All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

National Prescribing Indicators 2019–2020

Have some feedback or ideas for the next set of NPIs?
Please complete our survey at:
www.research.net/r/NPI_survey_2019

February 2019

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

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INTRODUCTION

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 for 2019–2020 draw on a variety of data sources such as CASPACluster, Medusa, Audit+ and the Medicines and Healthcare products Regulatory Agency (MHRA).

Each of the NPIs for 2019–2020 has a focus on safety, stewardship or efficiency, and have therefore been organised into these categories. It is intended that NPIs move towards a more patient-focussed approach, with measures considering whether the right patients are getting the right medicines, and whether these medicines are making a difference to their outcomes, as recommended by a Wales Audit Office report[1].

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 2018–2019 NPIs and discuss potential additional NPIs for 2019–2020.

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 for comment on the continued relevance of the 2018–2019 NPIs, additional priority areas that may be appropriate to monitor as an NPI and feedback on the NPI document, *Supporting Information for Prescribers* resource, and NPI slide set. This information then fed into the discussions of the NPI Task and Finish Group.

Key changes for 2019–2020

NPIs for retirement:

- *Opioid patch items as a percentage of all opioid prescribing in primary care*
  - Prescribing will continue to be monitored as a Local Comparator for two years post retirement, with prescribing data made available via SPIRA.
- *4C antimicrobial (co-amoxiclav, cephalosporins, fluoroquinolones and clindamycin) items combined as a percentage of total antibacterial items*
  - Prescribing will continue to be monitored as a Local Comparator for two years post retirement, with prescribing data made available via SPIRA.
- *Antimicrobial prophylaxis in colorectal surgery in secondary care*

NPI for inclusion:

- *Analgesics: Opioid burden*
  - Opioid burden User Defined Group (UDG) (opioid analgesics and co-codamol): ADQs per 1,000 patients.

Amendments to 2018–2019 NPIs:

- *Prescribing Safety Indicators (PSI)*
  - Inclusion of sodium valproate prescribing: Number of female patients aged 14–45 with a prescription for sodium valproate as a percentage of all patients with a prescription for sodium valproate.
- *Proton pump inhibitors (PPIs)*
  - Move PPI DDDs per 1,000 PUs from the efficiency category to the safety category.

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.
- The NHS Wales Informatics Service (NWIS) 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 NWIS 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.org website.

Targets

- 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 2018.
- Unless otherwise stated, the primary care thresholds are based on prescribing data for all general practices in Wales.
- The target may be to achieve movement to the highest prescribing quartile or the lowest prescribing quartile depending on the aim of the NPI.
- No target has been set for the Prescribing Safety Indicators.
- Adjustment of baseline figures and targets will be made for Abertawe Bro Morgannwg UHB and Cwm Taf UHB in quarterly NPI reports, to take account of changes to health board boundaries from April 2019.

Table 1 details the NPIs for 2019–2020, 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. NPIs 2019–2020

National Prescribing Indicator	Applicable to:	Unit of measure	Target for 2019–2020	Data source
Safety				
Prescribing Safety Indicators	Primary care	Number of patients identified as a percentage of the practice population or sub population	No target set	NWIS
Proton pump inhibitors	Primary care	PPI DDDs per 1,000 PUs	Maintain performance levels within the lower quartile, or show a reduction towards the quartile below	NWSSP
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
Analgesics	Primary care	Opioid burden UDG ADQs 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
Yellow Card Reporting	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 20% or greater increase from baseline (2018–2019) for Yellow Cards submitted by secondary care 50% or greater increase from baseline (2018–2019) 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	
Stewardship				
Antimicrobial stewardship	Primary care	Total antibacterial items per 1,000 STAR-PUs	Health board target: a quarterly reduction of 5% against a baseline of April 2017–March 2018	NWSSP
	Primary care	Number of 4C antimicrobial (co-amoxiclav, cephalosporins, fluoroquinolones and clindamycin) items per 1,000 patients	A quarterly reduction of 10% against a baseline of April 2017–March 2018	NWSSP
Efficiency				
Biosimilars	Primary + secondary care	Quantity of biosimilar medicines prescribed as a percentage of total 'reference' product plus biosimilar	Increase the appropriate use of cost-efficient biological medicines, including biosimilar medicines	NWSSP NWIS
Long-acting insulin analogues	Primary + secondary care	Items/number of long-acting insulin analogues expressed as a percentage of total long- and intermediate-acting insulin prescribed	Reduce prescribing of long-acting insulin analogues and achieve prescribing levels below the Welsh average	NWSSP NWIS

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 prudent healthcare agenda, which encourages the creation of a prescribing partnership where the process of prescribing, dispensing and administering medicines puts the patient at its centre and encourages shared decision making[2].

1.0 SAFETY INDICATORS

1.1 PRESCRIBING SAFETY INDICATORS

***Purpose*:**

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

Unit of measure:

- Number of patients with a peptic ulcer who have been prescribed NSAIDs without a PPI as a percentage of all patients.
- Number of patients with asthma who have been prescribed a beta-blocker as a percentage of all patients.
- Number of patients with concurrent prescriptions of verapamil and a beta-blocker as a percentage of all patients.
- Number of female patients with a past medical history of venous or arterial thrombosis who have been prescribed combined hormonal contraceptives, as a percentage of all female patients.
- Number of female patients with a current prescription of oestrogen-only hormone replacement therapy without any hysterectomy READ/SNOMED codes, as a percentage of all female patients.
- Number of patients with concurrent prescriptions of warfarin and an oral NSAID as a percentage of all patients.
- Number of patients under 12 with a current prescription of aspirin as a percentage of all patients.
- 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), as a percentage of all patients aged 65 years or over.
- Number of patients aged 65 years or over prescribed an antipsychotic, as a percentage of all patients aged 65 years or over.
- Number of patients aged 75 and over with an Anticholinergic Effect on Cognition (AEC) score of 3 or more for items on active repeat, as a percentage of all patients aged 75 and over.
- 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, as a percentage of all patients on the CKD register.
- 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, as a percentage of all patients who are not on the CKD register but have an eGFR of < 59 ml/min.
- Number of female patients aged 14–45 with a prescription for sodium valproate as a percentage of all patients with a prescription for sodium valproate.

Target for 2019–2020:

No target set

Figure 1. Prescribing Safety Indicators – First two quarters of 2018–2019*

*Currently no data available for 'Number of female patients aged 14–45 with a prescription for sodium valproate as a percentage of all patients with a prescription for sodium valproate.'

Background and evidence

There were 3,040 Yellow Card reports submitted in Wales in 2017–2018, an increase of 30% on the previous year. In the UK, it is estimated that up to around 6.5% of hospital admissions are related to adverse drug reactions[3]. Adverse drug reactions can often be predictable, making it possible to identify and address them before actual patient harm occurs[3]. Therefore, a process of identifying patients electronically could enable intervention and help to avoid harm. Patients identified by the NPI should be reviewed and/or monitored as appropriate.

In 2012, The Lancet published a paper entitled *A pharmacist-led information technology intervention for medication errors (PINCER): a multicentre, cluster randomised, controlled trial and cost-effectiveness analysis*. This study investigated the differences in a series of outcomes between intervention and control groups. It demonstrated that such an approach is an effective method for reducing a range of medication errors[4]. Some of the prescribing measures utilised in the PINCER trial have been incorporated as measures in this NPI. In addition, other measures have been added to make a series of 13. Some brief explanation for these is provided below. No target has been set for this NPI; however, data provided can be used to benchmark for future years.

This NPI supports 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[5].

NSAIDs in peptic ulcer patients without a PPI

NSAIDs have been shown to be the medicine group most likely to cause an adverse drug reaction requiring hospital admission due to such events as gastrointestinal bleeding and peptic ulceration[3]. A PPI can be considered for gastroprotection in patients at high risk of gastrointestinal complications with an NSAID e.g. previous peptic ulcer[6].

Beta-blockers in asthma patients

Beta-blockers should be avoided in patients with asthma due to the potential to precipitate bronchospasm[6]. If the benefits of using a beta-blocker in an asthma patient are justified the patient should be monitored closely[6].

Verapamil in combination with beta-blockers

Beta-blockers are associated with adverse drug reactions such as bradycardia and atrio-ventricular conduction disturbances[6]. 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[6].

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[6]. Any patients with a history of venous or arterial thrombosis who have been prescribed combined hormonal contraceptives are therefore at an increased risk[6].

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 need 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[7]. Conversely, women who have undergone a hysterectomy should not receive a progestogen component[7]. However, there may be instances where patients with an intact uterus may be prescribed oestrogen-only HRT in conjunction with a levonorgestrel containing IUD (e.g. Mirena®) for the prevention of endometrial hyperplasia during oestrogen replacement therapy.

Warfarin and oral NSAIDs
Anticoagulant medicines such as warfarin can cause haemorrhage[6]. NSAIDs can reduce platelet aggregation, which can worsen any bleeding event in warfarin treated patients[6]. Therefore, wherever possible, in patients taking warfarin, NSAIDs should be avoided[8].

Aspirin in under 12s
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[9]. 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[6,10].

NSAIDs in combination with aspirin or clopidogrel without gastroprotection in over 65s
Hospital admission due to gastrointestinal bleeding has been associated with aspirin and clopidogrel, as well as NSAIDs[3]. The harmful consequences of bleeds due to antiplatelet therapy increase with age[11]. PPIs are recommended in older patients undergoing antiplatelet treatment[11,12]. 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 H2-receptor antagonists does not prevent NSAID related ulcers[13].

Over 65s prescribed an antipsychotic medicine
In 2009 the Banerjee report called for a review of the use of antipsychotic medicines for elderly patients with dementia[14]. These medicines have only a limited benefit in treating behavioural and psychological symptoms of dementia and carry significant risk of harm[14]. 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[15]. NICE guidance on *Dementia: assessment, management and support for people living with dementia and their carers* states that reviews should be carried out at least every six weeks for people living with dementia and also prescribed antipsychotics[16]. This is further supported by the National Assembly for Wales, Health, Social Care and Sport Committee report, *Use of antipsychotic medication in care homes*, which contains a number of recommendations regarding medication reviews[17]. This indicator will also report the number of patients aged 65 years or over prescribed an antipsychotic and who are resident in a care home.

Over 75s with AEC score of 3 or more
A high proportion of the older population are exposed to multiple medicines with low anticholinergic activity and the cumulative burden of these medicines over many years may be associated with accelerated cognitive decline and mortality[18]. The AEC scale (see Appendix 1) was developed to illustrate the negative anticholinergic effects of drugs on cognition[19]. It is good practice to use medicines with AEC scores of zero and to avoid those scored 1, 2 or 3. The clinician should discuss with the patient and carer the benefits and potential risks of continued use of these medicines with the aim of either stopping them or switching to an alternative drug with a lower AEC score (preferably zero)[19,20]. NICE guidance on *Dementia: assessment, management and support for people living with dementia and their carers* includes a recommendation to consider minimising the use of medicines with increased anticholinergic burden, when assessing whether to refer a person with suspected dementia for diagnosis, and during medication reviews with people living with dementia[16].

Use of NSAIDs in patients with renal impairment
This measure consists of two parts:
1. The first of these considers NSAID use in known CKD patients. The aim is to identify patients on the CKD register (CKD stage 3–5) who have received a repeat prescription for an NSAID within the last three months. *NICE Clinical Guideline (CG)*

182 highlights that in patients with CKD, the long-term use of NSAIDs may be associated with disease progression. NICE recommends caution, and monitoring of the effects on GFR, when using NSAIDs in people with CKD over prolonged periods of time[21].

2. The second will consider patients not on the CKD register but who have renal impairment identified via their estimated glomerular filtration rate (eGFR) and who have received a repeat prescription for an NSAID within the last three months. NSAIDs may precipitate renal failure, and vulnerable (particularly elderly) patients may be at increased risk[22]. Regular review of the ongoing need for an NSAID and reassessment of the risk versus benefit is appropriate and processes for this should be in place.

