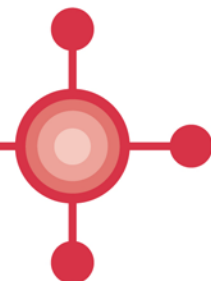


All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan



National Prescribing Indicators 2017–2018

February 2017

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 way 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, 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. 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.

Setting

Traditionally, NPIs have been set to compare prescribing in primary care, as accurate prescribing data are available, and standardised targets can be set. However, the principles and evidence base supporting the NPIs have always been applicable to all care settings.

For 2016–2017, NPIs specific to secondary care were developed and introduced, and these will continue in 2017–2018.

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 2016–2017 NPIs and discuss potential additional NPIs for 2017–2018.

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 2016–2017 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:

- Introduction of two new NPIs to be monitored via Audit+:
 - Anticholinergic Effect on Cognition
 - NSAIDs in CKD
- Introduction of a new NPI to be monitored via CASPA
 - Opioid patches
- Change of inhaled corticosteroid (ICS) NPI measure from low-strength to high-strength ICS items as a percentage of all ICS prescribing.
- Retirement of two NPIs:
 - Lipid-regulating drugs: Items of bile acid sequestrants, fibrates, nicotinic acid and omega-3 fatty acid compounds as a percentage of total lipid-regulating items
 - NSAIDs: Ibuprofen and naproxen as a percentage of all NSAID prescribing
- Change of title for the antibiotic indicators to 'Antimicrobial Stewardship'.

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 CASPA.net, SPIRA or Medusa.
- The ADQ and STAR-PU measurements are used for certain indicators instead of the DDD measurement and PU weighting, despite not being available on CASPA.net, in order to benchmark with the 'Medicines Optimisation Key Therapeutic Topics' (MO KTT) comparators in England. These data are available on a quarterly basis through the NHS Wales Shared Services Partnership: Primary Care Services.
- Audit+ will provide data on the anticholinergic burden and NSAIDs in CKD NPIs. Data will be accessed by the Welsh Analytical Prescribing Support Unit (WAPSU) at a health board, locality and cluster level.
- Yellow Card Centre (YCC) Wales will monitor Yellow Card reporting by GP practice, providing feedback at health board and practice level.
- Secondary care measures will be monitored using mainly the Medusa data warehouse. CASPA data will also be reported for some measures as secondary care prescribing decisions can significantly influence primary care prescribing.

Targets

Primary care NPI targets should be challenging but achievable, and based on the principle of encouraging all health boards, local cluster groups and practices to achieve prescribing rates in the best quartile. The target is therefore not an absolute value and can be achieved if there is movement towards the threshold set.

- The threshold is based on prescribing data for all general practices in Wales.
- For each NPI, the threshold will normally be set at the 75th percentile, (i.e. the prescribing rate of the best performing 25% of practices) for the quarter ending 31 December 2016.
- The target may be to achieve movement to the highest prescribing quartile or the lowest prescribing quartile depending on the aim of the NPI.
- One NPI has been included without a target – Antimicrobial Stewardship: total antibacterial items. Seasonal variation prevents a target being set based on prescribing in any one particular quarter; however, year on year prescribing will be monitored, aiming for a reduction in prescribing.

Targets are not currently set for the NPIs in secondary care, as it is not possible to weight the prescribing data. However, where appropriate and relevant, monitoring of prescribing will be undertaken to ensure the principle and evidence base supporting the NPI is considered and implemented in all settings.

Table 1 details the NPIs for 2017–2018, with units of measure and targets for 2017–2018.

Table 1. AWMMSG NPIs 2017–2018

Primary Care Indicator	Unit of measure	Target for 2017–2018
Proton pump inhibitors (PPIs)	PPI DDDs per 1,000 PUs	Maintain performance levels within the lower quartile, or show a reduction towards the quartile below
Inhaled corticosteroids (ICS)	High strength ICS items as a percentage of all ICS prescribing	Maintain performance levels within the lower quartile, or show a reduction towards the quartile below
Hypnotics and anxiolytics	Hypnotic and anxiolytic ADQs per 1,000 STAR-PUs	Maintain performance levels within the lower quartile, or show a reduction towards the quartile below
Analgesics	Tramadol DDDs per 1,000 patients	Maintain performance levels within the lower quartile, or show a reduction towards the quartile below
	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
	Gabapentin and pregabalin DDDs per 1,000 patients	Maintain performance levels within the lower quartile, or show a reduction towards the quartile below
Antimicrobial stewardship	Total antibacterial items per 1,000 STAR-PUs	No performance target set; aim for reduction in prescribing year on year, measuring quarter to December only
	Co-amoxiclav items per 1,000 patients Co-amoxiclav items as a percentage of total antibacterial items	Maintain performance levels within the lower quartile, or show a reduction towards the quartile below
	Cephalosporin items per 1,000 patients Cephalosporin items as a percentage of total antibacterial items	Maintain performance levels within the lower quartile, or show a reduction towards the quartile below
	Fluoroquinolone items per 1,000 patients Fluoroquinolone items as a percentage of total antibacterial items	Maintain performance levels within the lower quartile, or show a reduction towards the quartile below
Anticholinergic burden	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	Maintain performance levels within the lower quartile, or show a reduction towards the quartile below
Non-steroidal anti-inflammatory drugs (NSAIDs)	NSAID ADQs per 1,000 STAR-PUs	Maintain performance levels within the lower quartile, or show a reduction towards the quartile below
	Number of patients on the CKD register (CKD 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	Maintain performance levels within the lower quartile, or show a reduction towards the quartile below
	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	
Yellow Cards	Number of Yellow Cards submitted per practice and per health board	Target for GP practice – submit one Yellow Card per 2,000 practice population Target for each health board – submit Yellow Cards in excess of one per 2,000 health board population

