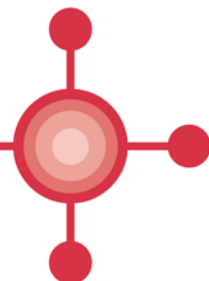


All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan



National Prescribing Indicators 2018–2019

February 2018

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This report 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 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 2018–2019 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 2018–2019 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 report¹.

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 2017–2018 NPIs and discuss potential additional NPIs for 2018–2019.

Prior to the NPI Task and Finish Group meeting, Health Board Medicines and Therapeutics Committees and the Primary Care Pharmacists Delivery Group were invited to comment on the continued relevance of the 2017–2018 NPIs and identify other priority areas that may be appropriate to monitor as an NPI. This information then fed into the discussions of the NPI Task and Finish Group.

Key changes for 2018–2019

Retired NPIs:

- *High strength inhaled corticosteroids (ICS) as a percentage of all ICS prescribing*
- *Non-steroidal anti-inflammatory drug (NSAID) ADQs per 1,000 STAR-PUs*

Each retired NPI will continue to be monitored as a Local Comparator for two years, with prescribing data made available via SPIRA.

New NPIs:

- [Prescribing Safety Indicators \(PSIs\)](#) Data will be obtained via Audit+.
- [Yellow Card reporting in secondary care and by the public](#). Data will be obtained from the MHRA.

Amendments to 2017–2018 NPIs:

- *Antimicrobial stewardship*
 - *Total antibacterial items per 1,000 STAR-PUs*
A target of a 5% reduction against a baseline of April 2016–March 2017 items will be introduced for health boards.
 - *4C antimicrobials – items per 1,000 patients and items as a percentage of total antibacterial items*
The monitoring of co-amoxiclav, cephalosporins and fluoroquinolones will be combined, with the addition of clindamycin, to create the 4Cs antimicrobial basket.
A target will be introduced – absolute measure $\leq 7\%$ or a proportional reduction of 10% against a baseline of April 2016–March 2017.
 - *Colorectal surgical prophylaxis*
This will be amended from the proportion of elective colorectal patients receiving surgical prophylaxis for more than 24 hours, to the proportion of elective colorectal patients receiving a single dose antimicrobial for surgical prophylaxis.
A target will be introduced – absolute measure $\geq 90\%$ or a proportional increase of 20% against performance for 2017–2018.
- *Anticholinergic burden*
This indicator will be moved into the PSIs:
 - 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.
- *NSAIDs and chronic kidney disease (CKD)*
These indicators will be moved into the PSIs:
 - 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.

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 DDIs 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 items within therapeutic groups.

- Where possible, measures used should be accessible to all medicines management teams through CASPACcluster, 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 CASPACcluster and STAR-PU measurements are updated on a quarterly basis by the NHS Wales Shared Services Partnership (NWSSP): Primary Care Services.
- Audit+ will provide 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 use of medicines will be monitored using 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.

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 each NPI 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 2017.
- Unless otherwise stated, the threshold is 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. Baseline data will be collected during 2018–2019.

Table 1 details the NPIs for 2018–2019, with units of measure and targets, where applicable.

Table 1. NPIs 2018–2019

NPIs	Applicable to:	Unit of measure	Target for 2018–2019	Data source
Safety				
Prescribing Safety Indicators	Primary care	Number of patients identified as a percentage of the practice population	No target set	Audit+
Hypnotics and anxiolytics	Primary care	Hypnotic and anxiolytic 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	Tramadol DDDs per 1,000 patients	Maintain performance levels within the lower quartile, or show a reduction towards the quartile below	NWSSP
		Opioid patch items as a percentage of all opioid prescribing	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		In excess of one Yellow Card per 2,000 health board population	
			In excess of a 20% increase from baseline for Yellow Cards submitted by secondary care	
			In excess of a 50% increase from baseline 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 reduction of 5% against a baseline of April 2016–March 2017	NWSSP
	Primary care	4C antimicrobials (co-amoxiclav, cephalosporins, fluoroquinolones and clindamycin): - the number of 4C items per 1,000 patients - the number of 4C items as a percentage of total antibacterial prescribing.	Absolute measure ≤7% or a proportional reduction of 10% against a baseline of April 2016–March 2017	NWSSP
	Secondary care	Prophylaxis in colorectal surgery: proportion of elective colorectal patients receiving a single dose of antimicrobial for surgical prophylaxis	Absolute measure ≥90% or a proportional increase of 20% against performance for 2017–2018	Data collection by antimicrobial pharmacists
Efficiency				
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
Biosimilars	Primary + secondary care	Quantity of biosimilar medicines prescribed as a percentage of total 'reference' product plus biosimilar	Increase the appropriate use of cost-effective biological medicines, including biosimilar medicines.	NWSSP Medusa
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 Medusa

Evidence

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

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 making².

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:

1. Number of patients with a peptic ulcer who have been prescribed NSAIDs without a PPI, as a percentage of all patients.
2. Number of patients with asthma who have been prescribed a beta-blocker, as a percentage of all patients.
3. Number of patients with concurrent prescriptions of verapamil and a beta-blocker, as a percentage of all patients.
4. 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.
5. 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.
6. Number of patients with concurrent prescriptions of warfarin and an oral NSAID, as a percentage of all patients.
7. Number of patients under 12 with a current prescription of aspirin, as a percentage of all patients.
8. Number of patients aged 65 years or over prescribed an NSAID plus aspirin and/or clopidogrel but without gastroprotection (PPI or H₂ receptor antagonist), as a percentage of all patients aged 65 years or over.
9. Number of patients aged 65 years or over prescribed an antipsychotic, as a percentage of all patients aged 65 years or over.
10. 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.
11. 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.
12. 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.

Target for 2018–2019: No target set

Background and evidence

There were 2,330 Yellow Card reports submitted in Wales in 2016–2017, an increase of 28% on the previous year. In the UK, it is estimated that around 6.5% of hospital admissions are related to adverse drug reactions³. Adverse drug reactions can often be predictable, making it possible to identify and address them before actual patient harm occurs³. Therefore, a process of identifying patients electronically could enable intervention and help to avoid harm.

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 errors⁴. 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 12. Some brief explanation for these is provided below. No target has been set for this NPI for 2018–2019 as data from this year can provide a baseline for future years.

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 ulceration³. A PPI can be considered for gastroprotection in patients at high risk of gastrointestinal complications with an NSAID e.g. previous peptic ulcer⁵.

Beta-blockers in asthma patients

Beta-blockers should be avoided in patients with asthma due to the potential to precipitate bronchospasm⁵. If the benefits of using a beta-blocker in an asthma patient are justified the patient should be monitored closely⁵.

Verapamil in combination with beta-blockers

Beta-blockers are associated with adverse drug reactions such as bradycardia and atrio-ventricular conduction disturbances⁶. 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 alone⁶.

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 contraceptives⁵. Any patients with a history of venous or arterial thrombosis who have been prescribed combined hormonal contraceptives are therefore at an increased risk⁵.

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 therapy⁷. Conversely, women who have undergone a hysterectomy should not receive a progestogen component⁷. 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 haemorrhage⁵. NSAIDs can reduce platelet aggregation, which can worsen any bleeding event in warfarin treated patients⁵. Therefore, wherever possible, in patients taking warfarin, NSAIDs should be avoided⁸.

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 age⁹. 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^{5,10}.

NSAIDs in combination with aspirin or clopidogrel without gastroprotection

Based upon work by NHS Scotland two additional measures have been included within this NPI due to their focus on patient safety¹¹. The first of these will look at the use of gastroprotection in patients aged 65 years or over and prescribed an NSAID plus aspirin and/or clopidogrel. Hospital admission due to gastrointestinal bleeding has been associated with aspirin and clopidogrel, as well as NSAIDs³. The harmful consequences of bleeds due to antiplatelet therapy increase with age¹². PPIs are recommended in older

patients undergoing antiplatelet treatment^{12,13}. PPIs are preferred to H₂-receptor antagonists because there is less evidence to support use in conjunction with low dose aspirin¹⁴.

Over 65s prescribed an antipsychotic medicine

A second measure that has been based on work by NHS Scotland will consider the use of antipsychotics in patients aged 65 years or over¹¹. In 2009 the Banerjee report called for a review of the use of antipsychotic medicines in elderly patients with dementia¹⁵. These medicines have only a limited benefit in treating behavioural and psychological symptoms of dementia and carry significant risk of harm¹⁵.

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 mortality¹⁶. The AEC scale (see Appendix 1) was developed to illustrate the negative anticholinergic effects of drugs on cognition¹⁷. 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)^{17,18}.

Use of NSAIDs in patients with renal impairment

The final two measures in this NPI consider the use of NSAIDs in patients with renal impairment.

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 time¹⁹.

The second measure 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 risk²⁰. 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.

Useful resources

- MHRA (2014) [Antipsychotics learning module](#)
- WeMeReC (2015) [Medicines-related admissions](#)
- AWMSG (2014) [Polypharmacy: Guidance for Prescribing](#)
- PrescQIPP (2016) [Bulletin 140: Anticholinergic drugs](#)

1.2 HYPNOTICS AND ANXIOLYTICS

Purpose: To encourage a reduction in the inappropriate prescribing of hypnotics and anxiolytics in primary care.

Unit of measure: Hypnotic and anxiolytic ADQs per 1,000 STAR-PU.

Target for 2018–2019: Maintain performance levels within the lower quartile, or show a reduction towards the quartile below.