Sodium valproate in females of child bearing age

Valproate-containing medicines are widely used in the treatment of epilepsy and bi-polar disorder. In March 2018, the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh)[†] 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[23]. If valproate is taken during pregnancy, up to 4 in 10 babies are at risk of developmental disorders and approximately 1 in 10 are at risk of birth defects[24]. 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[25] to ensure that patients are fully aware of the risks and the need to avoid becoming pregnant. This measure aims to identify the number of females of childbearing age that have received prescriptions for sodium valproate, in order to support the MHRA advice to GPs to identify and recall all women and girls on valproate who may be of childbearing potential, to provide the patient guide and check that they have been reviewed by a specialist in the last year (i.e. they have an in-date Risk Acknowledgement Form) and are on highly effective contraception[26]. In addition, the measure will contribute to the monitoring of the effectiveness of actions to ensure safe and appropriate use of valproate-containing medicines, and allow benchmarking of prescribing in this patient group with Clinical Commissioning Groups (CCGs) in England. Further advice from the MHRA in December 2018 notes that although use of valproate medicines in female patients continues to slowly decline, there is wide variation in prescribing between CCGs. All healthcare professionals must continue to identify and review all female patients on valproate, and provide them with the patient information materials every time they attend their appointments or receive their medicines[27].

Useful resources

- WeMeReC (2015) Medicines-related admissions
- AWMSG (2014) Polypharmacy: Guidance for Prescribing
- MHRA (2014) Antipsychotics e-learning module
- AWMSG (2018) Antipsychotics in dementia audit
- PrescQIPP (2016) Bulletin 140: Anticholinergic drugs
- South London and Maudsley NHS Foundation Trust (2017) Medichec: The Anticholinergic Effect on Cognition Tool (Android Medichec app available, app for iOS due out shortly)
- Sanofi (2018) Guide for healthcare professionals: Information on the risks of valproate▼ use in girls (of any age) and women of childbearing potential
- AWMSG (2015) CEPP All Wales Audit: Towards Appropriate NSAID Prescribing
- AWMSG (2017) CEPP National Audit: Medicines Management for CKD

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

1.2 PROTON PUMP INHIBITORS

***Purpose*:**
To encourage appropriate use of proton pump inhibitors (PPIs) in primary care.
Unit of measure:
PPI DDDs per 1,000 PUs
Target for 2019–2020:
Maintain performance levels within the lower quartile, or show a reduction towards the quartile below

Figure 2. Trend in PPI DDDs per 1,000 PUs to quarter ending September 2018

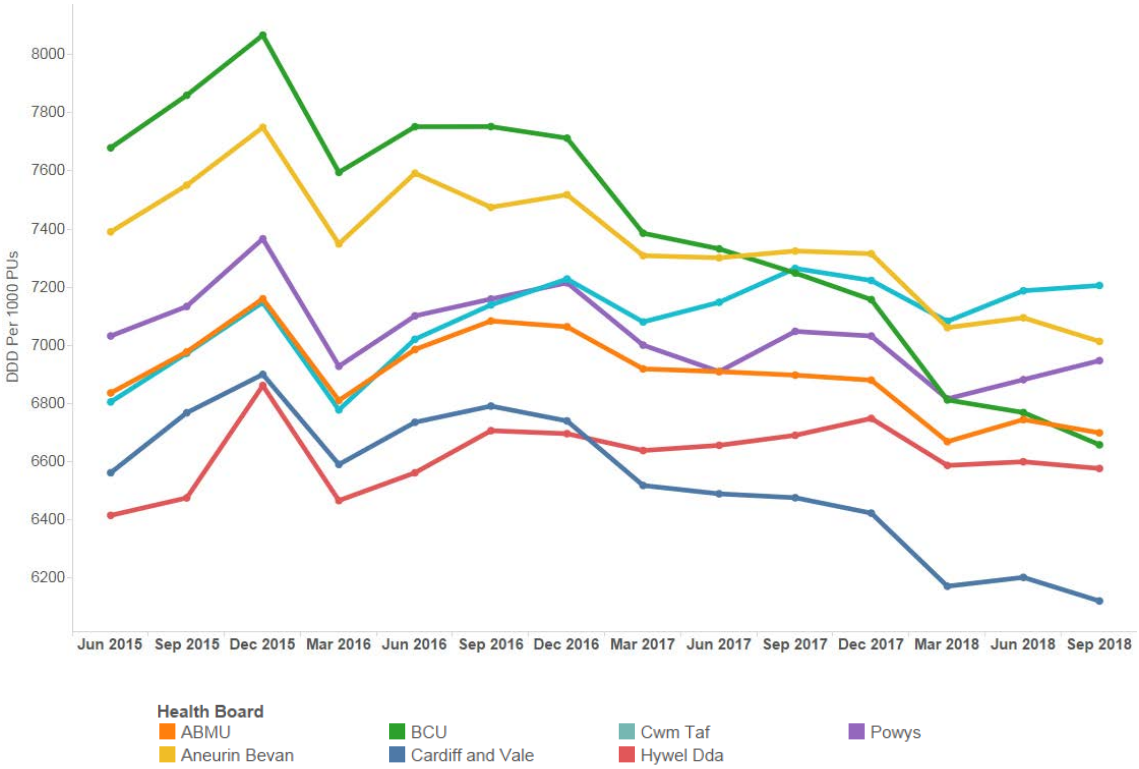
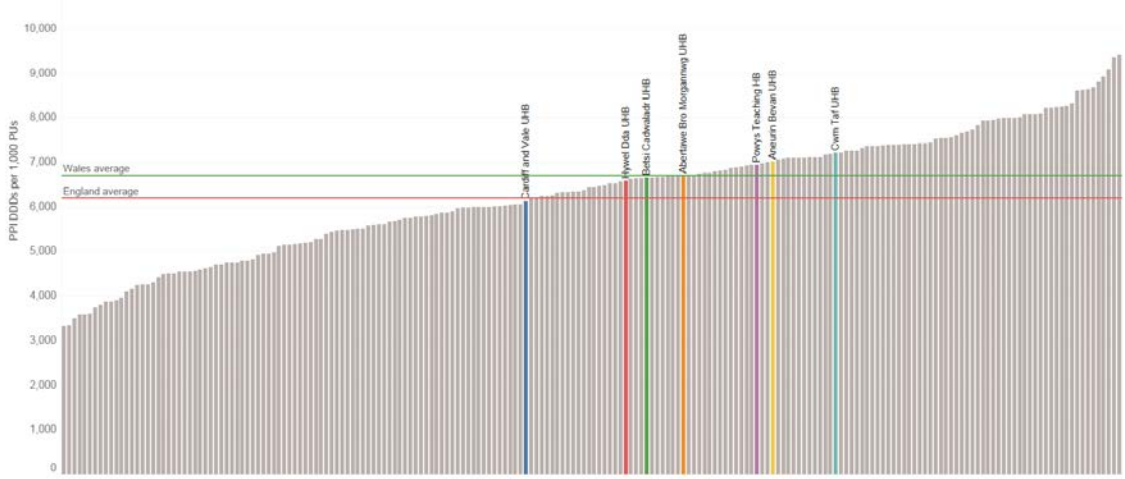


Figure 3. PPI DDDs per 1,000 PUs Welsh health boards and English CCGs Quarter ending September 2018



Background and evidence

PPIs are licensed and prescribed for a range of indications including uninvestigated dyspepsia, gastro-oesophageal reflux disease, peptic ulcer and non-ulcer (or functional) dyspepsia, eradication of *Helicobacter pylori* (in combination with antibiotics), controlling excessive acid secretion in Zollinger–Ellison syndrome, and the prevention and treatment of non-steroidal anti-inflammatory drug (NSAID)-associated ulcers[6,28].

Five PPIs are currently available in the UK: lansoprazole, omeprazole, pantoprazole, rabeprazole and esomeprazole. Differences between the PPIs in terms of clinical efficacy and safety are minimal.

In the financial year 2017–2018, over 4.4 million prescriptions for PPIs were dispensed in Wales[29]. Assuming each patient received 13 (28-day) prescriptions during the year, this amounts to 340,306 patients (10.9% of the population) receiving PPIs[29,30]. This is probably an underestimate of the number receiving PPIs, as many patients will take these medicines as required and would therefore not receive 13 prescriptions in the course of a year. It has been suggested that the effectiveness of PPIs along with a reduction in cost, due to patent expiry, and their availability over-the-counter (OTC) has contributed to more liberal usage for a wide variety of upper gastrointestinal (GI) symptoms[31,32]. Additionally, recommendations on the importance of gastroprotection, particularly for patients on combinations of high-risk medicines, e.g. NSAIDs for the treatment of osteoarthritis[33] and rheumatoid arthritis (RA)[34], have contributed to increased PPI use.

Initial recommendations for people with dyspepsia are to offer simple lifestyle advice on healthy eating, weight reduction, smoking cessation and avoiding factors that the patient associates with their dyspepsia, such as alcohol, coffee, chocolate and fatty foods[28]. Eating well before bedtime (e.g. 3–4 hours) and raising the head of the bed may also be helpful[28]. In a co-productive relationship (an important part of Prudent Healthcare), patients can benefit from expert lifestyle advice on improving symptoms without the need for a prescription[32]. Community pharmacists are well placed to offer initial and ongoing help for people with symptoms of dyspepsia, including OTC medication, help with prescribed medicines and advice about when to consult a GP, in addition, pharmacies providing the Common Ailments Service can provide appropriate treatment and advice to patients experiencing indigestion and reflux, without the need for them to see their GP[35].

PPIs should only be considered for short courses (4 weeks) where needed. If symptoms continue or recur, a PPI can be continued at the lowest dose possible to control symptoms or on an 'as-required' basis[28], ensuring that the indication is clearly recorded in the patient's record.

PPIs are generally well tolerated, with a low incidence of short-term adverse effects. There is, however, increasing evidence regarding the potential consequences of long-term treatment with PPIs, including *C. difficile* infection, fractures and hypomagnesaemia[32].

A 2017 Drug and Therapeutic Bulletin reported on a number of meta-analyses which looked at association between PPIs and *C. difficile*. Despite a weak association in the general population, data indicated that those at high risk of *C. difficile* infection (old age and frailty, antibiotic treatment, other serious comorbidities, hospitalisation and previous history of *C. difficile* infection) should be carefully managed, reviewing PPI use in those who are at risk of *C. difficile* infection and, wherever possible, avoiding PPIs in those who have had previous episodes of *C. difficile*[36].

In 2012, the MHRA issued a Drug Safety Update regarding the increased risk of fracture associated with long-term use of PPIs. Observational studies on a risk of fracture

associated with PPIs suggested there may be a modest increase in the risk of hip, wrist or spine fracture, especially if PPIs are used in high does and over long durations (> 1 year). The increased risk was observed mainly in elderly patients, and it is possible that other risk factors contributed to the increased risk[37]. A systematic review also found a significant association between regular use of PPIs and risk of hip fracture. The increased risk was no longer evident after PPI use had stopped for two years. This highlights the importance of carefully evaluating the need for long-term, continuous use of PPIs[38].

A second Drug Safety Update in 2012 highlighted reports of patients developing hypomagnesaemia following long-term use of PPIs[39]. A review of case reports found that hypomagnesaemia occurred most commonly after one year of PPI treatment. Serious manifestations of hypomagnesaemia – fatigue, tetany, delirium, convulsions, dizziness, and ventricular arrhythmia – can occur, but they may begin insidiously and be overlooked[39]. For patients expected to be on prolonged treatment with PPIs, especially those also taking other drugs that may cause hypomagnesaemia, clinicians should consider measuring magnesium levels before starting PPIs and repeat measurements periodically during treatment[39].

Other possible serious adverse effects include acute interstitial nephritis, vitamin B_{12} deficiency and rebound acid hypersecretion syndrome[40]. NICE states that rebound hypersecretion "may exacerbate symptoms once PPI therapy is discontinued, although this is a theoretical concern as there are no data that support acid rebound as a clinical problem in patients"[28]. Patients should be warned about the risk of an increase in symptoms and advised to manage them with simple antacids or alginates. If a step-down in dose does not adequately control symptoms, the PPI should be resumed at the lowest effective dose and frequency with a view to stepping down and stopping treatment at a later date[36]. Long-term PPI prescriptions should be reviewed at least annually and patients should be advised that it may be appropriate for them to return to self-treatment with antacid and/or alginate therapy[28]. Patients may be more willing to try self-care to improve their symptoms if they are aware of the potential long-term effects of PPIs[32].

When the potential adverse effects are taken into consideration, the possible risks of treatment may outweigh the potential benefits, particularly in patients without a clear indication for a PPI, or when the patient is at increased risk of medicine-related adverse effects, e.g. frail, older people, or those with significant co-morbidities[32].