Secondary Care Indicator	Unit of measure	Aim for 2017–2018
Insulin prescribing	Items/number of long-acting insulin analogues expressed as a percentage of total insulin prescribed within primary and secondary care	Reduce prescribing of long-acting insulin analogues and achieve prescribing levels below the Welsh average
Prescribing of biosimilars	Quantity of biosimilar medicines prescribed as a percentage of total 'reference' product plus biosimilar	Increase the appropriate use of biosimilar medicines in line with guidance
Antibiotic surgical prophylaxis	Proportion of elective colorectal patients receiving surgical prophylaxis for more than 24 hours	Maintain performance below the Welsh average (PPS data) or show a reduction towards the Welsh average

Evidence

The evidence and supporting prescribing messages are outlined in the body of the document, and prescribing data, where available, to support the NPIs for 2017–2018, are contained within Appendices 1 and 2.

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 making¹.

PRIMARY CARE

1.0 PROTON PUMP INHIBITORS

Purpose: To encourage appropriate use of PPIs.

Unit of measure: PPI DDDs per 1,000 PUs.

Target for 2017–2018: Maintain performance levels within the lower quartile, or show a reduction towards the quartile below.

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^{2,3}.

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.

PPI use (measured in DDDs) is continuing to increase across Wales at a rate of almost 4% per year⁴. In the financial year 2015–2016, over 4.4 million prescriptions for PPIs were dispensed in Wales⁴. Assuming each patient received 13 (28-day) prescriptions during the year, this amounts to 338,461 patients (11.2% of the population) receiving PPIs⁴. 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 reduction in cost, with patent expiry, has led to more liberal usage of PPIs for a wide variety of upper gastrointestinal (GI) symptoms^{5,6}. Additionally, recommendations on the importance of gastroprotection, particularly for patients on combinations of high-risk medicines, e.g. NSAIDs for the treatment of osteoarthritis⁷ and rheumatoid arthritis (RA)⁸, 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 associated with dyspepsia such as alcohol, coffee, chocolate and fatty foods. Eating well before bedtime (e.g. 3–4 hours) and raising the head of the bed may also be helpful². 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 prescription⁶.

If medication is required, first-line treatment should be with an alginate either 'as required' or regularly. 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' basis².

PPIs are generally well tolerated, with a low incidence of short-term side-effects including headache, diarrhoea, nausea, abdominal pain, constipation, dizziness and skin rashes. There is, however, increasing evidence regarding the potential consequences of long-term treatment with PPIs, including *Clostridium difficile* infection, increased risk of bone fractures and increased mortality in older patients⁶.

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 infection⁹.

In 2012, the Medicines and Healthcare products Regulatory Agency (MHRA) issued a Drug Safety Update regarding the increased risk of fracture associated with long-term use of PPIs. It noted that patients at risk of osteoporosis should be treated according to current clinical guidelines to ensure they have an adequate intake of vitamin D and calcium¹⁰.

A second Drug Safety Update in 2012 highlighted reports of patients developing hypomagnesaemia following long-term use of PPIs¹¹. A review of case reports found that hypomagnesaemia occurred most commonly after one year of PPI treatment, and presented with fatigue, tetany, delirium, convulsions, dizziness, and ventricular arrhythmia¹¹. 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 treatment¹¹.

Other possible serious adverse effects include acute interstitial nephritis, vitamin B₁₂ deficiency and rebound acid hypersecretion syndrome¹². 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'¹². There is a lack of strong evidence to support the association between these adverse effects and long-term PPI use; however, the association is biologically plausible¹².

When these 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-morbidities⁶.

It is therefore recommended that all patients receiving a PPI should be offered an annual review and are encouraged to step down from treatment doses where appropriate¹³. Stepping down may involve a lower dose, as-required dosing, or changing to an antacid and/or alginate preparation¹⁴. Tapering the dose of the PPIs in patients who have been taking them for a long period of time is recommended to reduce the risk of rebound hypersecretion¹³; in addition, reassuring patients on how to manage this with simple antacids might avoid the re-initiation of the PPI. Patients may be more willing to try self-care to improve their symptoms if they are aware of the potential long-term effects of PPIs⁶.

Useful resources

- WAPSU (2013) [All Wales PPI and Dyspepsia Resource Pack](#)
- AWMSG (2014) [Polypharmacy: Guidance for Prescribing](#)
- WeMeReC (2015) [Proton pump inhibitors bulletin](#)
- PrescQIPP (2015) [Bulletin 92: Safety of long term PPIs](#)

2.0 INHALED CORTICOSTEROIDS

Purpose: To encourage the routine review of ICS in people with asthma, particularly those on high doses, encouraging step down of the dose when clinically appropriate.