Figure 1. Trend in hypnotic and anxiolytic ADQs per 1,000 STAR-PU to quarter ending September 2017

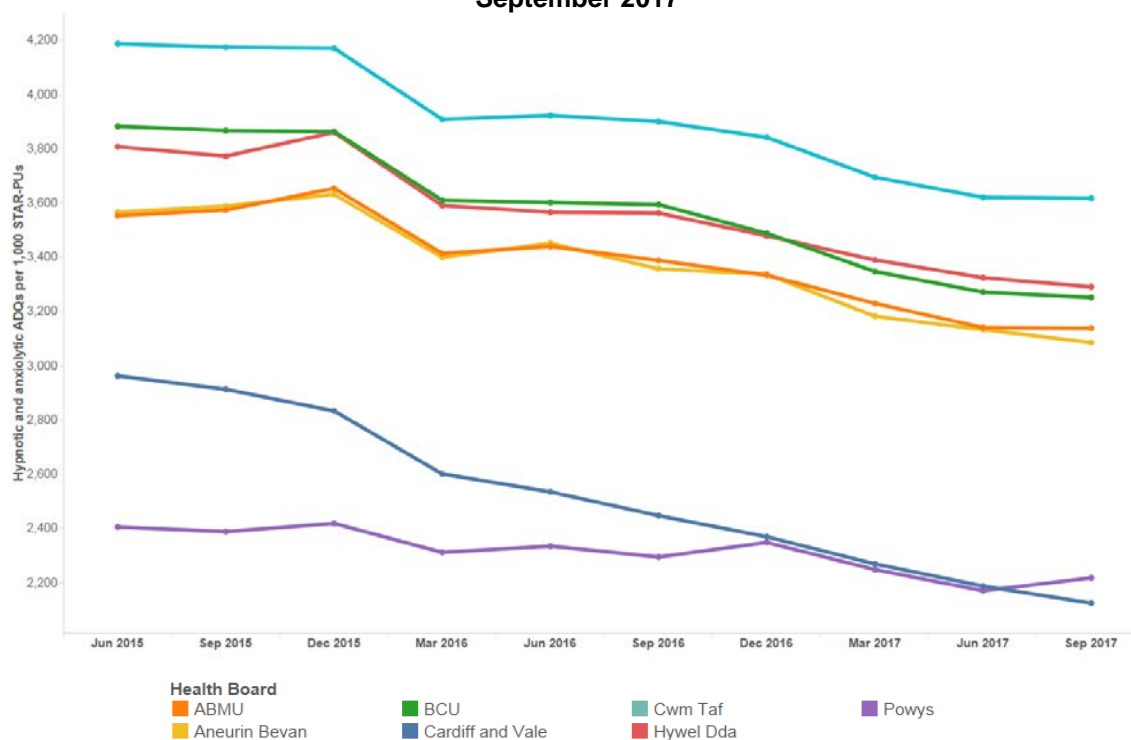
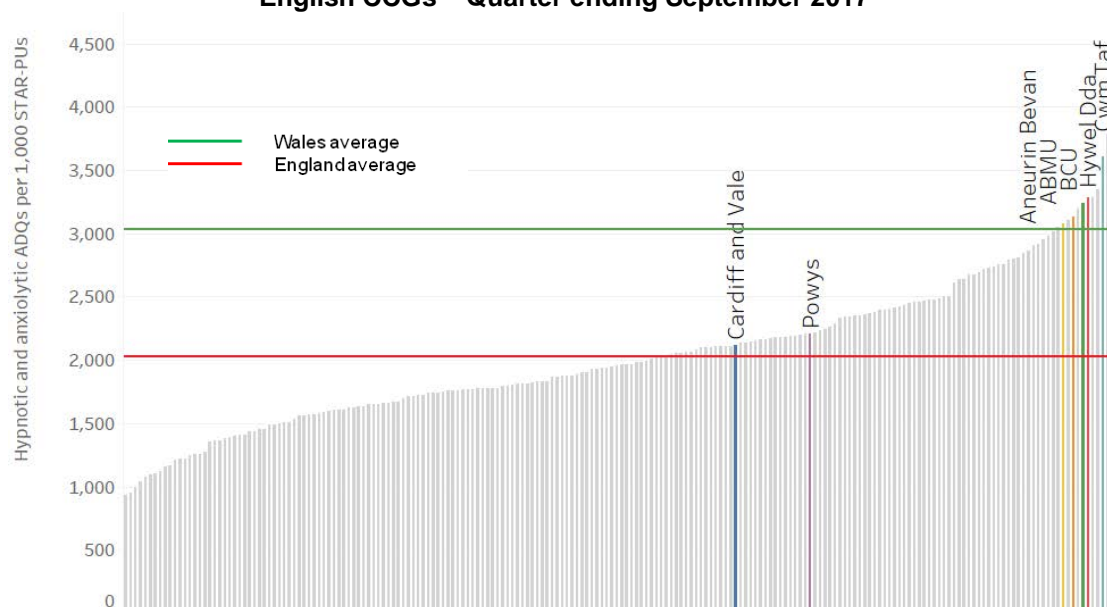


Figure 2. Hypnotic and anxiolytic ADQs per 1,000 STAR-PU Welsh health boards and English CCGs – Quarter ending September 2017



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 benzodiazepines²¹. 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 clinical commissioning groups (CCGs) in England^{22,23}.

In the financial year 2016–2017, the number of items dispensed was 1,351,939, compared with 1,401,094 the previous year: a reduction of 3.5%²². Despite a reduction in prescribing, the number of deaths associated with benzodiazepines has increased. Data from the Office for National Statistics demonstrate that drug-related deaths (drug poisoning and drug misuse) where any benzodiazepine is mentioned on the death certificate (deaths registered in England and Wales) has increased from 284 in 2012 to 406 in 2016²⁴.

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 distress²⁵. NICE guidance on the use of zaleplon, 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^{26,27}: 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 crises²⁸.

Benzodiazepine hypnotics and anxiolytics are known to significantly increase risk of falls²⁹. 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 injury⁵. NICE Clinical Knowledge Summary: Falls – risk assessment, advises reviewing psychoactive drugs, such as benzodiazepines, in patients at high risk of falls³⁰.

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 analgesics³¹. 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 problem³¹.

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 used³². Another observational study suggested benzodiazepines increase the risk of dementia³³. 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 exposure³⁴.

Dependence (both physical and psychological) and tolerance can occur leading to difficulty in withdrawing the drug after it has been taken by the patient regularly for more than a few weeks⁵. 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 2011³⁵.

Useful resources

- AWMSG (2016) [Educational Pack: Material to Support Appropriate Prescribing of Hypnotics and Anxiolytics across Wales](#)
- AWMSG (2014) [Polypharmacy: Guidance for Prescribing](#)

1.3 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 more³⁶. 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 high³⁷. A number of analgesic medicines with different mechanisms of action and licensed indications are available; however, these NPIs focus on tramadol, opioid patches 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.

1.3.1 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 2018–2019: 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 3. Trend in tramadol DDDs per 1,000 patients to quarter ending September 2017

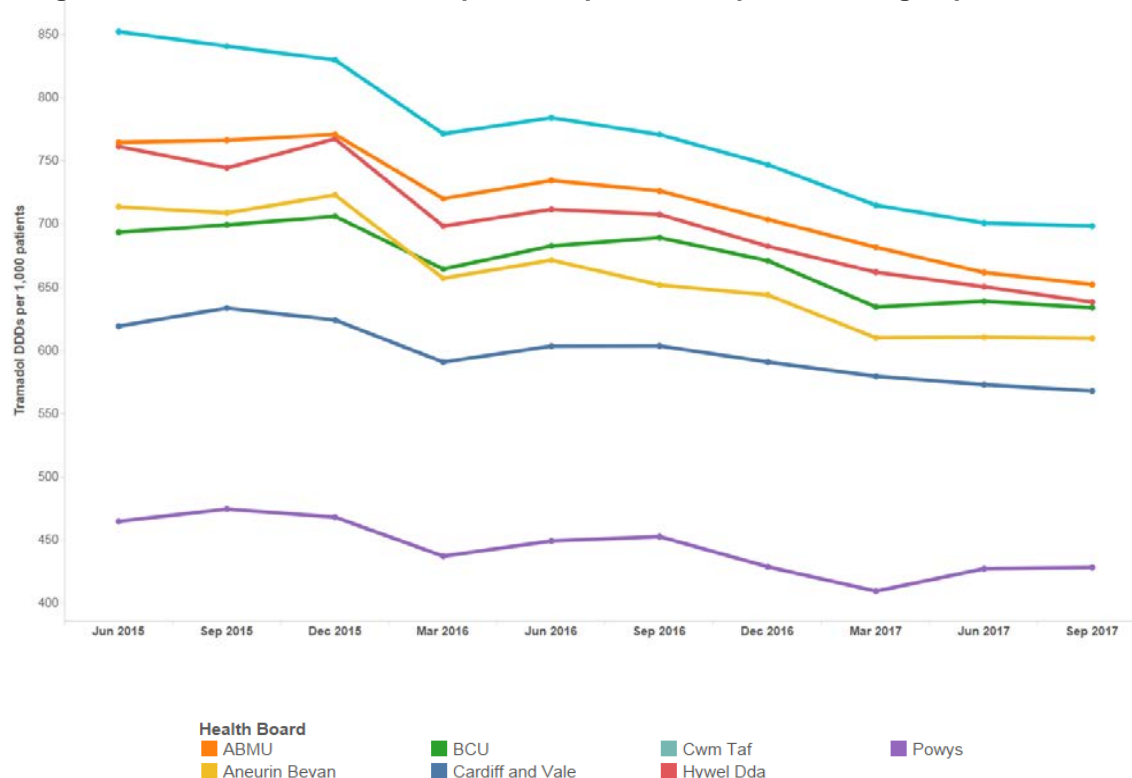
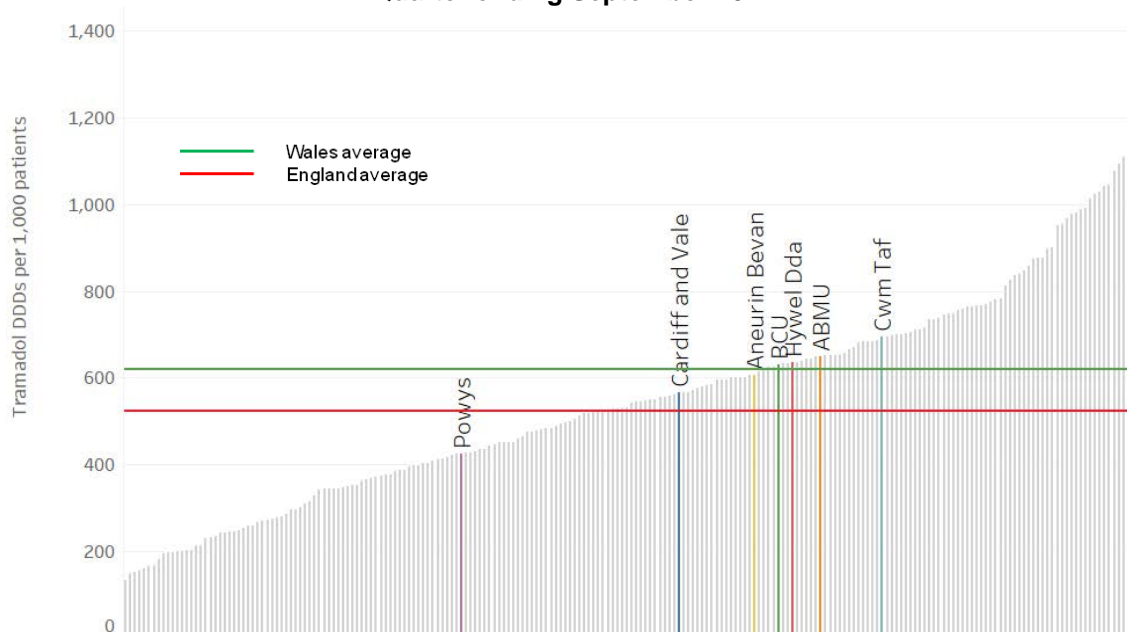


Figure 4. Tramadol DDDs per 1,000 patients Welsh health boards and English CCGs Quarter ending September 2017



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 pathways⁵. It has fewer of the typical opioid side effects, e.g. less respiratory depression and constipation, but psychiatric reactions have been reported⁵. The unique dual-action pharmacological profile of tramadol increases the risk of adverse effects seen in overdose³⁸.