Useful resources

- AWMSG (2018) Safe Use of Proton Pump Inhibitors
- WeMeReC (2015) Proton pump inhibitors bulletin
- PrescQIPP (2015) Bulletin 92: Safety of long term PPIs
- WeMeReC (2010) Stopping Medicines - Proton Pump Inhibitors

1.3 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 2019–2020:
Maintain performance levels within the lower quartile, or show a reduction towards the quartile below.

Figure 4. Trend in hypnotic and anxiolytic ADQs per 1,000 STAR-PUs to quarter ending September 2018

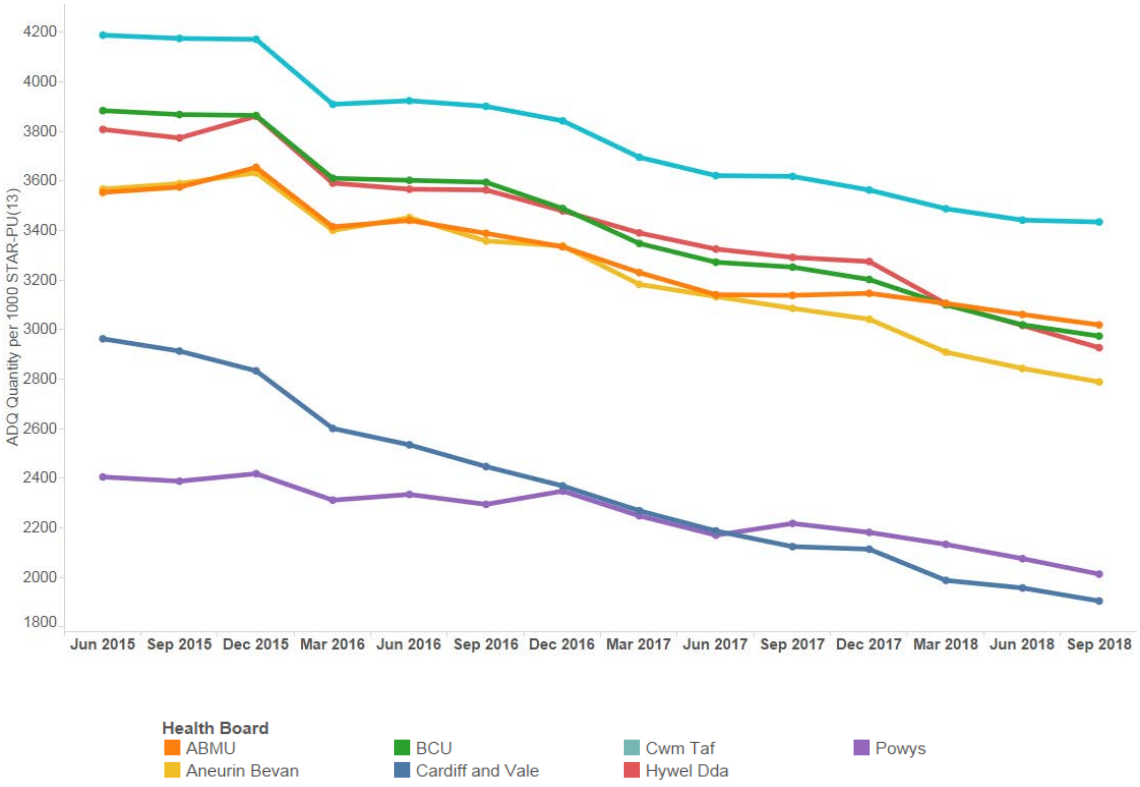
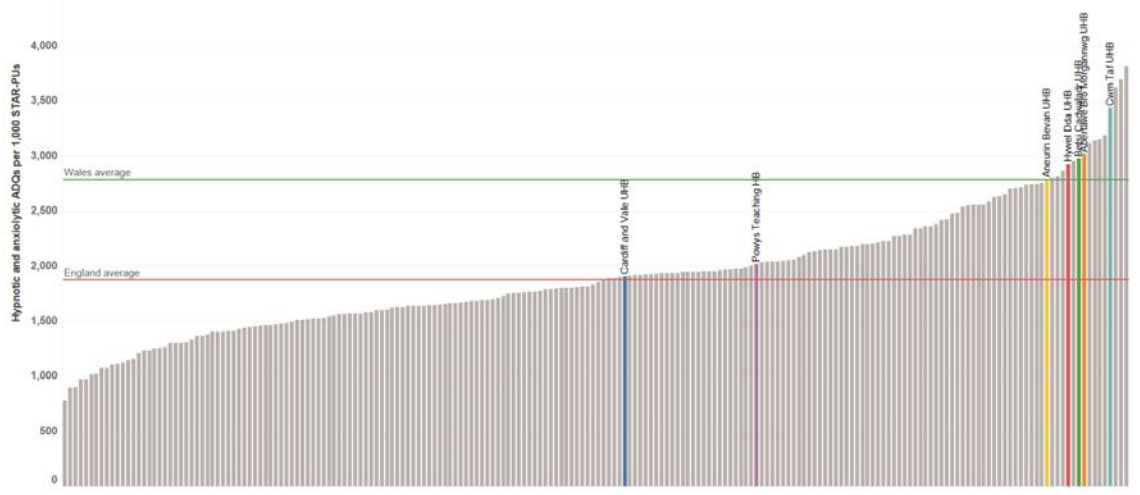


Figure 5. Hypnotic and anxiolytic ADQs per 1,000 STAR-PUs Welsh health boards and English CCGs – Quarter ending September 2018



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[41]. Although the prescribing volume of hypnotics and anxiolytics in Wales has declined over recent years, there is considerable variation in prescribing rates of these medicines across health boards and between GP practices, and 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[29,42].

In the financial year 2017–2018, the number of items dispensed was 1,284,294, compared with 1,351,939 the previous year: a reduction of 5%[29]. There has also been a 3.7% decrease in the number of drug-related deaths (drug poisoning and drug misuse) where any benzodiazepine is mentioned on the death certificate (deaths registered in England and Wales) compared with the previous year; however, the number of deaths remains high and data from the Office for National Statistics demonstrate a 38% increase over the last five years from 284 in 2012 to 391 in 2017[43].

The problems associated with benzodiazepines (development of tolerance, dependence potential and withdrawal causing rebound insomnia) are well known. Warnings about the risk of dependence with benzodiazepines were issued by the Committee on Safety of Medicines (CSM) in 1988. The CSM recommended that benzodiazepines should be used for no more than two to four weeks for insomnia and anxiety, and only if it is severe, disabling, or subjecting the individual to unacceptable distress[44]. NICE guidance on the use of zaleplon (now discontinued), zolpidem and zopiclone for the short-term management of insomnia and the NICE Clinical Knowledge Summary for insomnia also advise 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[45,46]: no more than 4 weeks with benzodiazepines, zopiclone and zolpidem. NICE guidance on generalised anxiety disorder (GAD) in adults recommends that benzodiazepines should not be offered for the treatment of GAD in primary or secondary care except as a short-term measure during crises[47].

Benzodiazepine hypnotics and anxiolytics are known to significantly increase risk of falls[48]. The BNF states that benzodiazepines and the Z-drugs should be avoided in the elderly as they are at greater risk of becoming ataxic and confused, leading to falls and injury[6]. *NICE Clinical Knowledge Summary: Falls – risk assessment* advises reviewing psychoactive drugs, such as benzodiazepines, in patients at high risk of falls[49].

In 2017, the Advisory Panel on Substance Misuse (APoSM) in Wales reported on substance misuse in an ageing population. The report highlighted that the most common types of prescription only medicines that older adults misuse are the most likely to lead to dependence; these are benzodiazepines and Z-drugs, and opioid analgesics[50]. The report noted that older people may not realise that they are developing a dependence on their prescribed medication, and concluded that substance misuse among older adults is a significant and growing problem[50].

There is conflicting evidence regarding benzodiazepine use and an increased risk of Alzheimer's disease. An observational study in Canada showed that the risk of Alzheimer's disease was increased by 43–51% among those who had used benzodiazepines in the past. Risk increased with increased exposure and when long-acting benzodiazepines were used[51]. Another observational study concluded that benzodiazepines are associated with an increase in the risk of dementia[52]. However, a more recent prospective population based cohort study concluded that the risk of dementia was slightly higher in people with minimal exposure to benzodiazepines, but not with the highest level of exposure[53].

Dependence (both physical and psychological) and tolerance can occur and this may lead to difficulty in withdrawing the drug after it has been taken by the patient regularly for more than a few weeks[6]. 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. Analysis of primary care dispensing data has shown that the trend in Z-drug usage reduced significantly across Wales in the 12-month period following introduction of the pack in 2011[54].

Useful resources

- AWMSG (2016) Educational Pack: Material to Support Appropriate Prescribing of Hypnotics and Anxiolytics across Wales
- AWMSG (2014) Polypharmacy: Guidance for Prescribing
- WeMeReC (2015) Bulletin: Sedative medicines in older people
- WeMeReC (2009) Stopping Medicines – benzodiazepines

1.4 ANALGESICS

Analgesics are medicines used in the treatment of pain. Pain can be defined as acute or persistent, depending on the length of time the person has experienced pain. Persistent, also known as chronic, pain is usually defined as occurring when pain has been present for three months or more[55]. Analgesic medicines have been the mainstay of pain treatment for decades; however, for persistent pain, individual response rates to analgesics vary greatly and failure rates are high[56]. A number of analgesic medicines with different mechanisms of action and licensed indications are available; however, these NPIs focus on total opioid use, tramadol, and gabapentin and pregabalin, 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[57]. 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[57]. Due to the growing problem of dependence and addiction to prescription medicines, Public Health England has been commissioned to review the evidence for dependence on, and withdrawal from, prescribed medicines including opioids and gabapentinoids, with the report due in Spring 2019[58].

1.4.1 Opioid burden

***Purpose*:**
To encourage the appropriate use and review of opioids in primary care, minimising the potential for dependence, diversion, misuse and ADRs.
Unit of measure:
Opioid burden UDG ADQs per 1,000 patients.
Target for 2019–2020:
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 6. Trend in opioid burden ADQs per 1,000 patients to quarter ending September 2018

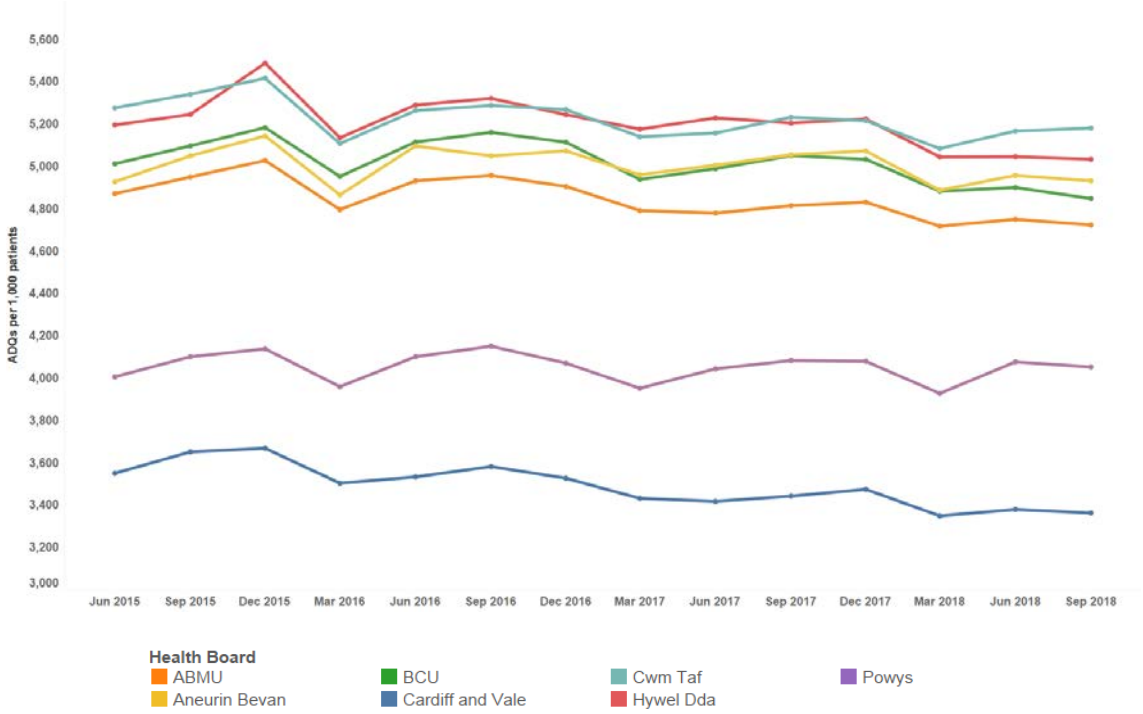
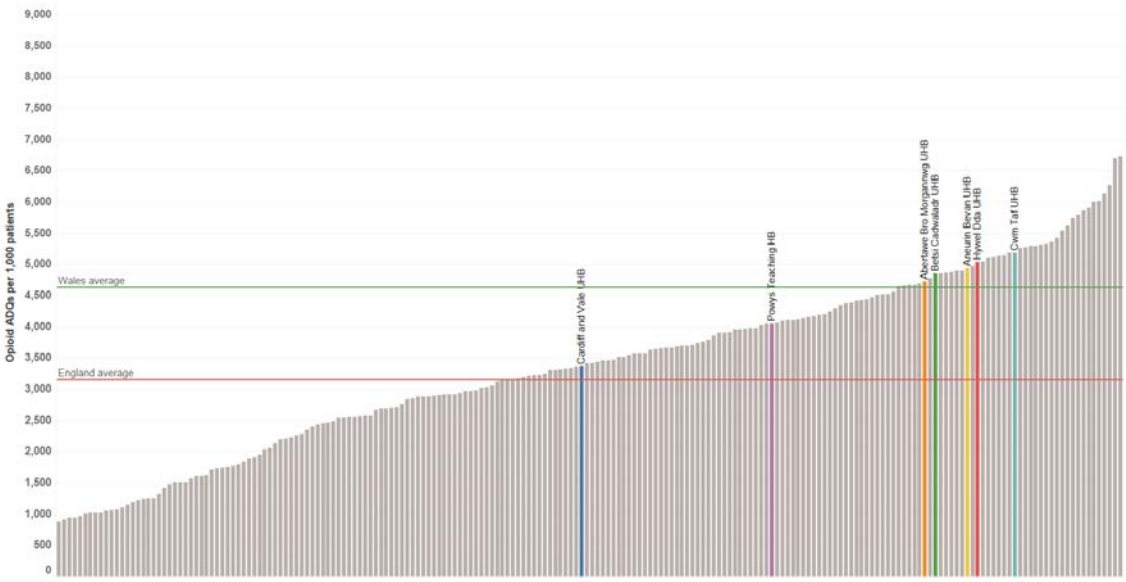