Unit of measure: High-strength ICS* items as a percentage of all ICS prescribing.

Target for 2017–2018: Maintain performance levels within lower quartile, or show a reduction towards the quartile below.

*High-strength ICS: As per the SIGN categorisation of ICS by dose – adults¹⁵ (see Appendix 3 for the specific basket of medicines to be monitored).

Background and evidence

This NPI focuses on use of ICS in asthma; however, prescribing data obtained from CASPA do not differentiate between the indications for ICS, namely asthma and chronic obstructive pulmonary disease (COPD). Quality and Outcomes Framework (QOF) data from 2015–2016 show that the prevalence of asthma in Wales is 6.9%, and the prevalence of COPD is 2.2%¹⁶. Prevalence data therefore suggest that the majority of ICS prescribed in Wales should be for the management of asthma. In Wales, almost 1.7 million primary care ICS prescriptions were dispensed in the financial year to the end of March 2016, costing NHS Wales £54.5 million⁴.

Until May 2009, all doses of ICS were referenced against beclometasone dipropionate (BDP) given via chlorofluorocarbon metered dose inhalers (CFC-MDIs). BDP-CFC is now unavailable, therefore doses of ICS are expressed as very low (generally paediatric dose), low (generally starting dose for adults), medium and high¹⁵.

Low-dose or very low-dose ICS is the first-choice regular preventer therapy for adults and children with asthma for achieving overall treatment goals¹⁵. ICS should be considered for adults, children aged 5–12 and children under the age of five with any of the following features: using inhaled β_2 agonists three times a week or more; symptomatic three times a week or more; or waking one night a week. In addition, ICS should be considered in adults and children aged 5–12 who have had an asthma attack requiring oral corticosteroids in the last two years¹⁵. Patients should be started at a dose of ICS appropriate to the severity of disease. A reasonable starting dose of ICS will usually be low dose for adults and very low dose for children. To minimise side effects from ICS in people with asthma, the *British guideline on the management of asthma* recommends that the dose of ICS should be titrated to the lowest dose at which effective control of asthma is maintained¹⁵.

The *British guideline on the management of asthma* advocates considering a dose reduction every 3 months, decreasing the dose by approximately 25–50% each time, thereby moving along the treatment pathway to find and maintain the lowest controlling therapy¹⁵. Despite this being a recommendation, it is often not implemented leaving some patients overtreated¹⁵.

A proportion of patients may not be adequately controlled with low-dose ICS alone. Before initiating a new drug therapy practitioners should check adherence with existing therapies, check inhaler technique and eliminate trigger factors¹⁵. Many patients will benefit more from add-on therapy than from increasing ICS above doses as low as 200 micrograms BDP/day. At doses of ICS above 800 micrograms BDP/day side effects become more frequent. An absolute threshold for introduction of add-on therapy in all patients cannot be defined¹⁵.

NICE TA138, on ICS for the treatment of chronic asthma in adults and children aged 12 years and over, recommends that where an ICS and a long-acting beta-2 agonist (LABA) are both indicated, a combination inhaler used within its marketing authorisation would be appropriate¹⁷. In clinical practice it is generally considered that combination inhalers aid adherence and also have the advantage of guaranteeing that the LABA is not taken without the ICS¹⁵.

Retrospective prescribing data for 685 people with asthma in 46 general practice surgeries in Scotland were analysed in a 2013 study. The authors found that initiating combination ICS plus LABA therapy resulted in widespread increases in ICS dose¹⁸. ICS dose, before moving to a combination inhaler, was compared to the dose in the newly prescribed combination inhaler. The average increase in ICS dose was about 54%. Many people received a high-dose combination inhaler regardless of their baseline ICS dose. The authors suggest the need for evaluation of the appropriateness of high-dose ICS prescribing in primary care¹⁸. The study also raises the question of whether there is sufficient awareness regarding ICS doses in the different combination preparations¹⁸.

NICE CG101 on COPD in over 16s recommends that ICS should only be considered in combination with a LABA in patients with stable COPD who remain breathless or have exacerbations despite using short-acting bronchodilators¹⁹.

The *British guideline on the management of asthma* notes that high doses of ICS should only be used after referring the patient to secondary care¹⁵. Draft NICE guidance on the management of chronic asthma recommends considering increasing the dose of ICS to a high maintenance dose only where asthma is uncontrolled in adults on a moderate maintenance ICS dose with LABA, either as maintenance and reliever therapy (MART) or a fixed-dose regimen, and with or without a leukotriene receptor antagonist (LTRA)²⁰.

In 2006, the MHRA advised that the prolonged use of high-dose ICS carries a risk of systemic side effects, such as adrenal suppression or crisis, growth retardation in children and young people, decrease in bone mineral density, cataracts and glaucoma²¹. The MHRA advises that in addition to these known systemic side effects, the prolonged use of high doses of ICS carries the risk of a range of psychological or behavioural effects (e.g. psychomotor hyperactivity, sleep disorders, anxiety, depression and aggression)²². The Committee on Safety of Medicines (CSM) issued advice on the risk of adrenal suppression with the use of high-dose ICS, particularly in children and in relation to fluticasone propionate²³.

