose</td><td>24hr total dose</td><td>Patch strength STABLE PAIN ONLY</td><td>Patch strength STABLE PAIN ONLY</td><td>24hr total dose</td><td>24hr total dose</td><td>24hr total dose</td></tr>
<tr><td>5</td><td rowspan="3"></td><td rowspan="4"></td><td></td><td>60</td><td>50</td><td rowspan="4"></td></tr>
<tr><td>10</td><td rowspan="2">5</td><td>120</td><td>100</td></tr>
<tr><td>15</td><td></td><td>150</td></tr>
<tr><td>20</td><td>10</td><td rowspan="2">10</td><td>240</td><td>200</td></tr>
<tr><td>30</td><td>15</td><td rowspan="5"></td><td>300</td></tr>
<tr><td>40</td><td>20</td><td rowspan="2">12</td><td>20</td><td>400</td><td rowspan="2">100</td></tr>
<tr><td>60</td><td>30</td><td rowspan="2">35</td><td rowspan="4"></td></tr>
<tr><td>80</td><td>40</td><td rowspan="3">25</td><td rowspan="2">200</td></tr>
<tr><td>100</td><td>50</td><td rowspan="2">52.5</td></tr>
<tr><td>120</td><td>60</td><td>300</td></tr>
<tr><td colspan="7">Doses above this level are not recommended in chronic pain
If patient is still complaining of pain despite opioids at this level, then opioids are not working and should be reduced and stopped even if there is no other treatment available.</td></tr>
<tr><td>140</td><td>70</td><td rowspan="2">37</td><td rowspan="2">70</td><td rowspan="7"></td><td rowspan="7"></td><td></td></tr>
<tr><td>160</td><td>80</td><td rowspan="2">400</td></tr>
<tr><td>180</td><td>90</td><td rowspan="2">50</td><td rowspan="3">105</td></tr>
<tr><td>200</td><td>100</td><td>500</td></tr>
<tr><td>240</td><td>120</td><td>62</td><td rowspan="3"></td></tr>
<tr><td>280</td><td>140</td><td rowspan="2">75</td></tr>
<tr><td>320</td><td>160</td><td rowspan="2">140</td></tr>
<tr><td>360</td><td>180</td><td>100</td></tr>
</table>

Each row is roughly equivalent e.g.: 60 mg bd oral morphine = 30 mg bd oral oxycodone = 25 mcg/hr fentanyl patch

NB: This is to be used as a guide rather than a set of definite equivalences. Some doses suggested may be 'off-licence', but are based on clinical experience. Refer to the Summary of Product Characteristics for further details. Most data on doses are based on single-dose studies so it may be less accurate in chronic use where similar data are unavailable. Consider that individual patients may metabolise different drugs at varying rates. **The advice is to always calculate doses using morphine as standard and to adjust them to suit the patient and the situation – consider making a reduction in morphine equivalence dose of 20–50% when changing drugs.** Caution should be used in renal and hepatic failure. Avoid patch use in unstable pain.

Appendix 2. Anticholinergic effect on cognition (AEC) score[91]

Drugs with AEC score of 0		Drugs with AEC score of 1	Drugs with AEC score of 2	Drugs with AEC score of 3
Alprazolam	Lorazepam	Amiodarone	Amantadine	Alimemazine (trimeprazine)
Amlodipine	Losartan	Aripiprazole	Chlorphenamine	Amitriptyline
Amoxicillin	Lovastatin	Bromocriptine	Desipramine	Atropine
Aspirin	Lurasidone	Carbamazepine	Dicycloverine (dicyclomine)	Benztropine
Atenolol	Meloxicam	Citalopram	Dimenhydrinate	Chlorpromazine
Atorvastatin	Metoclopramide	Diazepam	Diphenhydramine	Clemastine
Bupropion	Metopralol	Domperidone	Disopyramide	Clomipramine
Cephalexin	Moclobemide	Fentanyl	Levomepromazine	Clozapine
Cetirizine	Morphine	Fluoxetine	Olanzapine	Cyproheptadine
Chlordiazepoxide	Naproxen	Fluphenazine	Paroxetine	Dothiepin (dosulepin)
Cimetidine	Omeprazole	Hydroxyzine	Pethidine	Doxepin
Ciprofloxacin	Paracetamol	Iloperidone	Pimozide	Hyoscine hydrobromide
Clopidogrel	Pantoprazole	Lithium	Prochlorperazine	Imipramine
Darifenacin	Pravastatin	Mirtazepine	Promazine	Lofepramine
Diclofenac	Propranolol	Perphenazine	Propantheline	Nortriptyline
Diltiazem	Rabeprazole	Prednisolone	Quetiapine	Orphenadrine
Enalapril	Ranitidine	Quinidine	Tolterodine	Oxybutynin
Entacapone	Risperidone	Sertindole	Trifluoperazine	Procyclidine
Fexofenadine	Rosiglitazone	Sertraline		Promethazine
Fluvoxamine	Simvastatin	Solifenacin		Trihexyphenidryl (benzhexol)
Furosemide	Theophylline	Temazepam		Trimipramine
Gabapentin	Thyroxine (levothyroxine)			
Gliclazide	Tramadol			
Haloperidol	Trazodone			
Ibuprofen	Trimethoprim			
Ketorolac	Trospium			
Lamotrigine	Venlafaxine			
Levadopa	Valproate			
Lisinopril	Warfarin			
Loperamide	Ziprasidone			
Loratadine	Zolpidem			

Score 3	Review and withdraw or switch
Score 2	Review and withdraw or switch
Score 1	Caution required
Score 0	Safe to use