Figure 7. Opioid burden ADQs per 1,000 patients Welsh health boards and English CCGs – Quarter ending September 2018



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[59]. 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[60].

There is a lack of consistent good-quality evidence to support strong clinical recommendation for the long term use of opioids for patients with chronic pain[61]. Often, the WHO's analgesic ladder is used as a guide to the treatment of chronic pain, resulting in patients receiving increasing doses of strong opioids; however, it has never been

validated in this setting[61], and this simple approach is not appropriate for chronic pain, which is highly complex[62].

An estimated 49% of patients in the UK suffering from chronic pain also suffer from depression[61], and there is variable interplay between biological, psychological and social factors[63]. With so many issues affecting the patient's experience and reporting of chronic pain, it is not surprising that pain scores do not respond in any predictable fashion to opioids. Attempts to lower pain scores using opioids have led to overuse and adverse outcomes without any appreciable lowering of the chronic pain burden at the population level[62].

Opioid analgesics have well established side effects including constipation, nausea and vomiting, and respiratory depression, and repeated administration may cause tolerance and dependence[6]. Whilst concerns regarding tolerance and dependence should be no deterrent in the control of pain in terminal illness[6], 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[64].

The Royal College of Anaesthetists Faculty of Pain Medicine highlights that patients who do not achieve useful pain relief from opioids within two to four weeks are unlikely to gain benefit in the long term[65]. 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 risk of harm increases substantially at high dose, and above an oral morphine equivalent daily dose of 120 mg, further benefit is unlikely. If benefit in pain reduction and improved function is not achieved at low dose, opioids should be discontinued, even if no other treatment is readily available[61]. There is no evidence of efficacy of high dose opioids in long-term pain[65]. A table providing approximate equivalence values for opioids can be found in Appendix 2.

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[59]. Across Wales, 1,010,579 prescriptions for opioid analgesics were dispensed during 2007–2008[66]. This increased by 50% over ten years, with more than 1.5 million prescriptions dispensed during 2017–2018[29]. During the same period, opioid related deaths in Wales increased from 96 in 2007, to 153 in 2017, an increase of 59.4%[43]. Concerns about the harms caused by extensive prescribing of opioids have become particularly pertinent as a result of their extensive misuse in the USA[61], with subsequent increases in prescription opioid deaths and admissions for misuse[62]. 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 make clinical decisions about opioid reduction and optimal pain management[67].

NICE guidance on *Controlled drugs: safe use and management* highlights that when making decisions about prescribing controlled drugs, consideration should be given to: the benefits of treatment; the risks of prescribing, including dependency, overdose and diversion; all prescribed and non-prescribed medicines the person is taking, and whether the person may be opioid naïve[70]. The Royal College of Anaesthetists Faculty of Pain Medicine has produced a checklist to aid prescribers when discussing opioid treatment with patients[71].

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[61]. If it is thought opioid therapy may play a role in a patient's pain management, a trial should be initiated to establish whether a patient achieves a reduction in pain with the use of opioids – if not they should be stopped. Patients should be fully informed of potential benefits and harms from this trial[61]. Dose escalation should be limited as risk of harm rises as dose increases, especially if there is inadequate relief of pain[61].

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

- MHRA Opioids e-learning module
- RCoA Faculty of Pain Medicine Opioids Aware (2019) Tapering and stopping opioids AWMSG (2016) Persistent pain resources
- RCoA Faculty of Pain Medicine (2019) Opioids Aware
- RCoA Faculty of Pain Medicine (2019) Checklist for Prescribers
- WeMeReC (2010) Stopping compound medications containing codeine

1.4.2 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 2019–2020:
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 8. Trend in tramadol DDDs per 1,000 patients to quarter ending September 2018

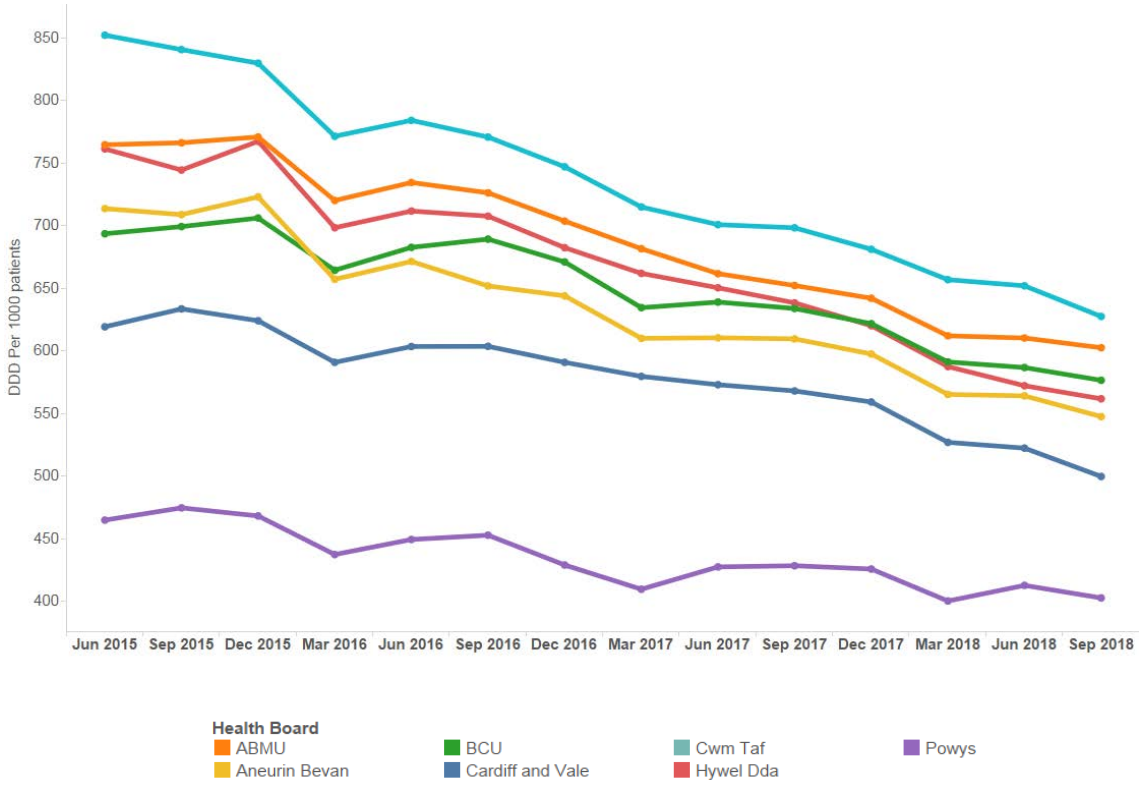
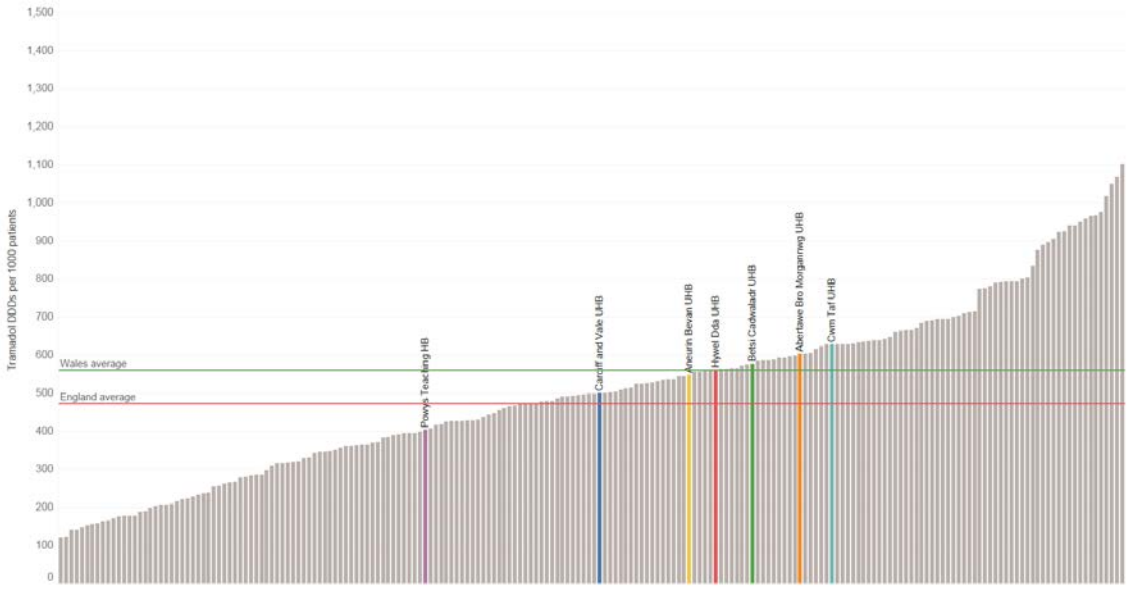


Figure 9. Tramadol DDDs per 1,000 patients Welsh health boards and English CCGs Quarter ending September 2018



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[6]. It has fewer of the typical opioid side effects (notably, less respiratory depression, less constipation and less addiction potential); psychiatric reactions have been reported[6]. The unique dual-action pharmacological profile of tramadol increases the risk of adverse effects seen in overdose[72].

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[72]. The changes came into force in June 2014. Deaths involving tramadol in England and Wales have fallen by 23% since 2014, from 240 deaths in 2014, to 185 deaths registered in 2017[43].

Dizziness and nausea are the most commonly reported adverse effects of tramadol. Headache, drowsiness, vomiting, constipation, dry mouth, fatigue and sweating are other common side effects[73]. Rare side effects include hallucinations, confusion, sleep disturbance, anxiety and nightmares, as well as cases of dependence and withdrawal[73]. 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[73]. 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)[73]. The use of tramadol is contra-indicated in uncontrolled epilepsy and in patients receiving, or who have recently discontinued (within the previous two weeks) monoamine oxidase inhibitors[73].

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[72,74]. 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[75].