In 2013, the Advisory Council for 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 tramadol³⁸. The changes came into force in June 2014. Deaths involving tramadol in England and Wales fell for the second year in a row, from 208 deaths in 2015, to 184 deaths registered in 2016²⁴.

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 effects³⁹. Hallucinations, confusion and convulsions, as well as rare cases of dependence and withdrawal symptoms, have been reported with tramadol at therapeutic doses⁴⁰. 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 so³⁹. 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)³⁹. 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 inhibitors³⁹.

Opioid analgesics, such as tramadol, are increasingly used to treat persistent pain; however, their safety and efficacy in the long-term management of pain is uncertain, as is the propensity for these medicines to cause problems of tolerance and dependence⁴¹. The Royal College of Anaesthetists Faculty of Pain Medicine highlights that opioids are often not very effective for persistent pain, and patients who do not achieve useful pain relief from opioids within two to four weeks are unlikely to gain benefit in the long term⁴².

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^{38,43}. 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 required⁴⁴.

The NPI does not measure the prescribing of Tramacet[®] (tramadol/paracetamol combination) as there are no DDDs available. Tramacet[®] currently accounts for 1.36% of all tramadol prescribed (quarter 1 2017–2018)²². Despite a reduction in Tramacet[®] use, health boards may wish to identify high prescribers of this combination product to review alongside this NPI.

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.

1.3.2 Opioid patches

Purpose: To encourage the appropriate use and review of opioid patches in primary care, minimising the potential for diversion, misuse and ADRs.

Unit of measure: Opioid patch items as a percentage of all opioid prescribing.

Target for 2018–2019: Maintain performance levels within lower quartile, or show a reduction towards the quartile below.

Note

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

Figure 5. Trend in opioid patch items as a percentage of all opioid prescribing to quarter ending September 2017

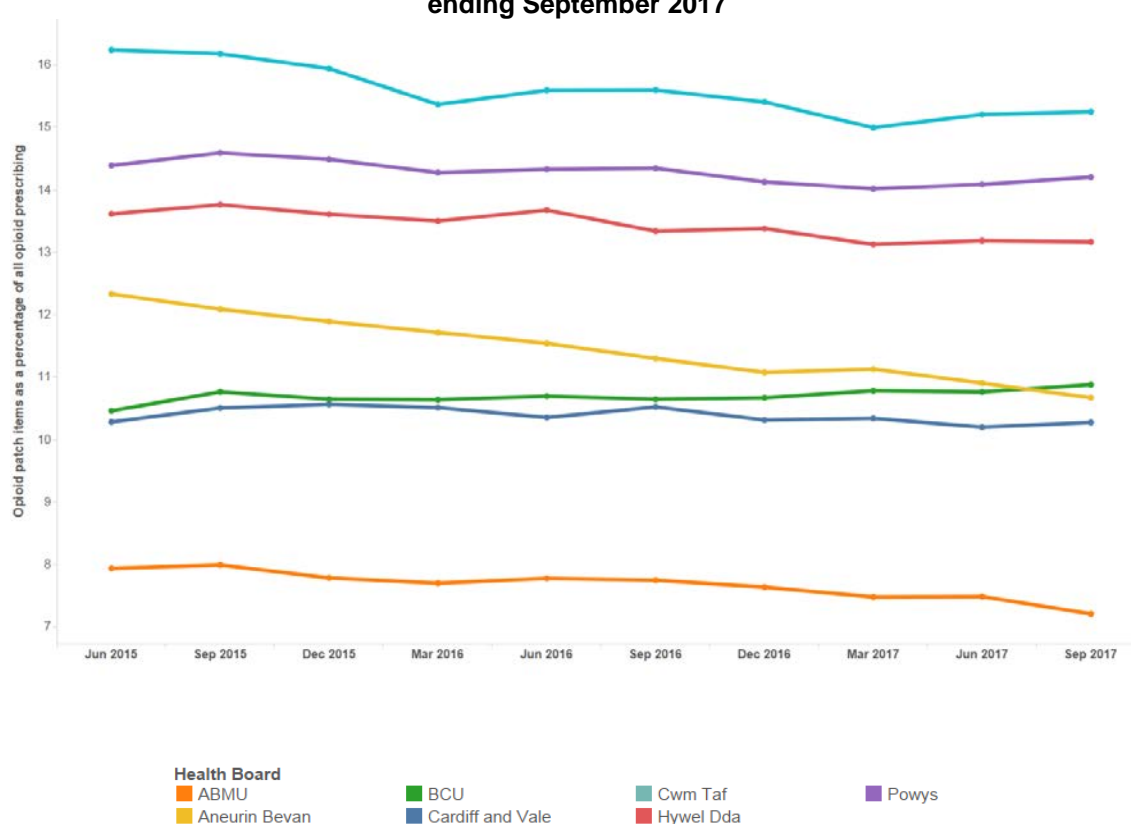
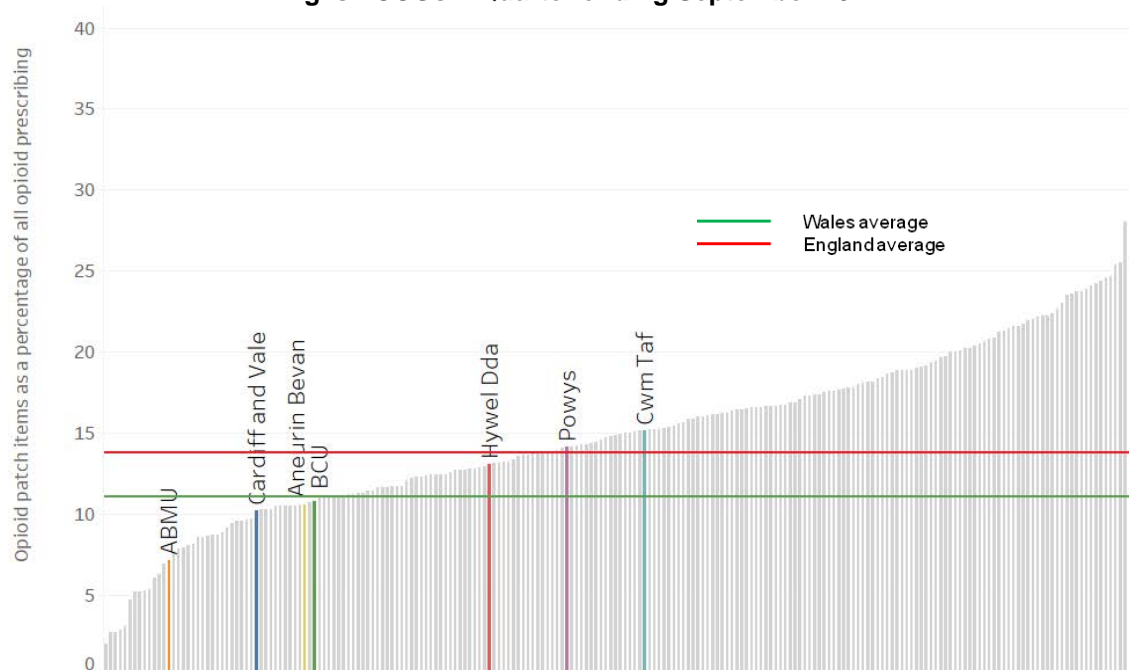


Figure 6. Opioid patch items as a percentage of all opioid items Welsh health boards and English CCGs – Quarter ending September 2017



Background and evidence

Fentanyl and buprenorphine are currently available as transdermal patches in several different brands and formulations, with different licensed indications⁴⁵⁻⁴⁷. As a number of safety concerns around the use of opioid patches have been highlighted⁴⁸⁻⁵⁰, and anecdotal evidence suggests that patches are not always prescribed appropriately, the aim of this NPI is to promote a prudent approach to prescribing opioid patches.

Where a strong opioid is indicated, modified release morphine is recommended as the treatment of choice⁵¹. NICE Clinical Guideline 140 recommends oral sustained-release morphine as first-line maintenance treatment for patients who require strong opioids in palliative care⁵². Fentanyl and buprenorphine patches are not suitable for acute pain, or in patients whose analgesic requirements are changing rapidly, because the long time to steady state prevents rapid titration of the dose⁵.

Opioid patches are recommended as a treatment option only where analgesic requirements are stable and where oral opioids are unsuitable⁵². Opioid patches should be reserved for patients who are unable to tolerate the side effects of oral morphine, have difficulty swallowing, or have compliance issues⁵³. In addition, fentanyl, and buprenorphine (as well as alfentanil) are the safest opioids for use in renal impairment⁵⁴. Fentanyl is metabolised to inactive, non-toxic metabolites whilst buprenorphine is primarily excreted in the bile. Whilst there is limited evidence for the use of these drugs in renal impairment, on the basis of their pharmacokinetics they can be used cautiously. Patients must be monitored for signs of toxicity⁵⁴.

It is important to note the difference in relative potencies of fentanyl and buprenorphine patches:

- Fentanyl is a strong opioid analgesic indicated for malignant and non-malignant chronic intractable pain⁵. A 25 microgram per hour fentanyl patch equates to a daily dose of oral morphine of up to 90 mg⁵³. There have been reports of life-threatening reactions and fatalities from fentanyl overdose, with a number of incidents occurring as a result of inappropriate strength of fentanyl patches prescribed in opioid naive patients⁵⁰. Fentanyl patches should only be used in patients who have previously tolerated opioids, because of the risk of significant respiratory depression in opioid naive patients⁵⁰, and the initial dose of fentanyl should be based on a patient's opioid history.
- Buprenorphine is a partial opioid agonist indicated for moderate to severe pain⁵. A 52.5 microgram per hour buprenorphine patch equates to a daily dose of oral morphine of up to 90 mg⁵³. Prescribers should ensure that they are familiar with the correct use of transdermal patches as inappropriate use has caused fatalities.