Use of ICS has long been associated with an increased risk of pneumonia. A review conducted by the European Medicines Agency (EMA) in 2016 confirmed the risk of pneumonia with ICS in patients with COPD, but did not find any conclusive evidence of differences in risk between different inhaled corticosteroids²⁴. The review noted that there is some evidence of an increased risk of pneumonia with increasing steroid dose, but this was not demonstrated conclusively across all studies. Overall, the benefits of ICS in treating COPD continue to outweigh their risks²⁴.

The *British guideline on the management of asthma* and NICE quality standard on asthma state that inhalers should only be prescribed after patients have received training in the use of the device and have demonstrated satisfactory technique^{15,25}. In addition, generic prescribing of inhalers should be avoided as this might lead people to being given an unfamiliar inhaler device which they are not able to use properly¹⁵.

Useful resources

- SIGN (2016) [SIGN 153: British guideline on the management of asthma](#)
- NICE (2010) [CG101: Chronic obstructive pulmonary disease in over 16s: diagnosis and management](#)

3.0 HYPNOTICS AND ANXIOLYTICS

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

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

Target for 2017–2018: Maintain performance levels within the lower quartile, or show a reduction towards the quartile below.

Background and evidence

There has been concern with regard to the high level of hypnotic and anxiolytic prescribing within NHS Wales, with the substance misuse strategy of the Welsh Government (*Working together to reduce harm*) calling for the reduction of inappropriately prescribed benzodiazepines²⁶. 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 six out of seven health boards in Wales within the highest prescribing quartile when compared to clinical commissioning groups (CCGs) in England^{4,27}.

In the financial year 2015–2016, the number of items dispensed was 1,401,094, compared with 1,456,026 the previous year: a reduction of 3.8% (total quantity of tablets reduced by 6.1% from 39,322,721 to 36,928,281 for the same period)⁴.

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 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 distress²⁸. NICE guidance on short-term management of insomnia also advises that if, after non-drug therapies have been explored, hypnotics are considered, they should be used in the lowest dose possible for the shortest duration possible in strict accordance with their licensed indications²⁹: 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 crises³⁰.

Benzodiazepine hypnotics and anxiolytics are known to significantly increase risk of falls³¹. NICE Clinical Knowledge Summary: Falls – risk assessment, advises reviewing psychoactive drugs, such as benzodiazepines, in patients at high risk of falls³².

More recently, there has been 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 used³³. Another observational study suggested benzodiazepines increase the risk of dementia³⁴. However, a 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 exposure³⁵.

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. This may be via consultation or by letter; both have been used successfully in practices within Wales.

Useful resources

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

4.0 ANALGESICS

4.1 Purpose: To encourage the appropriate use and review of tramadol, minimising the potential for diversion and misuse.

Unit of measure: Tramadol DDDs per 1,000 patients.

Target for 2017–2018: Maintain performance levels within lower quartile, or show a reduction towards the quartile below.

4.2 Purpose: To encourage the appropriate use and review of opioid patches.

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

Target for 2017–2018: Maintain performance levels within lower quartile, or show a reduction towards the quartile below.

4.3 Purpose: To encourage the appropriate use and review of gabapentin and pregabalin, minimising the potential for diversion and misuse.

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

Target for 2017–2018: 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.

Background and evidence

Pain is an unpleasant sensory and emotional experience that can have a significant impact on a person's quality of life. Acute pain can occur as a result of trauma, surgery or an acute illness, and chronic or persistent pain has historically been defined as occurring when pain has been present for three months or more. However, it is now recognised that persistent pain can present as a complex problem before this time³⁶. Persistent pain is common, affecting around 14 million people in the UK³⁷; this equates to over 600,000 people in Wales³⁸.

The term 'persistent non-malignant pain' can be used to refer to a wide range of painful conditions affecting patients physically, psychologically and socially. These conditions can have a significant impact on quality of life and the ability of patients to undertake everyday activities³⁹. Opioid analgesics 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 dependence⁴⁰. 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 term⁴¹.

Persistent pain is becoming an increasingly significant problem as pain prevalence increases, for example with ageing and with more cancer survivors and trauma survivors³⁶. Unrelieved persistent pain is a major socio-economic burden for the health service and the community³⁶.

4.1 Tramadol

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 pathways³. It has fewer of the typical opioid side effects, e.g. less respiratory depression and constipation, but psychiatric reactions have been reported³. The unique dual-action pharmacological profile of tramadol increases the risk of adverse effects seen in overdose⁴².

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 tramadol⁴². The changes came into force in June 2014. Deaths involving tramadol in England and Wales fell for the first time, from 240 deaths in 2014 to 208 in 2015, marking a reversal of the upward trend seen since the first recorded death in 1966⁴³.

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 effects⁴⁴. Hallucinations, confusion and convulsions, as well as rare cases of dependence and withdrawal symptoms, have been reported with tramadol at therapeutic doses⁴⁵.

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 so⁴⁶. 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)⁴⁶. 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 inhibitors⁴⁴.

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. 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 by 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 required⁴⁷.