The 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

- AWMSG (2013) Tramadol Educational Resource Materials
- AWMSG (2013) Tramadol Audit Materials
- AWMSG (2013) Tramadol Shared Decision Making Toolkit
- AWMSG (2013) Tramadol Patient Information Leaflet
- AWMSG (2016) Persistent pain resources

1.4.3 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 2019–2020:
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 10. Trend in gabapentin and pregabalin DDDs per 1,000 patients to quarter ending September 2018

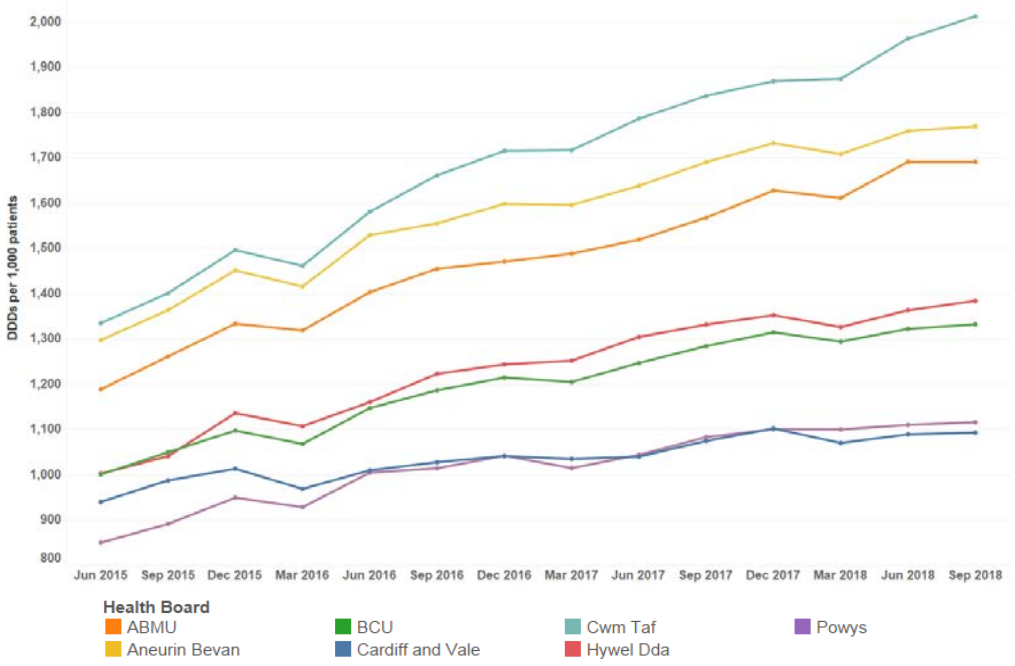
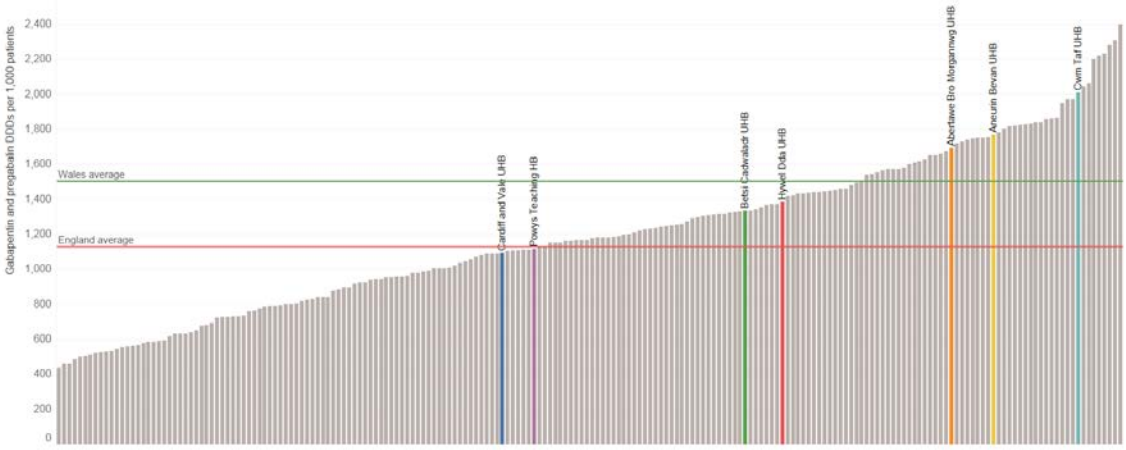


Figure 11. Gabapentin and pregabalin DDDs per 1,000 patients Welsh health boards and English CCGs – Quarter ending September 2018



Background and evidence

NICE recommends gabapentin or pregabalin as first-line options in the treatment of neuropathic pain, along with amitriptyline and duloxetine[76]. Gabapentin is licensed for peripheral neuropathic pain and epilepsy[77-79], whilst pregabalin is licensed for peripheral and central neuropathic pain, in addition to epilepsy and generalised anxiety disorder[80-82].

There has been increasing use of gabapentin and pregabalin in primary care over the last five years, with prescribing data from the quarter ending September 2018, compared with the quarter ending September 2013, demonstrating an increase of over 83% in prescription items across Wales[29]. Current prescribing of gabapentin and pregabalin in Wales is high in comparison with England, with 1,501 DDDs per 1,000 patients in Wales[29], compared with 1,128 DDDs per 1,000 patients in England[42] for the quarter ending September 2018.

In order to assess whether the patient's pain is neuropathic in nature, a number of pain scales are available, including the Leeds assessment of neuropathic symptoms and signs (LANSS)[83] and the Pain Detect pain questionnaire[84]. No single drug works for all neuropathic pain, and given the diversity of pain mechanisms, patient's responses and diseases, treatment must be individualised[85]. 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[76]. 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[86]. 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[87]. Use of pain scales may also assist in determining response to treatment.

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[76]. If the patient has not shown sufficient benefit within eight weeks of reaching the maximum tolerated dose, drug treatment should be reduced and stopped[85]. The summaries of product characteristics for both gabapentin and pregabalin indicate that they can be discontinued gradually over a minimum of one week, independent of indication[78,81]; 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[88].

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[85]. Both gabapentin and pregabalin are commonly prescribed for non-neuropathic pain syndromes; however, there is little evidence to support this practice[88]. A recent 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[89]. This highlights the need for treatment to be reviewed when either pregabalin or gabapentin are prescribed outside of their licensed indications.

The SPCs for both gabapentin and pregabalin highlight that cases of misuse, abuse and dependence have been reported. Therefore, caution should be exercised in prescribing either drug for patients with a history of substance abuse, and the patient should be monitored for symptoms of misuse or dependence[77-82]. Pregabalin may have a higher abuse potential than gabapentin due to its rapid absorption, faster onset of action and higher potency[90]. Pregabalin causes a 'high' or elevated mood in users[90] and individuals

misusing gabapentin and pregabalin describe improved sociability, euphoria, relaxation and a sense of calm[88]. Pregabalin misusers achieve these effects by taking large quantities, ranging from 200 mg to 5 g as a single dose[88].

A Welsh Health Circular issued in July 2016 noted the potential for misuse of gabapentin and pregabalin and provided suggestions for balanced and rational use[91]. This followed advice published by the Advisory Council on the Misuse of Drugs (ACMD) in January 2016 which highlighted the potential risk of dependence, misuse and diversion of gabapentin and pregabalin and the importance of appropriate prescribing to minimise these risks[90]. The ACMD advised that both gabapentin and pregabalin should be controlled under the Misuse of Drugs Act 1971 as Class C substances, and scheduled under the Misuse of Drugs Regulations 2001 (as amended) as Schedule 3, so as not to preclude legitimate use on prescription[90]. The Home Office undertook a consultation to seek views on controlling these medicines under the Misuse of Drugs Act; and in October 2018 published its conclusion that gabapentin and pregabalin would be reclassified as Class C controlled substances from April 2019[92].

Both pregabalin and gabapentin have the propensity to cause depression of the central nervous system[88], and when used in combination with other depressants they can cause drowsiness, sedation, respiratory failure and death[90]. In October 2017, the MHRA issued a drug safety update for gabapentin warning of the risk of severe respiratory depression even without concomitant opioid medicines. It noted that dose adjustment may be necessary in patients at higher risk of respiratory depression[93]. Increasing use of gabapentin and pregabalin has resulted in an increase in the number of deaths where gabapentin or pregabalin was mentioned on the death certificate. This rose from 12 deaths registered in England and Wales in 2012, to a total of 196 deaths registered in England and Wales in 2017[43].

Neuropathic pain management is often complex and prescribers need to make evidence-based, informed decisions based on the individual needs of the patient. 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[94].

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

Useful resources

- AWMSG (2016) Persistent pain resources
- Faculty of Pain Medicine of the Royal College of Anaesthetists (2015) Opioids Aware.
- PrescQIPP (2016) Neuropathic pain: Pregabalin and gabapentin prescribing
- Public Health England (2014) Advice for prescribers on the risk of the misuse of pregabalin and gabapentin
- SIGN (2013) SIGN 136. Management of chronic pain
- AWMSG (2013) Tramadol Educational Resource Materials

1.5 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 2019–2020:

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 20%, or greater, increase from baseline (2018–2019), for Yellow Cards submitted by secondary care
- Demonstrate a 50%, or greater, increase from baseline (2018–2019), for Yellow Cards submitted by members of the public

Community pharmacy: no target set

Figure 12. Percentage of GP practices meeting the target of one Yellow Card per 2,000 practice population 2017–2018

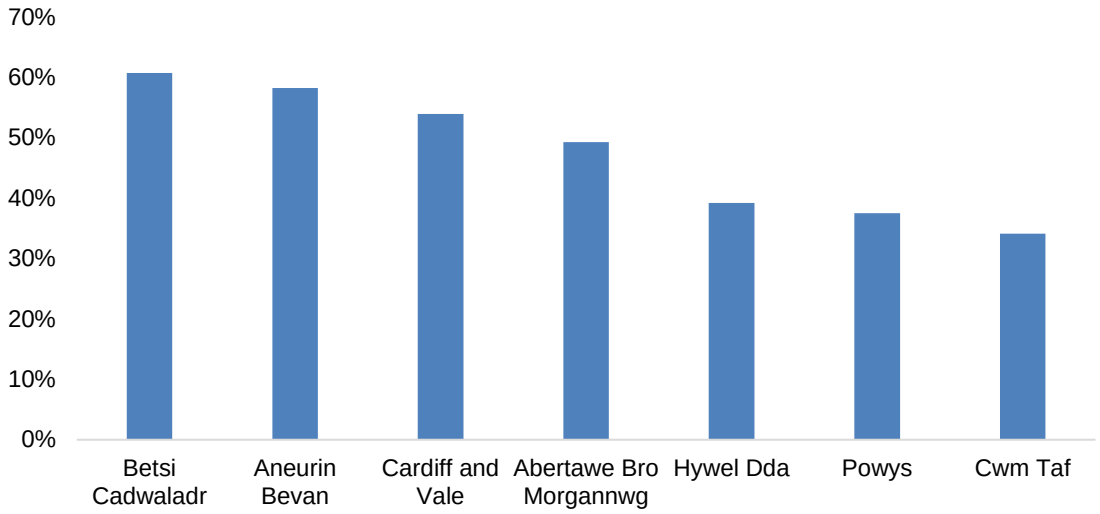


Table 2. Yellow Card data showing total number of reports, and number of secondary care and member of public reports in 2017–2018

Health board	Total number of reports	Secondary care reports	Member of public reports
ABMU	407	72	46
Aneurin Bevan	503	60	53
Betsi Cadwaladr	848	171	73
Cardiff and Vale	538	149	46
Cwm Taf	267	30	27
Hywel Dda	387	141	37
Powys	73	9	10
Velindre	17	17	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[3,95]. 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"*[96].

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. Reports can be made for suspected adverse reactions resulting from any medicine, including vaccines, blood factors and immunoglobulins, herbal medicines and homeopathic remedies, and any medical device available on the UK market. Reports can also be made where an overdose has occurred. The MHRA also collects reports of safety concerns associated with defective medicines, counterfeit or fake medicines or medical devices, and e-cigarettes.

ADRs reported on Yellow Cards are evaluated, together with additional sources of information such as clinical trial data, medical literature or data from international medicines regulators, to identify previously unknown safety issues. These reports are assessed by a team of medicine safety experts made up of doctors, pharmacists and scientists who study the benefits and risks of medicines. The MHRA takes action, whenever necessary, to ensure that medicines are used in a way that minimises risk, while maximising patient benefit.

Yellow Card Centre Wales (YCC Wales) is one of five regional ADR monitoring centres, acting on behalf of the MHRA to promote the use of the Yellow Card Scheme.