In 2008, the National Patient Safety Agency published a Rapid Response Report alerting health professionals to the risks of patients receiving unsafe doses of opioid medicines and combinations of opioids⁵⁵. In the same year, the MHRA issued a Drug Safety Update regarding reports of unintentional overdose of fentanyl due to dosing errors, accidental exposure, and exposure of patches to a heat source⁴⁸. A second Drug Safety Update was issued in 2014 again highlighting the risks of accidental exposure⁴⁹. The Welsh Government issued a Patient Safety Notice in December 2015 which highlighted a number of life-threatening reactions and fatalities from fentanyl overdose occurring as a result of failure to remove an old patch before applying a new one; exposure of the patch application site to a heat source; inadvertent ingestion of fentanyl patches; poorly affixed fentanyl patches transferring to another person; and children applying improperly disposed patches to their body believing the patches to be stickers or plasters⁵⁰. AWMSG has produced a counselling checklist for users of opioid patches⁵⁶. The checklist aims to assist healthcare professionals in the essential counselling of patients on the safe and effective use of opioid patches.

In order to ensure that opioid patches are used appropriately, prescribers need to make evidence-based, informed decisions based on the individual needs of the patient, and where an opioid patch is indicated, the patch with the lowest acquisition cost should be initiated⁵². This NPI promotes a prudent approach to prescribing opioid patches, taking into account the risks and benefits and encouraging timely review.

1.3.3 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.

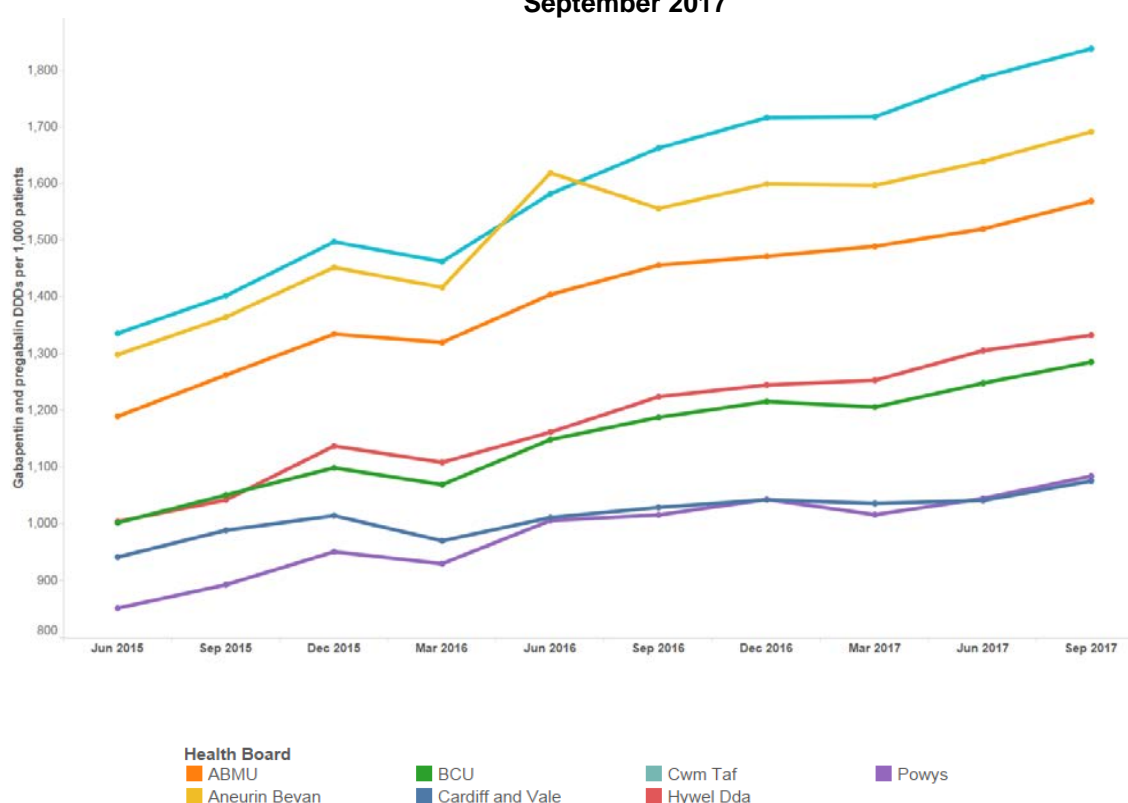
Unit of measure: Gabapentin and pregabalin DDDs per 1,000 patients.

Target for 2018–2019: Maintain performance levels within lower quartile, or show a reduction towards the quartile below.

Note

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

Figure 7. Trend in gabapentin and pregabalin DDDs per 1,000 patients to quarter ending September 2017



Note: DDDs per 1,000 patients for Aneurin Bevan UHB Q1 2016–2017 should be 1,530 rather than 1,619 as reported.

Figure 8. Gabapentin and pregabalin DDDs per 1,000 patients Welsh health boards and English CCGs
Quarter ending September 2017



Background and evidence

NICE recommends gabapentin or pregabalin as first-line options in the treatment of neuropathic pain, along with amitriptyline and duloxetine⁵⁷. Gabapentin is licensed for peripheral neuropathic pain and epilepsy, whilst pregabalin is licensed for peripheral and central neuropathic pain, in addition to epilepsy and generalised anxiety disorder⁵⁸⁻⁶².

There has been increasing use of gabapentin and pregabalin in primary care, with prescribing data from the quarter ending September 2017, compared with the quarter ending September 2013, demonstrating an increase of over 73% in prescription items across Wales²². This is similarly reflected in England where prescribing of gabapentin and pregabalin has increased by more than 75% during the same period²³. Current prescribing of gabapentin and pregabalin in Wales is high in comparison to England with 1,426 DDDs per 1,000 patients in Wales²², compared with 1,074 DDDs per 1,000 patients in England²³ for the quarter ending September 2017.

No single drug works for all neuropathic pain, and given the diversity of pain mechanisms, patient's responses and disease, treatment must be individualised⁶³. 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 account⁵⁷. 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 relief⁶⁴. 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 pregabalin⁶⁵.

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 need⁵⁷. If the patient has not shown sufficient benefit within eight weeks of reaching the maximum tolerated dose, drug treatment should be reduced and stopped⁶³. 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^{60,62}; 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 pregabalin⁶⁶.

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 pain⁶³. Both gabapentin and pregabalin are commonly prescribed for non-neuropathic pain syndromes; however, there is little evidence to support this practice⁶⁶. 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 benefit⁶⁷. 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 dependence⁵⁸⁻⁶². Pregabalin may have a higher abuse potential than gabapentin due to its rapid absorption, faster onset of action and higher potency⁶⁸. Pregabalin causes a 'high' or elevated mood in users⁶⁸ and individuals misusing it describe improved sociability, euphoria, relaxation and a sense of calm⁶⁶. Pregabalin misusers achieve these effects by taking large quantities, ranging from 200 mg to 5 g as a single dose⁶⁶.

Advice published by the Advisory Council on the Misuse of Drugs (ACMD) in January 2016, highlighted the potential risk of dependence, misuse and diversion of gabapentin and pregabalin and the importance of appropriate prescribing to minimise these risks⁶⁸. A Welsh Health Circular issued in July 2016 also noted the potential for misuse of these medicines and provided suggestions for balanced and rational use⁶⁹. 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 (amended) as Schedule 3, so as not to preclude legitimate use on prescription⁶⁸. At the time of writing, the Home Office is seeking views on controlling these drugs in line with the ACMD advice, through a public consultation⁷⁰.

Both pregabalin and gabapentin have the propensity to cause depression of the central nervous system⁶⁶, and when used in combination with other depressants they can cause drowsiness, sedation, respiratory failure and death⁶⁸. 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 depression⁷¹. 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 170 deaths registered in England and Wales in 2016²⁴.

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 prescribing⁷².

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](#)
- 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](#)
- AWMSG (2016) [Safeguarding Users of Opioid Patches by Standardising Patient/Caregiver Counselling](#)
- PrescQIPP (2014) [Opioid patches](#)
- WHO [Pain Relief Ladder](#)
- SIGN (2013) [SIGN 136. Management of chronic pain](#)
- AWMSG (2013) [Tramadol Educational Resource Materials](#)

1.4 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

Target for 2018–2019:

GP practices: Submit one Yellow Card per 2,000 practice population.

Health boards:

- Submit in excess of one Yellow Card per 2,000 health board population
- Demonstrate a 20%, or greater, increase from baseline, for Yellow Cards submitted by secondary care
- Demonstrate a 50%, or greater, increase from baseline, for Yellow Cards submitted by members of the public

Community pharmacy: no target set

Figure 9. Percentage of GP practices meeting the target of one Yellow Card per 2,000 practice population 2016–2017

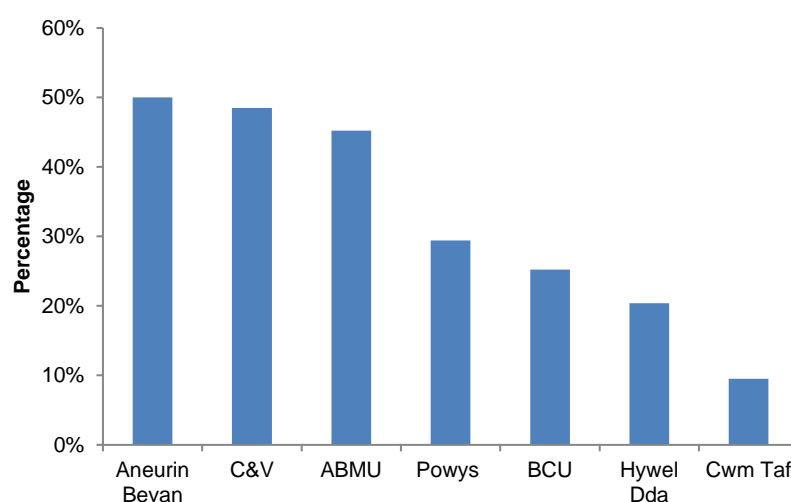


Table 2. Yellow Card data showing total number of reports, and number of secondary care and member of public reports in 2016–2017

Health board	Total number of reports	Secondary care reports	Member of public reports
ABMU	465	74	59
Aneurin Bevan	452	47	60
Betsi Cadwaladr	486	172	66
Cardiff and Vale	466	111	38
Cwm Taf	106	22	22
Hywel Dda	278	112	44
Powys	82	8	11

Table 3. Yellow Card data showing secondary care reports per 1,000 beds and member of public reports per 100,000 population in 2016–2017

Health board	Secondary care reports per 1,000 beds	Member of public reports per 100,000 population
ABMU	32	11
Aneurin Bevan	26	10
Betsi Cadwaladr	75	9
Cardiff and Vale	60	7
Cwm Taf	17	7
Hywel Dda	97	11
Powys	36	8

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 6.5% of hospital admissions in adults and 2.1% in children^{3,73}. 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”*⁷⁴.

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 all medicines including vaccines, blood factors and immunoglobulins, herbal medicines and homeopathic remedies, and all medical devices available on the UK market.

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 2016–2017, the number of Yellow Cards submitted by GPs in Wales increased by 58% compared with the previous year, to 1,346.