The NPI does not measure the prescribing of Tramacet[®] (tramadol/paracetamol combination) as there are no DDDs available. Tramacet[®] accounts for 1.4% of all tramadol prescribed (quarter 1 2016–2017)⁴. 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.

4.2 Opioid patches

Fentanyl and buprenorphine are currently available as transdermal patches in several different brands and formulations, with different licensed indications⁴⁸⁻⁵⁰. As a number of safety concerns around the use of opioid patches have been highlighted⁵¹⁻⁵³, 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 choice¹³. NICE Clinical Guideline 140 recommends oral sustained-release morphine as first-line maintenance treatment for patients who require strong opioids in palliative care⁵⁴. 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 dose³.

Opioid patches are recommended as a treatment option only where analgesic requirements are stable and where oral opioids are unsuitable⁵⁴. Opioid patches should be reserved for patients who are unable to tolerate the side effects of oral morphine, have difficulty swallowing, or have compliance issues⁵⁵. In addition, fentanyl, and buprenorphine (as well as alfentanil) are the safest opioids for use in renal impairment⁵⁶. 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, ensuring that patients are monitored for signs of toxicity⁵⁶.

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 pain³. A 25 microgram per hour fentanyl patch equates to a daily dose of oral morphine of up to 90 mg⁵⁵. 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 patients⁵³. Fentanyl patches should only be used in patients who have previously tolerated opioids, because of the risk of significant respiratory depression in opioid naive patients⁵³, 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 pain³. A 52.5 microgram per hour buprenorphine patch equates to a daily dose of oral morphine of up to 90 mg⁵⁵. 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 opioids⁵⁷. 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 source⁵¹. A second Drug Safety Update was issued in 2014 again highlighting the risks of accidental exposure⁵². 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 plasters⁵³. AWMSG has produced a counselling checklist for users of opioid patches⁵⁸. 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 initiated⁵⁴. This NPI promotes a prudent approach to prescribing opioid patches, taking into account the risks and benefits and encouraging timely review.

4.3 Gabapentin and pregabalin

Neuropathic pain is common and can have a significant impact on quality of life. It is often difficult to treat because the causes are complex and diverse.

NICE recommends amitriptyline, duloxetine, gabapentin or pregabalin as first-line treatment options for neuropathic pain⁵⁹. Amitriptyline does not have a UK marketing authorisation for this indication, duloxetine is licensed for diabetic peripheral neuropathic pain only, and gabapentin is licensed for peripheral neuropathic pain only, so use for other conditions would be off-label. In addition, the Lyrica® (Pfizer) brand of pregabalin has patent protection until July 2017 for its licensed indication of treatment of peripheral and central neuropathic pain; until such time as this patent expires, generic pregabalin products will not be licensed for this indication and their use for this condition would be off-label and may infringe the patent⁵⁹. Gabapentin is also licensed for use in epilepsy^{60,61}, and all brands of pregabalin are licensed for the treatment of generalised anxiety disorder and epilepsy in adults⁶²⁻⁶⁴.

CG173 does not recommend one particular medicine as superior to the others. The choice of treatment should be made on an individual basis and NICE recommends taking into account pain severity and how it affects the person's daily activities, the underlying cause of pain, comorbidities, concurrent medications and vulnerability to adverse effects when agreeing a treatment plan with the patient⁵⁹. Pregabalin is less cost-effective than gabapentin and amitriptyline⁵⁹, and SIGN 136: *Management of chronic pain* recommends pregabalin (Lyrica® brand) for the treatment of patients with neuropathic pain only if other first and second line pharmacological treatments have failed⁶⁵.

After starting or changing a treatment for neuropathic pain, NICE CG173 recommends early clinical review of dosage titration, tolerability and adverse effects to assess suitability of the chosen treatment. 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 need⁵⁹. If the patient has not shown sufficient benefit within eight weeks of reaching the maximum tolerated dose, gabapentin and pregabalin should be reduced gradually over a minimum of one week and stopped, except when moving to combination therapies⁶⁶.

NICE recommends considering gabapentin for the treatment of spasticity and oscillopsia in multiple sclerosis⁶⁷. However, gabapentin does not have a UK marketing authorisation for this indication⁶⁸.

Both gabapentin and pregabalin have known psychiatric side effects^{61,62,69,70}. For pregabalin, the incidence of euphoria is common ($\geq 1/100$ to $< 1/10$) and the incidence of hallucinations is uncommon ($\geq 1/1,000$ and $< 1/100$)⁶². The SPC for gabapentin lists hallucinations as a side effect, although the incidence is unknown⁶⁰.

Caution should be exercised in prescribing pregabalin for patients with a history of substance abuse⁶²⁻⁶⁴. 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 the appropriate prescribing to minimise these risks⁷¹. A Welsh Health Circular issued in July 2016 also noted the potential for misuse of these medicines and provided suggestions for balanced and rational use⁷². 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 prescription⁷¹.

The number of drug-related deaths involving gabapentin or pregabalin in England and Wales is increasing; from 48 deaths for both gabapentin and pregabalin in 2013⁷³ to a total of 137 deaths in 2015⁷⁴.