A strong safety culture requires good reporting of ADRs from across all professions and healthcare settings, as well as from patients and other members of the public.

Prior to April 2013, the number of reports from GPs across Wales had been in decline for several years. 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 2017–2018, the number of Yellow Cards submitted by GPs in Wales increased by 47% compared with the previous year, to 1,980.

It is anticipated that continuing to monitor Yellow Card reporting per practice population as an NPI for 2019–2020 will further increase reporting rates amongst GP practices. Within a general practice, other healthcare professionals such as practice nurses and pharmacists can contribute to the improvement of ADR reporting by submitting reports and/or promoting a culture of safety and pharmacovigilance.

This NPI also monitors the number of Yellow Cards submitted by all reporters per health board population. In 2017–2018 the number of Yellow Cards submitted by health boards in Wales increased by 30% compared with the previous year, to 3,040.

In March 2013, YCC Wales launched the Yellow Card Champion Scheme throughout Wales. This scheme now includes pharmacists and technicians from primary as well as secondary care. Within their secondary care settings each health board has a nominated hospital pharmacist or hospital pharmacy technician to act as a Yellow Card Champion[97].

In 2017–2018, 649 Yellow Card reports were submitted across Wales from within the secondary care setting. This is approximately 60 Yellow Card reports per 1,000 hospital beds and represents a 19% increase on the number reported in the previous year. This measure will enable each health board to compare how their secondary care sites are

progressing each quarter. It is not, however, intended to measure performance between health boards due to the varying size and nature of the services provided.

Following a pilot scheme, patient reporting for Yellow Cards was established in 2008[98]. This has been facilitated by improving the visibility of links to electronic Yellow Card reporting as well as the running of publicity campaigns[98]. Yellow Cards submitted by patients have been shown to provide a more complete indication of the *"profound effect that an ADR can have on people"*[99]. Continued monitoring of the number of Yellow Cards submitted by patients, their carers and/or parents will aim to ensure that reports from the general public continue to increase. In 2017–2018, 292 Yellow Card reports were submitted across Wales by members of the public. This is approximately nine Yellow Card reports per 100,000 population.

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[100,101]. As a result, community pharmacists are ideally placed to make a significant contribution to the number of Yellow Cards submitted. Therefore a further measure within this NPI will consider the total number of reports submitted by community pharmacists in each health board. In 2017–2018 across Wales there were 75 Yellow Cards submitted by community pharmacists.

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 web pages
- WeMeReC (2013) Pharmacovigilance Bulletin
- YCC Wales website
- The Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) e-learning module: Adverse Drug Reactions: Reporting makes medicines safer.
- NHS Education for Scotland e-learning modules on ADRs

Download the Yellow Card App:

- Android
- Apple

2.0 ANTIMICROBIAL STEWARDSHIP INDICATORS

Launched in 2016, the Antimicrobial Resistance (AMR) Delivery Plan for NHS Wales, *Together for Health: Tackling antimicrobial resistance and improving antibiotic prescribing*, sets out a series of priority actions related to optimising antimicrobial use, infection prevention and control; surveillance; education and training; and research[102]. Each priority is intended to have a direct impact on AMR by limiting its development or transmission. The delivery plan provides a framework for action by a wide range of stakeholders with an interest in antimicrobial usage and resistance. Under seven delivery themes, it sets out the Welsh Government's expectations of the NHS in Wales in delivering high quality prudent healthcare. 'Delivery Theme 2: Optimising prescribing practice' is linked to the expectation that health professionals will prescribe antibiotics responsibly adhering to the extensive range of guidance available[102].

The development of NPIs for antibiotic prescribing supports the two UK Government ambitions, published in 2016, to reduce healthcare associated infections (HCAI) and antimicrobial resistance:

- A 50% reduction in healthcare associated Gram-negative sepsis by March 2021.
- An overall reduction in inappropriate prescribing of antimicrobials of 50% by March 2021[103].

In support of these ambitions, the Welsh Government published a Welsh Health Circular (WHC) in May 2018 detailing their AMR improvement goals and HCAI reduction expectations to be achieved by March 2019[104]. These included health board specific improvement goals to reduce *Clostridium difficile* infection, *Staphylococcus aureus* bacteraemia, and Gram-negative bacteraemia due to *Escherichia coli*, *Pseudomonas aeruginosa* and *Klebsiella* spp., in addition to improvement goals for antimicrobial prescribing for 2018–2019[104]:

Primary and secondary care

5% reduction against the baseline year of April 2016–March 2017:

- *Primary care reduction in total volume measured as items/1,000 STAR-PUs.*
- *Secondary care reduction in total volume measured as DDDs/1,000 admissions*

Secondary care

- *Increase the proportion of antibiotic usage within the WHO Access category to ≥55% of total antibiotic consumption (as DDDs) OR increase by 3% from baseline 2016 calendar year.*

Both primary and secondary care have been asked to reduce the total volume of antimicrobial prescribing as the widespread and often excessive use of antimicrobials is one of the main factors contributing to the increasing emergence of AMR[102].

2.1 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 2019–2020:
A quarterly health board reduction of 5% against a baseline of data from April 2017–March 2018.

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

Table 3. Baseline data: total primary care antibacterial items per 1,000 STAR-PUs 2017–2018[105-108]

	June 2017	September 2017	December 2017	March 2018
Abertawe Bro Morgannwg	311	299	346	364
Aneurin Bevan	294	287	331	339
Betsi Cadwaladr	290	277	307	325
Cardiff and Vale	273	268	309	317
Cwm Taf	321	322	366	383
Hywel Dda	297	293	335	353
Powys	250	251	274	282
Wales	**294**	**286**	**326**	**340**

Figure 13. Trend in total primary care antibacterial items per 1,000 STAR-PUs to quarter ending September 2018

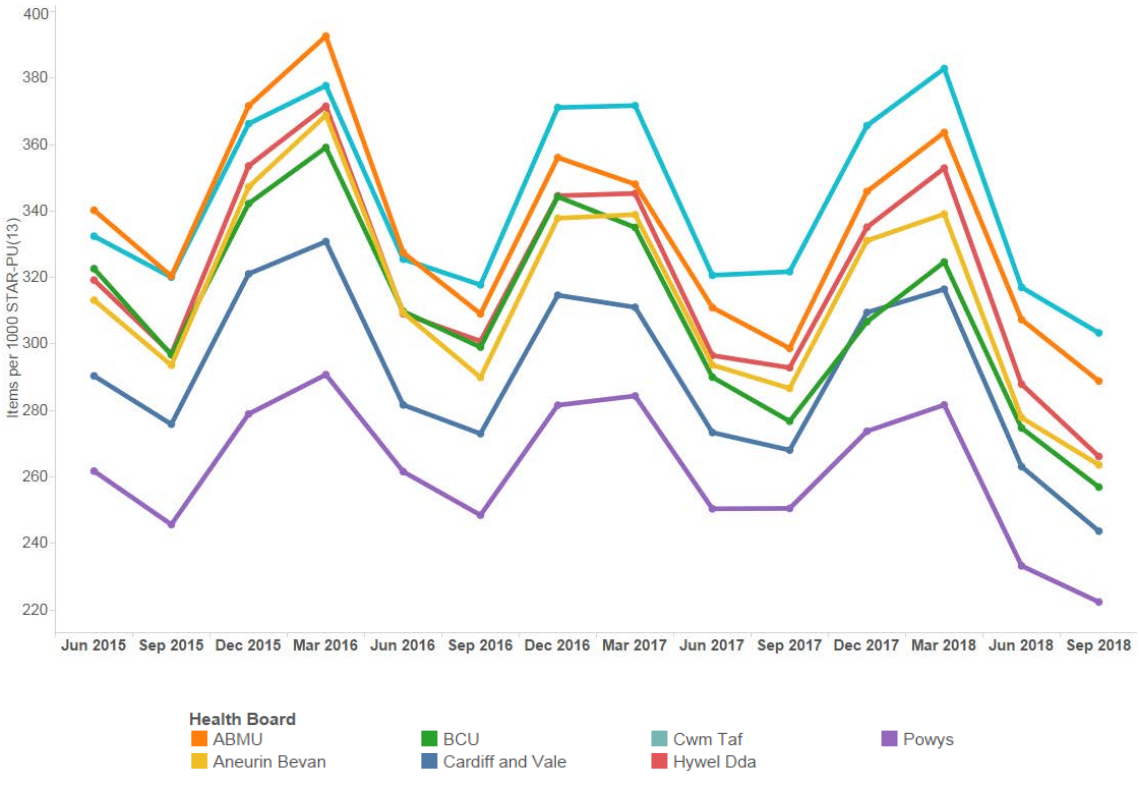
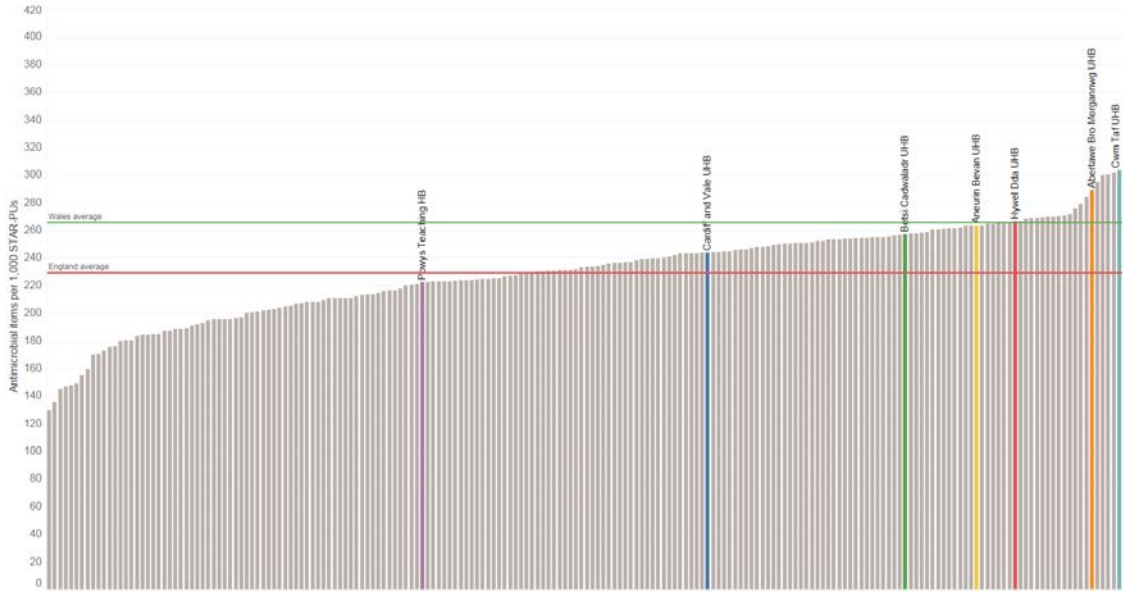


Figure 14. Total primary care antibacterial items per 1,000 STAR-PUs Welsh health boards and English CCGs – Quarter ending September 2018



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 and AMR have been increasing year on year for at least the last 7 years in acute hospital settings[102], although during the 5-year period 2013–2014 to 2017–2018, there was an 11.9% reduction in total antibacterial usage across GP practices in Wales[109]. This is a step in the right direction; however, variation still exists. For the quarter ending September 2018, primary care prescribing rates varied from 222 to 303 items per 1,000 STAR-PUs across Welsh health boards[108].

The Public Health Wales report *Antibacterial Resistance in Wales 2008–2017* presents the different AMR patterns across Wales[110]. 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[110].

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[111]. 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[111].

Ultimately, indiscriminate or inappropriate use of antibiotics is a key driver in the spread of antibiotic resistance[112]. Therefore, the ultimate aim has to be the reduction in inappropriate prescribing, measured as volume of antimicrobials.

2.2 4C ANTIMICROBIALS

***Purpose*:**
To reduce the prevalence of HCAI including *Clostridium 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 2019–2020:
A quarterly reduction of 10% against a baseline of data from April 2017–March 2018.