It is anticipated that continuing to monitor Yellow Card reporting per practice population as an NPI for 2018–2019 will further increase reporting rates amongst GP practices. Within a general practice, other healthcare professionals such as practice nurses 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 2016–2017 the number of Yellow Cards submitted by health boards in Wales increased by 28% compared with the previous year, to 2,330.

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 Champion⁷⁵.

An additional measure for this NPI to be introduced in 2018–2019 will consider the number of Yellow Cards reported in secondary care. In 2016–2017, 546 Yellow Card reports were submitted across Wales from within the secondary care setting. This is approximately 50 Yellow Card reports per 1,000 hospital beds and represents a 10% 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 nature of the services provided.

Following a pilot scheme, patient reporting for Yellow Cards was established in 2008⁷⁶. This has been facilitated by improving the visibility of links to electronic Yellow Card reporting as well as the running of publicity campaigns⁷⁶. 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”*⁷⁷. Another new Yellow Card measure to be introduced for this NPI in 2018–2019 will therefore be reports submitted by members of the public. This measure will encompass Yellow Cards submitted by parents and carers on behalf of patients, as well as those provided by patients themselves. In 2016–2017, 300 Yellow Card reports were submitted across Wales by members of the public. This is approximately nine Yellow Card reports per 100,000 population and represents a 44% increase on the number submitted in the previous year.

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^{78,79}. 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. However, no target will be set for 2018–2019.

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 on-line – [Yellow Card website](#)
- [MHRA web pages](#)
- WeMeReC (2013) [Pharmacovigilance Bulletin](#)
- [YCC Wales website](#)
- NHS Scotland [e-learning modules on ADRs](#)

Download the Yellow Card App:

- [Android](#)
- [Apple](#)

2.0 ANTIMICROBIAL STEWARDSHIP INDICATORS

The development of NPIs for antibiotic prescribing supports two of the Welsh Government's targets for the reduction of healthcare associated infections:

- A 50% reduction in the number of *E. coli* bacteraemia cases by March 2021 against a baseline rate of 2015–2016.
- An overall reduction in inappropriate prescribing of antimicrobials of 50% by 2021.

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 2018–2019: A reduction of 5% against a baseline of data from April 2016–March 2017

Note

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

Table 4. Baseline data: total antibacterial items per 1,000 STAR-PUs 2016–2017⁸⁰⁻⁸³

	June 2016	Sept 2016	Dec 2016	March 2017
Powys	262	248	282	284
Cardiff and Vale	282	273	315	311
Aneurin Bevan	310	292	338	339
Betsi Cadwaladr	310	298	344	335
Hywel Dda	309	301	345	345
ABMU	326	310	356	350
Cwm Taf	326	318	371	372
Wales	308	295	340	337

Figure 10. Trend in total antibacterial items per 1,000 STAR-PUs to quarter ending September 2017

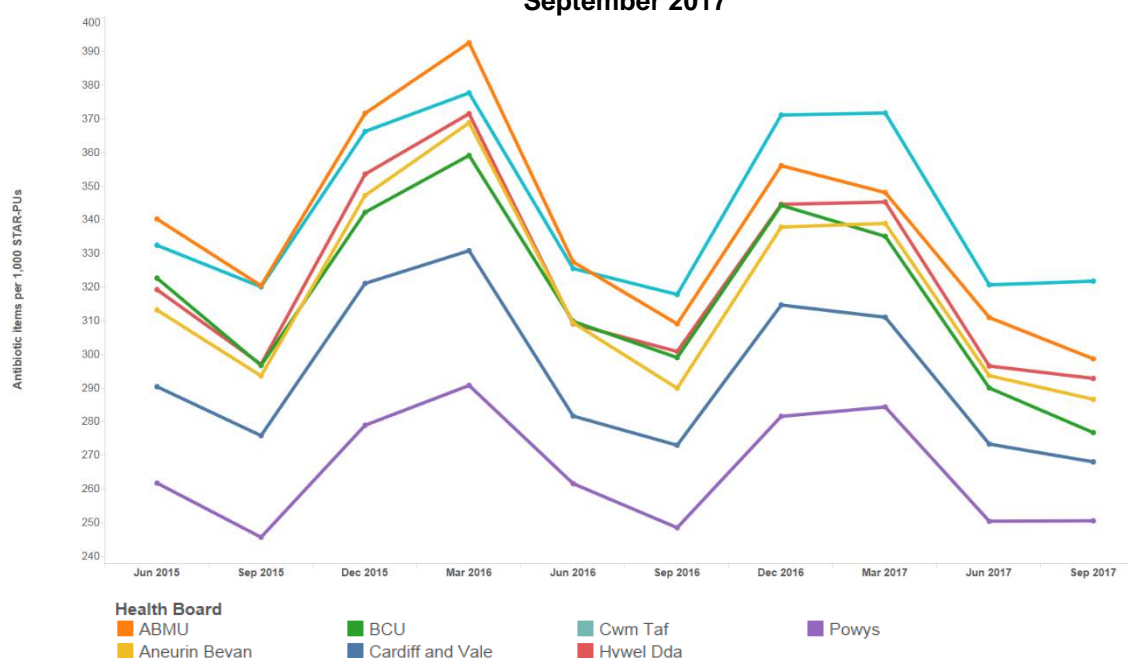
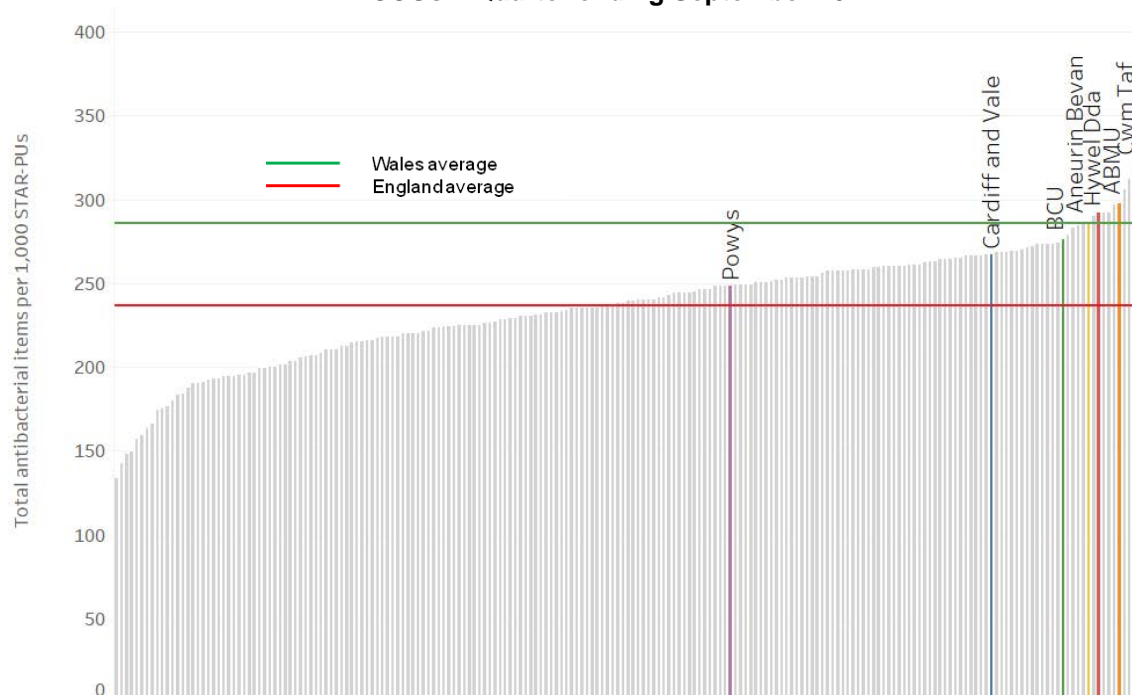


Figure 11. Total antibacterial items per 1,000 STAR-PU's Welsh health boards and English CCGs – Quarter ending September 2017



Background and evidence

Launched in 2016, the Antimicrobial Resistance (AMR) Delivery Plan for 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 research⁸⁴. 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 health care. 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 available⁸⁴.

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, although there has been a marginal reduction in primary care in the last 2 years⁸⁴. This is a step in the right direction; however, variation still exists. For the quarter ending September 2017, primary care prescribing rates varied from 251 to 322 items per 1,000 STAR-PU's across Welsh health boards⁸⁵.

The Public Health Wales report *Antimicrobial Resistance in Wales (2006–2015)* presents the different antimicrobial resistance (AMR) patterns across Wales⁸⁶. The report shows resistance rates in Wales for drug-bug combinations compared with UK aggregate rates, and finds that while there are small differences in some of the resistance rates, generally the trends in resistance are comparable. However, in some cases there is considerable variability in resistance rates between different areas and hospitals within Wales, suggesting an opportunity to reduce antibiotic use in some areas⁸⁶.

NICE Guideline 15 – *Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use* – makes recommendations for organisations on antimicrobial stewardship programmes and teams, antimicrobial stewardship interventions and

communication strategies. 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 also document in the patient's records the reason for prescribing, or not prescribing, an antimicrobial⁸⁷.

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"⁸⁸. The guidance advises when it may be appropriate to consider a broad-spectrum antibiotic.

A Welsh Health Circular in March 2017 set new targets for reducing *C. difficile* and MRSA bacteraemia healthcare-associated infections⁸⁹. To achieve the national target, each health board is currently required to reduce rates to no more than 26 per 100,000 population for *C. difficile* cases, and 20 per 100,000 population for *S. aureus* bacteraemias. There is an expectation that these targets will be met by health boards by March 2018⁸⁹.

2.2 4C ANTIMICROBIALS

Purpose: To encourage a reduction in variation and reduce overall prescribing of the 4C antimicrobials (co-amoxiclav, cephalosporins, fluoroquinolones and clindamycin).

Unit of measure:

Co-amoxiclav, cephalosporin, fluoroquinolone and clindamycin items combined, per 1,000 patients.

Co-amoxiclav, cephalosporin, fluoroquinolone and clindamycin items combined, as a percentage of total antibacterial items.

Target for 2018–2019: Absolute measure $\leq 7\%$ or a proportional reduction of 10% against a baseline of data from April 2016–March 2017.