Prescribing of gabapentin and pregabalin in Wales is high in comparison to England (1,321 DDDs/1,000 patients compared to 1,026 DDDs/1,000 patients, for the quarter ending September 2016)^{4,27} and primary care DDDs/1,000 patients are currently increasing at a rate of approximately 15% per year in Wales⁴.

Neuropathic 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 gabapentin and pregabalin, taking into account the risks and benefits of these medicines and encouraging timely review.

Useful resources

- AWMSG (2016) [Safeguarding Users of Opioid Patches by Standardising Patient/Caregiver Counselling](#)
- AWMSG (2016) [Persistent pain resources](#)
- PrescQIPP (2014) [Opioid patches](#)
- PrescQIPP (2014) [Pregabalin in neuropathic pain](#)
- Public Health England (2014) [Advice for prescribers on the risk of the misuse of pregabalin and gabapentin](#)
- WHO [Pain Relief Ladder](#)
- SIGN (2013) [SIGN 136. Management of chronic pain](#)
- AWMSG (2013) [Tramadol Educational Resource Materials](#)

5.0 ANTIMICROBIAL STEWARDSHIP

Purpose: To encourage the appropriate prescribing of antibiotics. The development of NPIs for antibiotic prescribing supports one of the key elements of the Welsh Antimicrobial Resistance Programme: to inform, support and promote the prudent use of antimicrobials⁷⁵.

5.1 Total items

Unit of measure:

Total antibacterial items per 1,000 STAR-PUs.

Target for 2017–2018:

No performance target set. Aim for reduction in prescribing year on year, measuring quarter to December only.

5.2 Co-amoxiclav

Units of measure:

Co-amoxiclav items per 1,000 patients.

Co-amoxiclav items as a percentage of total antibacterial items.

Target for 2017–2018:

Maintain performance levels within the lower quartile, or show a reduction towards the quartile below.

5.3 Cephalosporins

Units of measure:

Cephalosporin items per 1,000 patients.

Cephalosporin items as a percentage of total antibacterial items.

Target for 2017–2018:

Maintain performance levels within the lower quartile, or show a reduction towards the quartile below.

5.4 Fluoroquinolones

Units of measure:

Fluoroquinolone items per 1,000 patients.

Fluoroquinolone items as a percentage of total antibacterial items.

Target for 2017–2018:

Maintain performance levels within the lower quartile, or show a reduction towards the quartile below.

Note

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

Background and evidence

5.1 Total antibacterial items

Launched in 2016, the Antimicrobial Resistance (AMR) Delivery Plan for Wales *Together for Health: Tackling antimicrobial resistance and improving antibiotic prescribing*⁷⁶, sets out a series of priority actions related to optimising antimicrobial use, infection prevention and control; surveillance; education and training; and research. 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 available⁷⁶.

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 years⁷⁶. This is a step in the right direction; however, variation still exists. For the year April 2015–March 2016, primary care prescribing rates varied from 647 to 808 items per 1,000 patients across Welsh health boards⁴.

The Public Health Wales report *Antimicrobial Resistance in Wales (2006–2015)* presents the different antimicrobial resistance (AMR) patterns across Wales⁷⁷. The report shows Wales resistance rates for drug-bug combinations compared to 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 areas⁷⁷.

NICE Guideline 15 – *Antimicrobial stewardship: systems and processes for effective antimicrobial medicine* – 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 antimicrobial⁷⁸.

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 risk of *C. difficile*, methicillin-resistant *Staphylococcus aureus* (MRSA) and resistant urinary tract infections”⁷⁹. The guidance advises when it may be appropriate to consider a broad-spectrum antibiotic.

The Welsh Government set new targets in 2014 for reducing *C. difficile* and MRSA bacteraemia healthcare-associated infections. To achieve the national target, each of the health boards was required to reduce rates to no more than 31 per 100,000 population for *C. difficile* cases, and 2.6 per 100,000 population for MRSA bacteraemias⁸⁰. There is an expectation that these targets will be met by health boards by March 2017⁷⁶.

The principal risk factor for *C. difficile*-associated disease is prior antimicrobial therapy, especially with broad-spectrum antibiotics. Some antibiotics appear to have a much higher propensity to cause disease than others. The use of co-amoxiclav is associated with a moderate risk of *C. difficile* infection, whilst second and third generation cephalosporins and fluoroquinolones are associated with a high risk of *C. difficile* infection⁸¹.

5.2 Co-amoxiclav

Co-amoxiclav is a broad-spectrum penicillin with activity against beta-lactamase-producing organisms such as *S. aureus* and *Escherichia coli*⁸².

5.3 Cephalosporins

The cephalosporins are broad-spectrum antibiotics, which are used for the treatment of septicaemia, pneumonia, meningitis, biliary-tract infections, peritonitis and urinary tract infections³ mainly in secondary care settings.

5.4 Fluoroquinolones

The prescribing of fluoroquinolones in general practice remains a concern due to increasing resistance (e.g. quinolone-resistant *Neisseria gonorrhoeae*, *E. coli* and other Enterobacteriaceae). They are recommended first line only in limited situations (e.g. acute pyelonephritis or acute prostatitis)⁷⁹.

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](#)

6.0 ANTICHOLINERGIC BURDEN

Purpose: To encourage review of patients with an Anticholinergic Effect on Cognition (AEC) score of 3 or more, with the aim of reducing anticholinergic use where appropriate.