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

Table 4. Baseline data: 4C antimicrobials per 1,000 patients 2017–2018[29]

	June 2017	September 2017	December 2017	March 2018
Abertawe Bro Morgannwg	17.8	17.5	18.0	18.5
Aneurin Bevan	12.7	12.1	11.6	11.4
Betsi Cadwaladr	16.6	16.1	15.6	15.3
Cardiff and Vale	11.0	11.2	10.9	11.2
Cwm Taf	19.4	20.5	20.0	20.7
Hywel Dda	18.3	18.5	17.9	18.3
Powys	13.0	13.1	12.9	13.5
Wales	**15.5**	**15.4**	**15.1**	**15.2**

Figure 15. Trend in 4C antimicrobial items per 1,000 patients to quarter ending September 2018

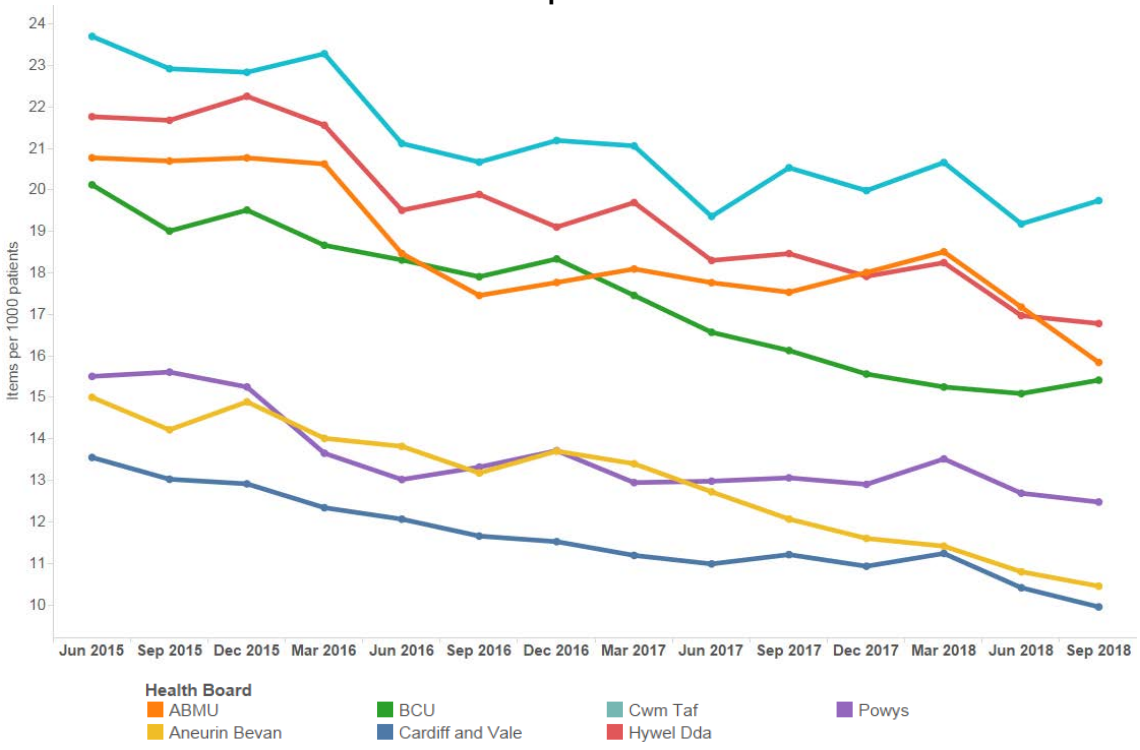
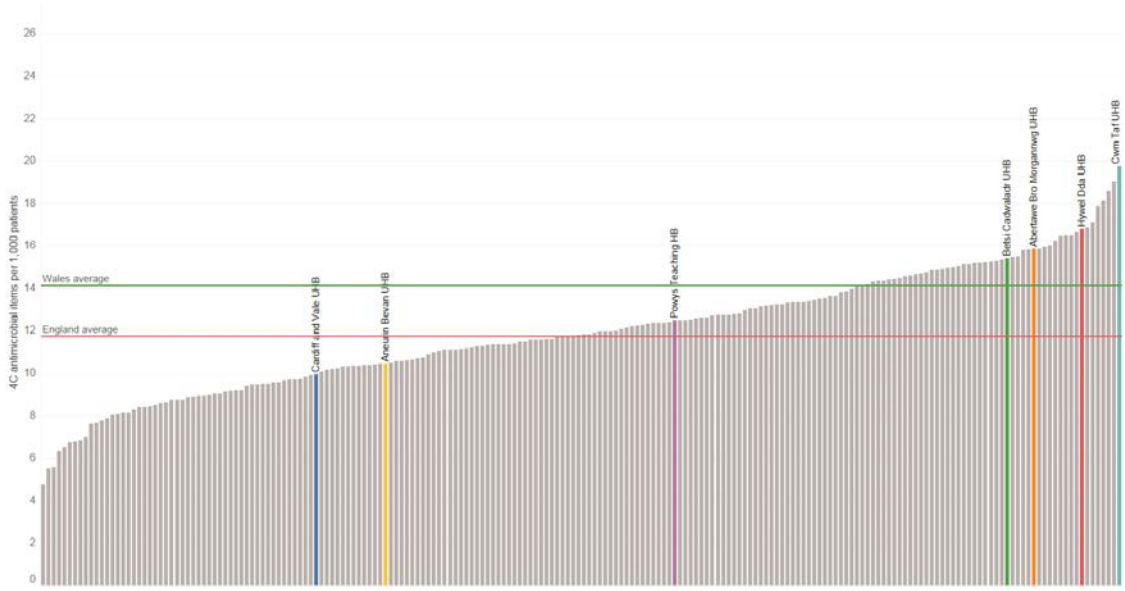


Figure 16. 4C antimicrobial items per 1,000 patients Welsh health boards and English CCGs – Quarter ending September 2018



Background and evidence

Public Health England guidance states "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"[113]. The guidance advises when it may be appropriate to consider a broad-spectrum antibiotic.

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[114]. *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[114]. The most commonly implicated antibiotics in *C. difficile* infection include clindamycin, cephalosporins (in particular second and third generation cephalosporins), fluoroquinolones and co-amoxiclav[114]. However, these antimicrobials have a very useful role in specific clinical situations, so should be reserved for use as per local guidelines.

Concerns regarding use of fluoroquinolone and quinolone antibiotics have recently been noted. In October 2018, the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) recommended restricting the use of fluoroquinolone and quinolone antibiotics following a review of disabling and potentially long-lasting side effects reported with these medicines. Very rarely, patients treated with fluoroquinolone or quinolone antibiotics have suffered long-lasting and disabling side effects, mainly involving muscles, tendons and bones, and the nervous system[115]. In November 2018, a Drug Safety Update from the MHRA highlighted the risk of aortic aneurysm and dissection in high-risk patients prescribed systemic and inhaled fluoroquinolones. It recommended that in patients at risk of aortic aneurysm and dissection, fluoroquinolones should only be used after careful assessment of the risks and benefits and after consideration of other therapeutic options. Patients, particularly

the elderly and those at risk, should be advised of the importance of seeking immediate medical attention in case of sudden-onset severe abdominal, chest or back pain[116].

Useful resources

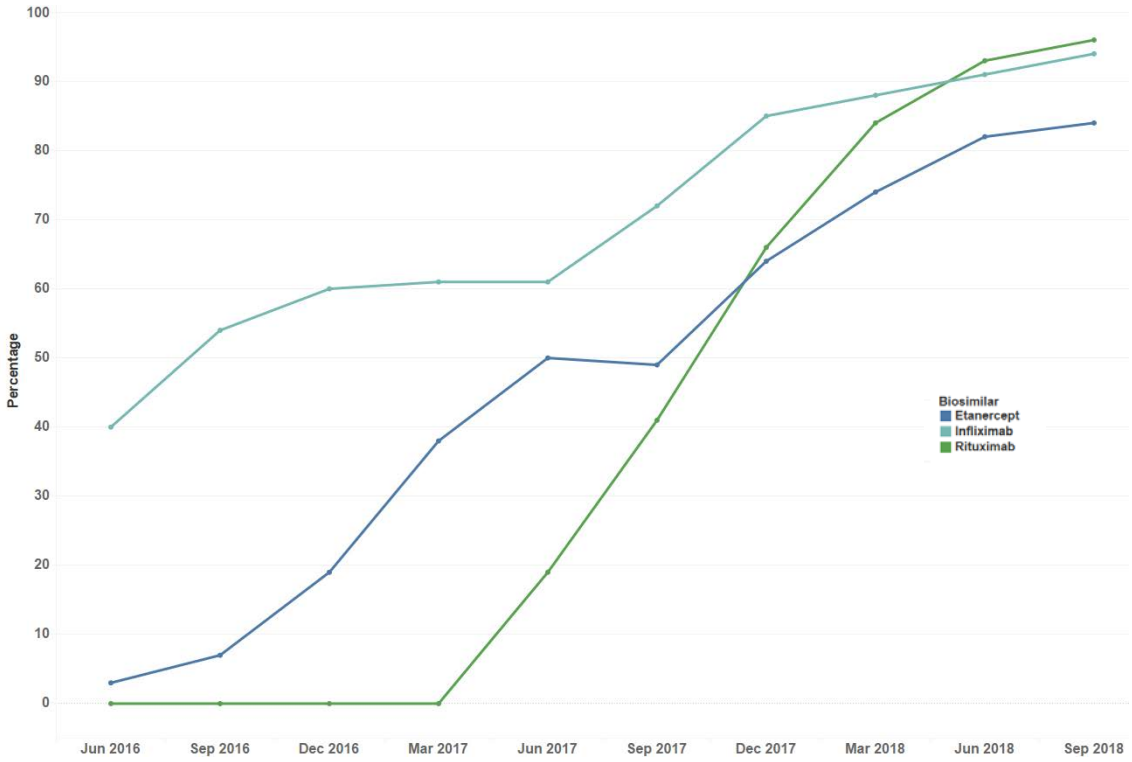
- AWMSG (2015) Primary care antimicrobial guidelines
- AWMSG (2013) CEPP National Audit: Focus on Antibiotic Prescribing
- WeMeReC (2012) Bulletin: Appropriate antibiotic use – whose responsibility?
- RCGP TARGET Antibiotics toolkit

3.0 EFFICIENCY INDICATORS

3.1 BIOSIMILARS

***Purpose*:**
To ensure prescribing of biological medicines supports cost-efficient prescribing in primary and secondary care in Wales.
Unit of measure:
Quantity of biosimilar medicines prescribed as a percentage of total 'reference' product plus biosimilar.
Target for 2019–2020:
Increase the appropriate use of cost-efficient biological medicines, including biosimilar medicines.

Figure 17. Trend in biosimilar percentage to quarter ending September 2018



Background and evidence

Biological medicines are medicines that are made or derived from a biological source and, as such, are complex, with inherent variability in their structure. A biosimilar medicine is a biological medicine that is developed to be highly similar and clinically equivalent to an existing biological medicine (i.e. 'reference medicine' or 'originator medicine')[117]. As the current regulatory authority, the EMA applies stringent criteria in their evaluation of the studies comparing the quality, safety and efficacy of the reference product and the biosimilar to show that there are no clinically meaningful differences[117-119].

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. Biological medicines account for a significant expenditure within the NHS and, as a number of these medicines

will lose their patent protection within the next five years[118], it seems an appropriate time to consider the pattern of prescribing across NHS Wales.

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[119].

The MHRA recommends that biological medicines, including biosimilar medicines, are prescribed by brand name to avoid automatic substitution[120]. Prescribing by brand name also supports the ongoing pharmacovigilance of individual biological products.

Where AWMSG or NICE has already recommended the reference biological medicine, the same guidance will normally apply to a biosimilar of the reference[121,122]. However, where a review of the evidence for a biosimilar medicine is considered necessary, NICE will consider producing a further evidence summary[121]. AWMSG does not normally appraise biosimilar medicines. However, AWMSG reserves the right to request a submission for appraisal of any biological medicine, when directed by the AWMSG Steering Committee[122].

The list of biological medicines being reported on will be determined by the requirements of the service. However, current biological medicines with biosimilar versions for use within NHS Wales and to be reported on within the NPI in 2019–2020 are:

- Infliximab – Inflectra®▼
- Etanercept – Benepali®▼, Erelzi®▼
- Rituximab – Truxima®▼
- Trastuzumab – Ontruzant®▼
- Adalimumab – Amgevita®▼, Hulio®▼, Hyrimoz®▼, Imraldi®▼

A black inverted triangle (▼) symbol indicates that these are new medicines under additional monitoring, and therefore all adverse drug reactions should be reported to the MHRA via the Yellow Card scheme[119].

Anticipated benefits

Continuing development of biological medicines, including biosimilar medicines, creates increased choice for patients and clinicians, increased commercial competition and enhanced value propositions for individual medicines[119]. Biosimilar data will be reported for the selected individual biological medicines as well as overall usage.