Note

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

Table 5. Baseline data: 4C antimicrobials per 1,000 patients 2016–2017²²

	June 2016	Sept 2016	Dec 2016	March 2017
ABMU	18.4	17.5	17.8	18.1
Aneurin Bevan	13.8	13.3	13.8	13.4
Betsi Cadwaladr	18.3	17.9	18.4	17.5
Cardiff and Vale	12.1	11.7	11.5	11.2
Cwm Taf	21.1	20.7	21.2	21.1
Hywel Dda	19.5	19.9	19.1	19.7
Powys	13.0	13.3	13.7	12.9
Wales	16.7	16.3	16.5	16.2

Figure 12. Trend in 4C antimicrobial items per 1,000 patients to quarter ending September 2017

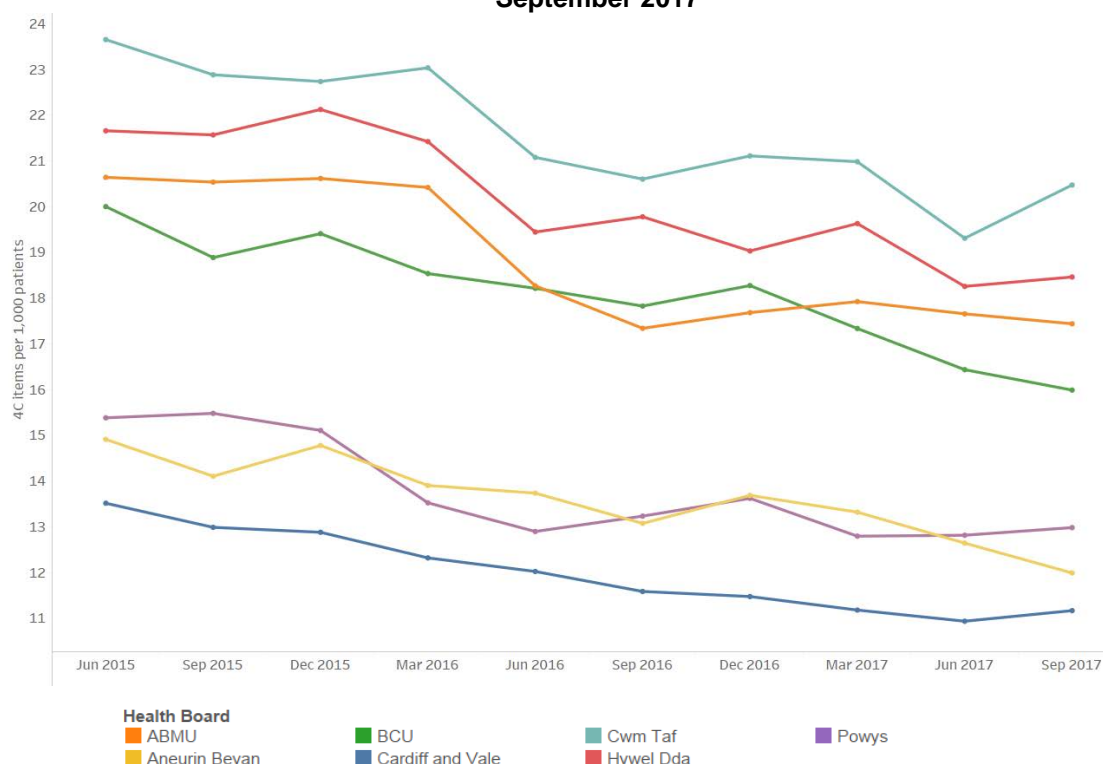


Figure 13. 4C antimicrobial items per 1,000 patients Welsh health boards and English CCGs – Quarter ending September 2017

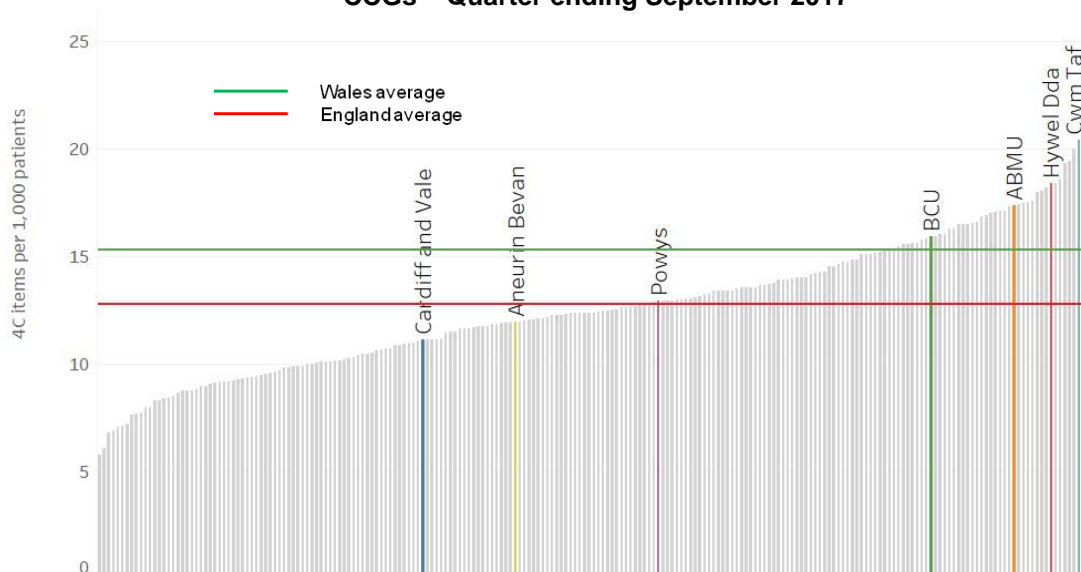


Table 6. Baseline data: 4C antimicrobial items as a percentage of total antibacterial items 2016–2017²²

	June 2016	Sept 2016	Dec 2016	March 2017
ABMU	9.92	9.93	8.75	9.14
Aneurin Bevan	7.87	8.01	7.15	6.97
Betsi Cadwaladr	10.2	10.3	9.14	8.94
Cardiff and Vale	7.9	7.87	6.75	6.63
Cwm Taf	11.6	11.6	10.2	10.1
Hywel Dda	10.7	11.2	9.41	9.68
Powys	8.28	8.91	8.09	7.56
Wales	9.51	9.67	8.46	8.44

Figure 14. Trend in 4C antimicrobial items as a percentage of total antibacterial items to quarter ending September 2017

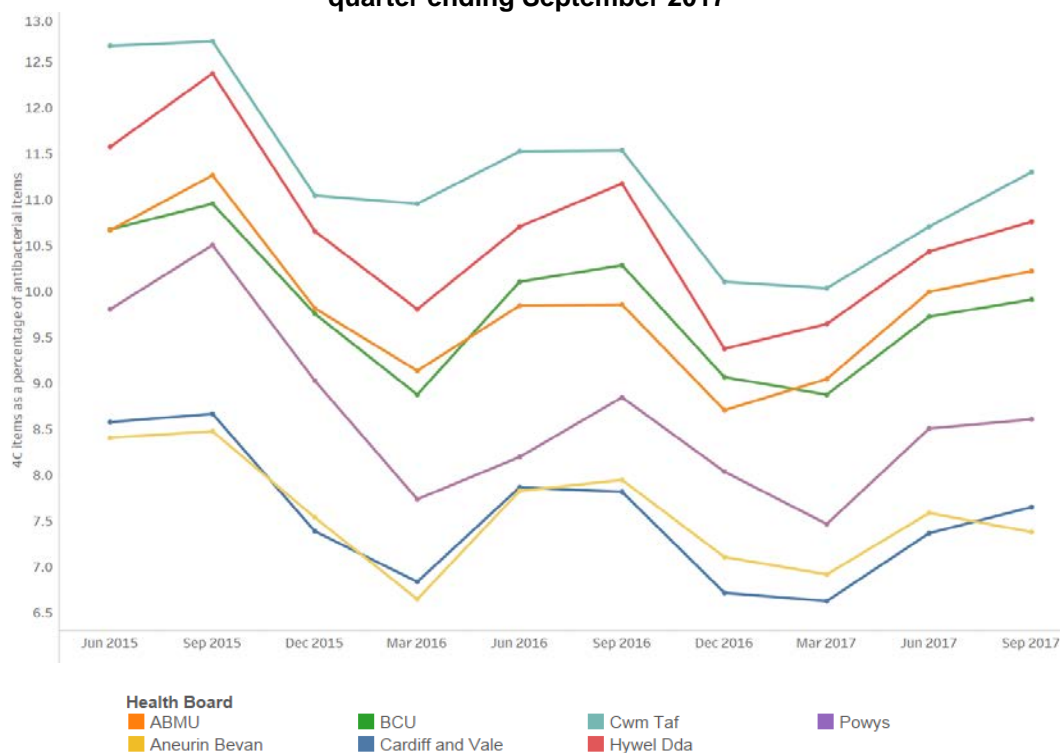
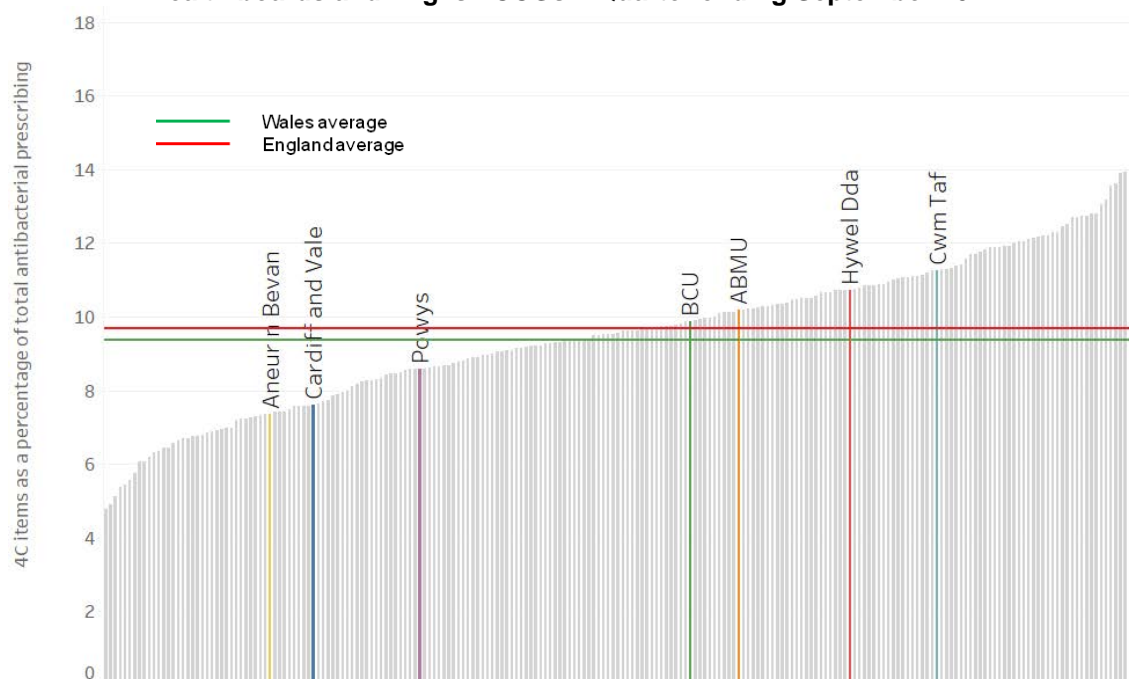


Figure 15. 4C antimicrobial items as a percentage of total antibacterial items Welsh health boards and English CCGs – Quarter ending September 2017



Background and evidence

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 urinary tract infections. 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 established⁹⁰. *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 death⁹⁰. The most commonly implicated antibiotics in *C. difficile* infection include clindamycin, cephalosporins (in particular second and third generation cephalosporins), fluoroquinolones and co-amoxiclav⁹⁰. However, these antimicrobials have a very useful role in specific clinical situations and should be reserved for use as per local guidelines.