Unit of measure: Number of patients aged 75 and over with an AEC of 3 or more for items on active repeat, as a percentage of all patients aged 75 and over.

Target for 2017–2018: Maintain performance levels within the lower quartile, or show a reduction towards the quartile below.

See Appendix 4 for AEC scale

Background and evidence

An increasing number of studies report that medicines with anticholinergic effects are associated with an increased risk of cognitive impairment, dementia and falls in older people, with research also suggesting a link to increased mortality with the number and potency of anticholinergic agents prescribed⁸³⁻⁸⁶. Anticholinergic medicines are used for a variety of conditions, including Parkinson's disease, overactive bladder, COPD, nausea and vomiting, and depression and psychosis⁸⁴.

Medicines with anticholinergic effects block the neurotransmitter acetylcholine to inhibit smooth muscle function, such as in the lungs, gastrointestinal tract and urinary tract⁸⁴. Some medicines, for example oxybutynin and hyoscine, are used for their anticholinergic effects, whilst others have anticholinergic activity not related to their primary mode of action⁸³, such as fentanyl or carbamazepine.

Anticholinergic medicines have differing affinities for muscarinic receptors within the brain and a variable ability to cross the blood–brain barrier⁸⁷. The wide distribution of muscarinic acetylcholine receptor subtypes (M1–M5) in the central nervous system (CNS) and the rest of the body largely accounts for the variety of peripheral and CNS adverse effects⁸⁸ including constipation, dry mouth, dry eyes, urinary retention, agitation, and confusion^{3,89,90}. Age-related changes including a reduction in M1 muscarinic receptors and an increase in blood–brain barrier permeability⁹¹ are likely to contribute to the high incidence of adverse outcomes in older people.

A high proportion of the older population are exposed to multiple medicines with low anticholinergic activity; however, the cumulative burden of these medicines over many years may be associated with accelerated cognitive decline and mortality⁹². A decline in cognitive function and the diagnosis of mild cognitive impairment is associated with a progression to dementia within 5 years, making primary prevention and avoidance of anticholinergic medication, wherever possible, of significant importance as a strategy to protect against persistent cognitive decline⁹³. The Department of Health dementia toolkit recommends considering stopping or reducing anticholinergic medicines, and notes that GPs have a role in minimising the use of these medicines in patients with dementia⁹⁴. When offering antimuscarinic medicines to treat overactive bladder, NICE Clinical Guidelines on the management of urinary incontinence in women state that use of existing medication affecting the total anticholinergic load should be taken into account⁸⁷; in addition it recommends that oxybutynin should not be offered to frail elderly people due to the risk of impairment of daily functioning, chronic confusion and in rare cases acute delirium⁸⁷.

The cumulative effect of taking one or more medicines with anticholinergic properties is referred to as anticholinergic burden, and a number of anticholinergic rating scales

have been developed⁹⁵⁻⁹⁸ to quantify this; however, there is no consensus on the most appropriate tool. There is considerable variation amongst these scales because of differences in scale development, selection of drugs and methods of evaluation of anticholinergic potency⁹⁸.

The AEC scale was developed to illustrate the negative anticholinergic effects of drugs on cognition using a clear, concise and systematic approach, which takes into consideration the muscarinic binding affinity of drugs, their selectivity, their penetration into the brain and whether or not reports of cognitive impairment exist⁹⁸. Over 165 drugs commonly used in older people were assessed, with 60 of them found to have a clear capacity to impair cognitive function to varying degrees (score of 1–3), 62 were given a score of 0 and, owing to insufficient information, 43 drugs could not be classified⁹⁸.

As risk of adverse clinical outcomes in older people prescribed anticholinergic medications increases with increasing anticholinergic exposure⁹¹, it is good practice to use drugs 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 drugs with the aim of either stopping them or switching to an alternative drug with a lower AEC score (preferably zero), or if they are on a range of drugs that add up to an AEC score of 3 or more, then an informed decision should be made to either discontinue medication, if there is no absolute need; to switch to a medication with a lower AEC score (preferably zero); or to prescribe a drug from a different class^{83,98}. For conditions with no therapeutic alternatives, prescribers should use the lowest effective dose and discontinue therapy if ineffective⁸⁶. If withdrawal of a drug is deemed appropriate, this should follow a gradual schedule to avoid rebound anticholinergic effects⁹⁸.

The majority of medicines commonly prescribed to older people are not routinely recognised as having anticholinergic activity and are prescribed based on their anticipated therapeutic benefits, overlooking the risk of cumulative anticholinergic burden⁹⁹. As cumulative anticholinergic use is associated with an increased risk for dementia, efforts to increase awareness among health care professionals and older adults about this potential medication-related risk are important to minimise anticholinergic use over time⁸⁶. The aim of this NPI is to encourage timely review to reduce the anticholinergic burden in older people by avoiding, reducing doses and deprescribing medicines with anticholinergic activity where clinically possible.

Useful resources

- PrescQIPP (2016) [Anticholinergic drugs bulletin](#)
- AWMSG (2014) [Polypharmacy: Guidance for Prescribing](#)

7.0 NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

7.1 Purpose: To ensure that the risks associated with NSAIDs are minimised by appropriate use.

Unit of measure: NSAID ADQs per 1,000 STAR-PUs.