The use of biosimilar medicines in place of the reference biological medicine could be associated with cost savings. The cost per item of biologics, including biosimilars, is to be monitored as part of the NPI analysis. These data will not be stated within the reports due to its confidential, commercially sensitive nature. Therefore, to ensure the most cost-efficient option, reference biological medicine or biosimilar medicine, is being utilised, it is suggested that individual health boards refer to the All Wales contract for information on these medicines. Further data on the use of biosimilar medicines is available via SPIRA.

Biological medicines are often supplied to patients via ‘homecare’ and it should be noted that not all the data on homecare medicines are currently captured within, and therefore retrievable from, the secondary care prescribing data system. Although this issue is being worked on within NHS Wales as a priority, some medicines use reports may currently be incomplete.

Useful resources

- AWTTC (2018) SPIRA – Biosimilar Efficiencies
- European Medicines Agency (2017) Biosimilars in the EU
- European Commission (2016) What I need to know about Biosimilar Medicines: Information for patients
- NHS England (2015) What is a biosimilar medicine?
- The Cancer Vanguard (2017) Biosimilars frequently asked questions for healthcare professionals
- AWMSG (2017) 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

3.2 INSULIN

***Purpose*:**

To encourage a reduction in the prescribing of long-acting insulin analogues in primary and secondary care in line with NICE guidance to maximise cost-effectiveness in Wales.

Unit of measure:

Items/number of long-acting insulin analogues as a percentage of total long- and intermediate-acting insulin prescribed.

Target for 2019–2020:

Reduce prescribing of long-acting insulin analogues and achieve prescribing levels below the Welsh average.

Table 5. Use of long-acting insulin analogues as a percentage of long- and intermediate-acting insulin in primary and secondary care across NHS Wales for 2016–2018

	2016–2017				2017–2018			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Percentage of long-acting insulin analogues (primary care)	89.7	89.8	89.7	89.2	88.9	88.5	88.3	88.1
Percentage of long-acting insulin analogues (secondary care)	79.6	77.7	73.7	73.3	72.7	76.0	76.1	75.7

Figure 18. Trend in long-acting analogue prescribing as a percentage of total long- and intermediate-acting insulin prescribed in primary care to quarter ending September 2018

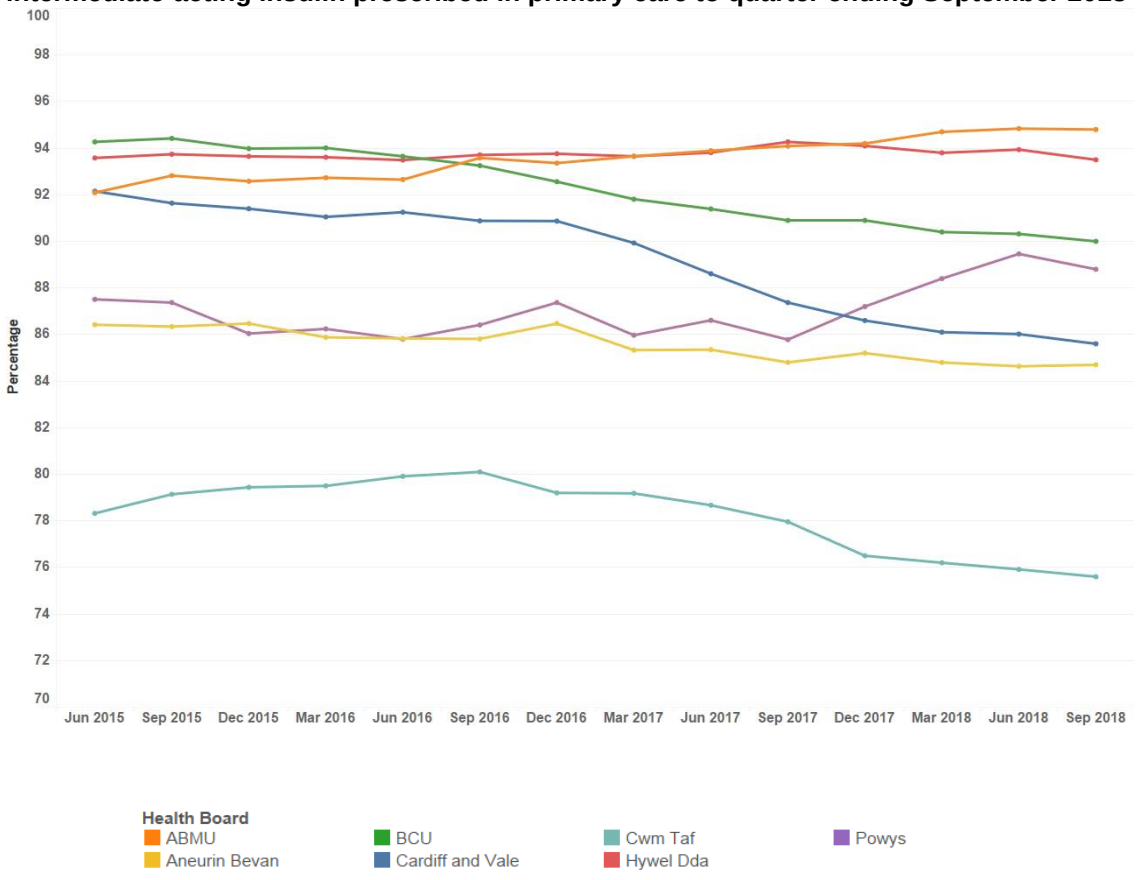
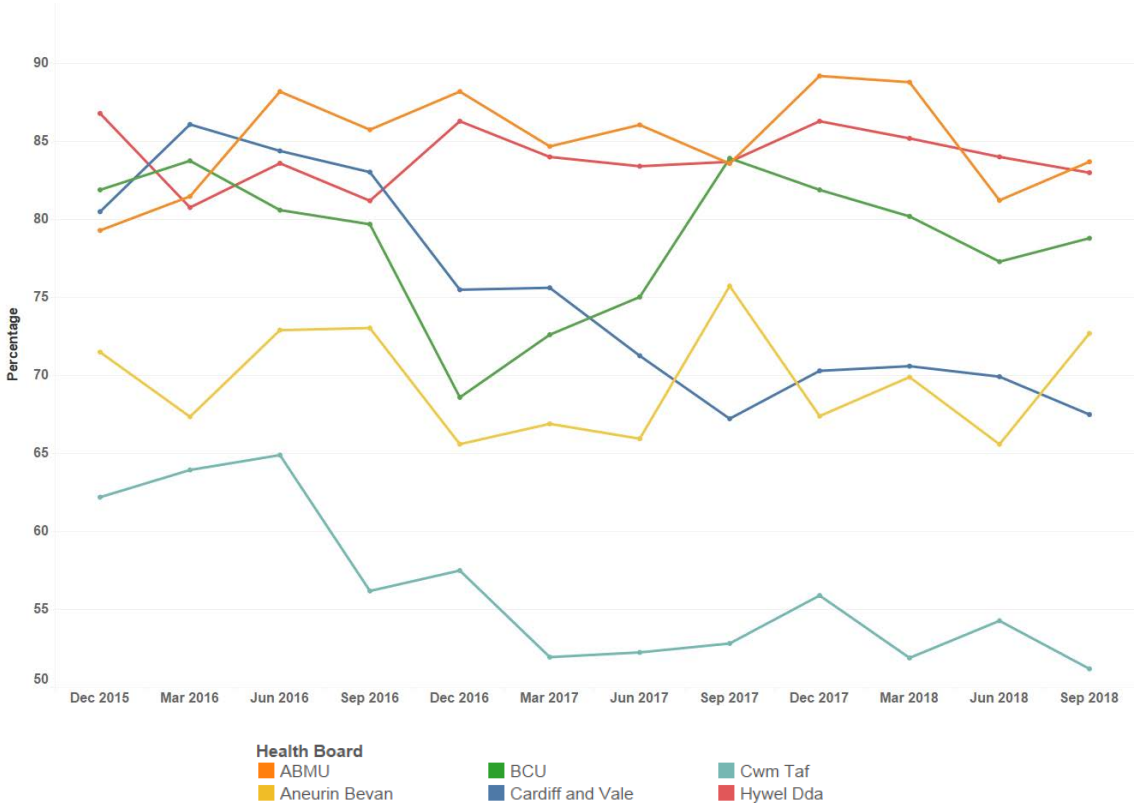


Figure 19. Trend in long-acting analogue prescribing as a percentage of total long- and intermediate-acting insulin prescribed in secondary care to quarter ending September 2018



Background and evidence

The 2015 NICE Guideline (NG) 28 on the management of type 2 diabetes mellitus recommends that when control of blood glucose remains or becomes inadequate on oral anti-diabetic therapy, then insulin should be considered as the next treatment option. Human isophane (neutral protamine Hagedorn [NPH]) insulin is recommended as the first choice regimen for the majority of people[123].

In 2007, the UK Cochrane Centre published an analysis of the available long-term trials considering the use of long-acting insulin analogues versus NPH insulin in type 2 diabetes, and concluded that insulin glargine and insulin detemir were almost identically effective compared with NPH insulin in long-term metabolic control (measured by glycated haemoglobin [HbA_{1c}])[124]. The report acknowledges that fewer patients experienced symptomatic or nocturnal hypoglycaemic episodes with either of the two analogues; however, no conclusive information on late complications or on possible differences in the number of fatalities exists. The report concludes that, in the absence of evidence to suggest the superiority of the long-acting insulin analogues over NPH insulin in terms of improved safety, glycaemic control or reduction of long-term diabetic complications, a cautious approach to prescribing the long-acting insulin analogues is advised[124].

Treatment and care of type 2 diabetes mellitus patients should take into account individual needs and preferences. Patients should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals[123]. Therefore preferred treatment should be discussed with the patient, taking into account comparative effectiveness of the specific insulin types.

When patients are started on an insulin therapy, a structured programme employing active dose titration should be used. In addition, this programme should encompass injection technique, continuing telephone support, self-monitoring, dietary

understanding, DVLA guidance, management of hypoglycaemia, management of acute changes in plasma glucose control, and support from an appropriately trained and experienced healthcare professional[123].

NG17 (2015), on the diagnosis and management of type 1 diabetes mellitus, recommends twice-daily insulin detemir as basal insulin therapy for adults with type 1 diabetes[125]. Prescribing data cannot differentiate between long-acting insulin analogues prescribed for type 1 diabetes and type 2 diabetes; therefore, monitoring of all long-acting insulin analogues is undertaken. In light of the fact that prevalence data suggest that only 10% of patients with diabetes have type 1 diabetes[126], the prescribing data indicates that long-acting insulin analogues are being widely used to manage type 2 diabetes[29].

Despite the recommendations outlined in NG28, the prescribing cost for long-acting insulin analogues was approximately £9.4 million across NHS Wales in 2017–2018[29].

The majority of insulin prescribing is initiated by a specialist clinician within secondary care and therefore review of hospital prescribing practice will affect the primary care prescribing trend. Prescribing will often continue in the primary care setting and it is therefore important to consider data for primary and secondary care.

In Wales, the proportion of insulin prescribed as long-acting insulin analogues in primary care for 2017–2018 was 88.4%; this is a slight decrease from the previous year (89.6%)[29].

In secondary care, the proportion of long-acting insulin analogues prescribed as a percentage of total long- and intermediate-acting insulin was 75.2% (April 2017–March 2018). This is also a slight decrease from the previous year (76.0%)[127].

Costs and cost savings

Diabetes medicines cost the NHS in England £1,012.4 million in 2017–2018, of which £350.5 million was spent on insulins[128]. A UK study by Holden and colleagues, published in the BMJ, concluded that the rise in usage of insulin analogues has had a substantial financial impact on the NHS, yet there has been no observable clinical benefit to justify the increased use of these medicines[129]. They estimated that if all patients using insulin analogues in the UK between 2000 and 2009 had received human insulin instead, the NHS would have saved £625 million[129].

Useful resources

- NICE (2015) NG28: Type 2 diabetes in adults: management
- Cochrane (2007) Long-acting analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus

APPENDIX 1. ANTICHOLINERGIC EFFECT ON COGNITION (AEC) SCORE[19]

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

APPENDIX 2. 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, Abertawe Bro Morgannwg 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="3"></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="6"></td><td rowspan="6"></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="4"></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.

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