2.3 PROPHYLACTIC ANTIBIOTICS IN COLORECTAL SURGERY

Purpose: To encourage appropriate antimicrobial prophylaxis for colorectal surgical patients in secondary care.

Unit of measure: Proportion of elective colorectal patients receiving a single dose antimicrobial for surgical prophylaxis.

Target for 2018–2019: Absolute measure $\geq 90\%$ or a proportional increase of 20% against performance for 2017–2018.

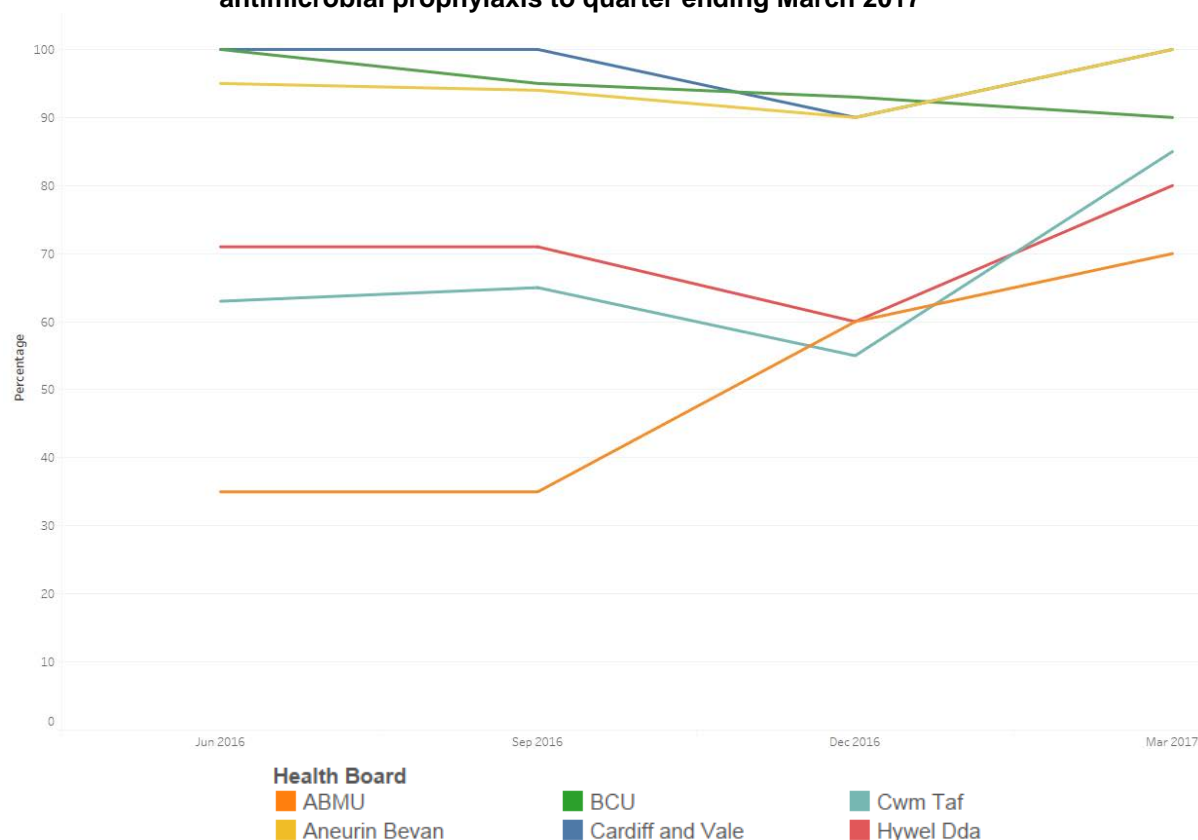
Note

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

Table 7. Baseline data: Percentage of colorectal patients receiving a static dose of antimicrobial prophylaxis

	June 2016	Sept 2016	Dec 2016	March 2017
ABMU	35%	35%	60%	70%
Aneurin Bevan	95%	94%	90%	100%
BCU	100%	95%	93%	90%
Cardiff and Vale	100%	100%	90%	100%
Cwm Taf	63%	65%	55%	85%
Hywel Dda	71%	71%	60%	80%
Powys	N/A	N/A	N/A	N/A
Wales	73%	74%	74%	84%

Figure 16. Trend in the percentage of colorectal patients who receive a static dose of antimicrobial prophylaxis to quarter ending March 2017



Background and evidence

The administration of antibiotic prophylaxis to surgical patients is intended to reduce the incidence of surgical site infection and minimise adverse effects to the patient⁹¹. Antibiotic prophylaxis in surgery is an adjunct to, not a substitute for, good surgical technique and is just one component of an effective policy for the control of healthcare associated infection⁹¹.

Antibiotic prophylaxis should be given to patients before:

- clean surgery involving the placement of a prosthesis or implant
- clean-contaminated surgery
- contaminated surgery⁹²

Antibiotic prophylaxis is not routinely recommended for clean non-prosthetic uncomplicated surgery⁹².

Advice from national organisations, including Public Health Wales, SIGN and NICE, recommends that antibiotic prophylaxis for surgical patients should be a single therapeutic dose of intravenous antibiotics in the majority of cases⁹¹⁻⁹³. This should be administered up to 60 minutes prior to incision to enable peak blood levels to be present at the start of the surgical procedure^{93,94}. A repeat dose of prophylaxis antibiotic is recommended when the operation is longer than the half-life of the antibiotic given⁹³. Certain circumstances, such as prolonged surgery, major blood loss, or specific surgery (e.g. hip arthroplasty), may require a longer course of antibiotic prophylaxis: when a maximum of 24 hours is recommended⁹¹. Any additional prophylactic antibiotic doses should be confirmed and justified in the patient's notes.

In common with therapeutic use, the use of antibiotics for prophylaxis carries a risk of adverse effects (including *C. difficile*-associated diarrhoea) and increased prevalence of antibiotic resistant bacteria. The choice of antibiotic prophylaxis should be influenced by the strength of the association between the antibiotic used and these adverse effects⁹⁵. Therefore, antibiotic choice should minimise *C. difficile* risk whilst ensuring adequate coverage of the expected pathogens for the operative site⁹¹. Antibiotic choice should reflect local, disease-specific information about the common pathogens and their antimicrobial susceptibility⁹¹. Narrow-spectrum, less expensive antibiotics should be the first choice⁹¹.

The data for 2016–2017 indicate that across Wales around 77% of colorectal patients received a static dose of antimicrobial prophylaxis.

Useful resources

- AWMSG (2015) [Primary care antimicrobial guidelines](#)
- AWMSG (2013) [CEPP National Audit: Focus on Antibiotic Prescribing](#)
- Welsh Medicines Resource Centre (WeMeReC) (2012) [Bulletin: Appropriate antibiotic use – whose responsibility?](#)
- Royal College of General Practitioners. [TARGET Antibiotics toolkit](#)
- Public Health Wales (2016) [Antimicrobial Usage in Secondary Care in Wales](#)
- Public Health Wales (2016) [Report on the Point Prevalence Survey of Antimicrobial Prescribing in Secondary Care in Wales](#)
- Public Health Wales (2016) [Antibacterial Resistance in Wales](#)

3.0 EFFICIENCY INDICATORS

3.1 PROTON PUMP INHIBITORS

Purpose: To encourage appropriate use of proton pump inhibitors (PPIs) in primary care.

Unit of measure: DDDs per 1,000 PUs

Target for 2018–2019: Maintain performance levels within the lower quartile, or show a reduction towards the quartile below

Figure 17. Trend in PPI DDDs per 1,000 PUs to quarter ending September 2017

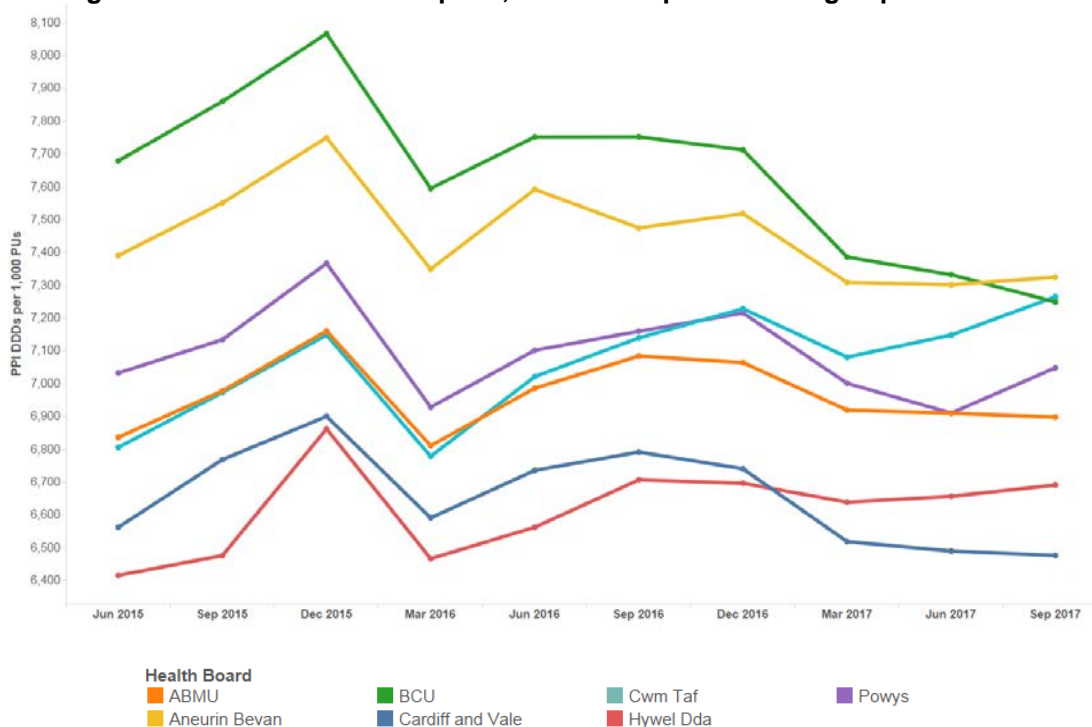
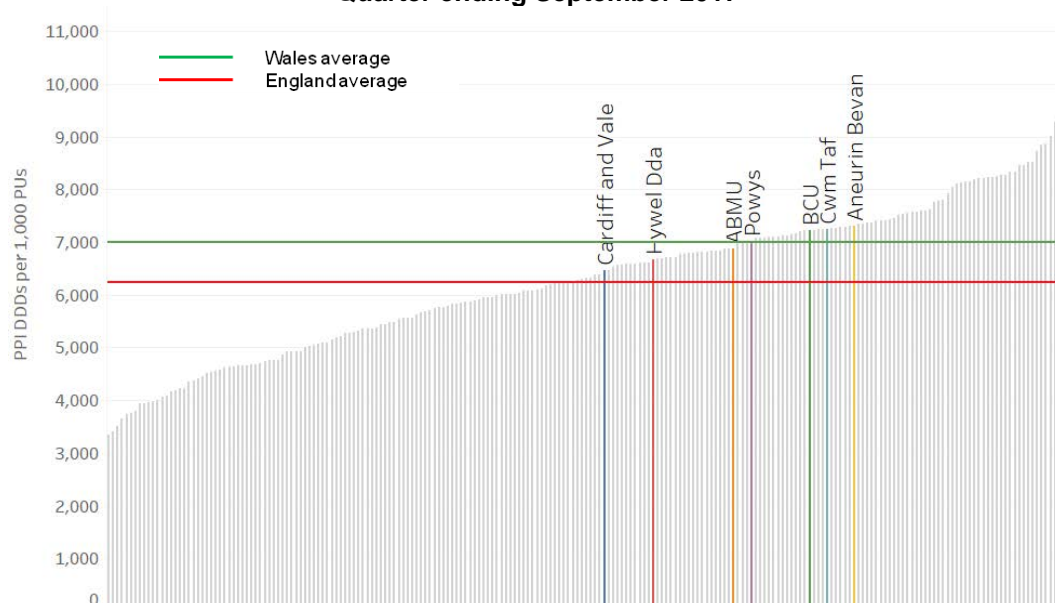


Figure 18. PPI DDDs per 1,000 PUs Welsh health boards and English CCGs Quarter ending September 2017



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^{5,96}.

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 2016–2017, over 4.4 million prescriptions for PPIs were dispensed in Wales²². Assuming each patient received 13 (28-day) prescriptions during the year, this amounts to 338,461 patients (11.2% of the population) receiving PPIs²². 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^{97,98}. Additionally, recommendations on the importance of gastroprotection, particularly for patients on combinations of high-risk medicines, e.g. NSAIDs for the treatment of osteoarthritis⁹⁹ and rheumatoid arthritis (RA)¹⁰⁰, 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 foods⁹⁶. Eating well before bedtime (e.g. 3–4 hours) and raising the head of the bed may also be helpful⁹⁶. 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 prescription⁹⁸. Community pharmacists are well placed to offer initial and ongoing help for people with symptoms of dyspepsia, including over the counter medication, help with prescribed medicines and advice about when to consult a GP.

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' basis⁹⁶, 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 hypomagnesaemia⁹⁸.

A MeReC rapid review highlighted a large observational study, which found that hospitalised patients taking daily PPIs were over 70% more likely to develop *C. difficile* infection than non-users. The review also discussed a second US study, which found that people who already have *C. difficile* infection and are treated with PPIs had a more than 40% increased relative risk of recurrence of infection¹⁰¹. It is advisable to review PPI use in those who are at risk of *C. difficile* infection and, wherever possible, avoid PPIs in those who have had previous episodes of *C. difficile*¹⁰².

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 doses 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 risk¹⁰³. A systematic review 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 PPIs¹⁰⁴.

A second Drug Safety Update in 2012 highlighted reports of patients developing hypomagnesaemia following long-term use of PPIs¹⁰⁵. 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 may be overlooked¹⁰⁵. 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 treatment¹⁰⁵.

Other possible serious adverse effects include acute interstitial nephritis, vitamin B₁₂ deficiency and rebound acid hypersecretion syndrome¹⁰⁶. 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’⁹⁶. 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 date¹⁰². 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 therapy⁹⁶. Patients may be more willing to try self-care to improve their symptoms if they are aware of the potential long-term effects of PPIs⁹⁸.

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-morbidities⁹⁸.

Useful resources

- AWMSG (2018) [Safe Use of Proton Pump Inhibitors](#)
- AWMSG (2014) [Polypharmacy: Guidance for Prescribing](#)
- WeMeReC (2015) [Proton pump inhibitors bulletin](#)
- PrescQIPP (2015) [Bulletin 92: Safety of long term PPIs](#)

3.2 BIOSIMILARS

Purpose: To ensure prescribing of biological medicines supports cost-effective prescribing in Wales.

Unit of measure: Quantity of biosimilar medicines prescribed as a percentage of total 'reference' product plus biosimilar.

Target for 2018–2019: Increase the appropriate use of cost-effective biological medicines, including biosimilar medicines.

Table 8. Reference and biosimilar usage percentages

	2016–2017				2017–2018
	Q1	Q2	Q3	Q4	Q1
Infliximab reference	59.8	53.9	47.3	43.5	40.8
Infliximab biosimilar (Inflectra[®]▼)	40.2	46.1	52.7	56.5	59.2
Insulin glargine reference	99.4	98.9	98.2	97.5	97.4
Insulin glargine biosimilar (Abasaglar[®]▼)	0.56	1.12	1.84	2.49	2.64
Etanercept reference	97.0	92.5	80.9	61.7	49.8
Etanercept biosimilar (Benepali[®]▼)	2.97	7.45	19.1	38.3	50.2

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')¹⁰⁷. As the 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 differences¹⁰⁷⁻¹⁰⁹.

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, it seems an appropriate time to consider the pattern of prescribing across NHS Wales¹⁰⁸.

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 with appropriate monitoring in place. The NHS England publication "What is a biosimilar medicine?" provides supportive information for the use of biosimilar medicines¹⁰⁹.

The MHRA recommends that biological medicines, including biosimilar medicines, are prescribed by brand name to avoid any potential confusion¹¹⁰. For example, the reference biological medicine of insulin glargine has two available brand names dependent upon which strength is prescribed, the 100 units per ml or the 300 units per ml product. Prescribing by brand name also supports the on-going pharmacovigilance of individual biological products. At the time of dispensing a biological medicine, there should be no automatic substitution with a biosimilar alternative.

Where AWMSG or NICE has already recommended the 'reference' biological medicine, the same guidance will normally apply to a biosimilar of the 'reference'. However, where a review of the evidence for a biosimilar medicine is considered necessary, AWMSG and/or NICE will consider producing a further evidence summary¹¹¹. The list of biological medicines being reported 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 within the NPI in 2018–2019 are:

- Infliximab – Inflectra®▼
- Etanercept – Benepali®▼
- Rituximab – Truxima®▼
- Insulin glargine – Abasaglar®▼

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 MHRA¹⁰⁹.

Anticipated benefits

The appropriate use of cost-effective biological medicines, including biosimilar medicines, will drive greater competition to release cost efficiencies to support the treatment of an increasing number of patients and the uptake of new and innovative medicines¹⁰⁹. Biosimilar data will be reported for the selected individual biological medicines as well as an overall usage.

The use of biosimilar medicines in place of the 'reference' biological medicine could be associated with cost savings. It should be noted that individual health board contracting prices, as well as national contracting prices, for biosimilar medicines and reference products may vary, which will impact on any 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-effective 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.

In the period April 2016–March 2017, the proportion of infliximab prescribed as the biosimilar medicine (Inflectra®) was 49.3%. In the same period the proportion of etanercept prescribed as the biosimilar (Benepali®) was 17.8%. For Abasaglar®, the biosimilar of insulin glargine, the usage is lower at 1.51%; however, usage has shown an upward trend during 2016–2017.

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 something that is being worked on within NHS Wales as a priority, for the time being some medicines use reports may be incomplete.

Useful resources

- NHS England (2015) [What is a biosimilar medicine?](#)

3.3 INSULIN

Purpose: To encourage a reduction in the prescribing of long-acting insulin analogues in line with NICE guidance to maximise cost-effectiveness in Wales.

Unit of measure: Items/number of long-acting insulin analogues expressed as a percentage of total long- and intermediate-acting insulin prescribed in primary and secondary care.

Aim for 2018–2019: To reduce prescribing of long-acting insulin analogues and to achieve prescribing levels below the Welsh average.

Table 9. Use of long-acting insulin analogues as a percentage of long- and intermediate-acting insulin in primary and secondary care across NHS Wales for 2016–2017

	2016–2017				2017–2018
	Q1	Q2	Q3	Q4	Q1
Percentage of long-acting insulin analogues (primary care)	89.7	89.8	89.7	89.2	88.9
Percentage of long-acting insulin analogues (secondary care)	78.4	77.7	73.7	73.2	72.7

1.1 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 people¹¹².

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}])¹¹³. 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 advised¹¹³.

A 2017 observational study concluded that compared with NPH insulin, long-term use of insulin glargine was associated with an increased risk of breast cancer in women with type 2 diabetes. The risk associated with insulin detemir was not significantly elevated; however, due to its more recent introduction to the UK market, further studies are needed to evaluate any similar relationship¹¹⁴.

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 treatment¹¹². 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 professional¹¹².

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 diabetes¹¹⁵. 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 diabetes¹¹⁶, the prescribing data indicates that long-acting insulin analogues are being widely used to manage type 2 diabetes²².

Despite the recommendations outlined in NG28, the prescribing cost for long-acting insulin analogues was approximately £9.2 million across NHS Wales in 2016–2017²².

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 2016–2017 was 89.6%; this is a slight decrease from the previous year (89.9%)²².

In secondary care, the proportion of long-acting insulin analogues prescribed as a percentage of total long- and intermediate-acting insulin was 76.0% (April 2016–March 2017). This is a decrease from the previous year (77.3%)¹¹⁷.

1.2 Costs and cost savings

As diabetes accounts for 10% of the NHS costs, and the number of diabetic patients continues to increase, any opportunities for cost savings are likely to have a significant impact on NHS Wales. 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 medicines¹¹⁸.

A report highlighting the cost of diabetes medicines suggests that £725 million was spent on diabetes medicines in the UK in 2010–2011 and, of this, £269 million was on basal analogue insulins¹¹⁹. Holden and colleagues 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 million¹¹⁸.

Useful resources

- NICE (2015) [NG28: Type 2 diabetes in adults: management](#)
- Cochrane (2007) [Long-acting analogues versus NPH insulin](#)

APPENDIX 1. ANTICHOLINERGIC EFFECT ON COGNITION (AEC) SCORE¹⁷

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

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

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