Target for 2017–2018: Maintain performance levels within the lower quartile, or show a reduction towards the quartile below.

7.2 Purpose: To encourage appropriate use and review of NSAIDs for patients on the CKD register, and patients who are not on the CKD register but who may have CKD.

Unit of measure:

- Number of patients on the CKD register (CKD 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.

Target for 2017–2018: Maintain performance levels within the lower quartile, or show a reduction towards the quartile below.

Background and evidence

All oral NSAIDs have analgesic effects of a similar magnitude^{7,8}. Pain relief starts soon after taking the first dose; however, it may take up to 3 weeks to achieve the full anti-inflammatory benefit. NSAIDs achieve their anti-inflammatory effect by inhibiting prostaglandin synthesis, through blockade of the enzymes cyclo-oxygenase-1 (COX-1) and cyclo-oxygenase-2 (COX-2). Most NSAIDs inhibit both COX-1 and COX-2; however, newer NSAIDs have been developed which are more selective inhibitors of COX-2. Selective COX-2 inhibition is associated with less gastro-intestinal (GI) toxicity³.

There are long-standing and well recognised GI¹⁰⁰ and renal¹⁰¹ safety concerns with all NSAIDs. Additionally, there have been increasing cardiovascular safety concerns with some NSAIDs, particularly COX-2 inhibitors and diclofenac¹⁰².

NSAIDs and gastro-intestinal events

NICE CGs recommend that if a person with osteoarthritis/rheumatoid arthritis (RA) needs to take low-dose aspirin, healthcare professionals should consider other analgesics before substituting or adding an NSAID including COX-2 inhibitors^{7,8}. Gastroprotection, with a PPI, is recommended particularly for patients on NSAIDs with osteoarthritis or RA^{7,8}. Ibuprofen and COX-2 inhibitors are associated with the lowest GI risk, but serious and fatal GI reactions have nevertheless been reported¹⁰³. Co-prescription of SSRIs may be associated with a similar increase in the risk of GI complications as co-prescription of low-dose aspirin¹⁰⁴.

NSAIDs and cardiovascular events

A number of reports from European and UK regulatory authorities have highlighted increased risks of cardiovascular events associated with certain NSAIDs. In 2005, a European Medicines Agency (EMA) review identified an increased risk of thrombotic events with COX-2 inhibitors¹⁰⁵. Whilst in 2007, the MHRA raised concerns about the

cardiovascular risks associated with diclofenac¹⁰⁰. In 2012, another EMA review on cardiovascular safety of NSAIDs highlighted further evidence that diclofenac is associated with a higher incidence of cardiovascular adverse events than other non-selective NSAIDs with risks similar to those of COX-2 inhibitors¹⁰². In 2013, an MHRA consultation concluded that diclofenac would no longer be available as a pharmacy (P) medicine¹⁰⁶. Diclofenac is now therefore only available on prescription. In January 2015, the MHRA updated the cardiovascular advice for aceclofenac in line with diclofenac and COX-2 inhibitors¹⁰⁷. In June 2015, the MHRA reported that an EMA review had confirmed the cardiovascular risk of high-dose ibuprofen ($\geq 2,400$ mg/day) as being similar to that of a COX-2 inhibitor and diclofenac¹⁰⁸.

NSAIDs and renal events

Acute kidney injury (AKI) is seen in 13–18% of all patients admitted to hospital and is increasingly being seen in primary care, particularly in older people. NSAIDs are nephrotoxic and can cause AKI, particularly in people with other risk factors e.g. heart failure, diabetes, liver disease and dehydration¹⁰⁹. NSAIDs in combination with diuretics and angiotensin converting enzyme inhibitors or angiotensin receptor blockers are associated with an increased risk of AKI¹¹⁰.

7.1 All NSAIDs

Despite ongoing reductions in the usage of NSAIDs in Wales, total prescribing (ADQs/1,000 STAR-PUs) remains 25% higher than that seen in England^{4,27}. Different NSAIDs vary in their potential GI, liver and cardio-renal toxicity; therefore, when choosing the agent and dose, it is important to take into account individual patient risk factors, including age^{7,8}. If an oral NSAID is indicated, prescribing should be based on the safety profiles of individual NSAIDs or selective COX-2 inhibitors, and on individual patient risk profiles (e.g. GI and cardiovascular). The MHRA recommends that people should use the lowest effective dose, for the shortest duration necessary to control symptoms, in order to minimise adverse effects. A patient's need for symptomatic relief and response to treatment should be re-evaluated periodically¹¹¹.

7.2 NSAIDs and CKD

NICE CG182 highlights that in patients with chronic kidney disease (CKD), the chronic use of NSAIDs may be associated with progression and acute use is associated with a reversible decrease in glomerular filtration rate (GFR). It recommends caution and monitoring of the effects on GFR when treating people with CKD with NSAIDs over prolonged periods of time¹¹². NSAIDs may precipitate renal failure, and vulnerable (particularly elderly) patients may be at increased risk. 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 place¹¹³.

Useful resources

- AWMSG (2015) [CEPP All Wales Audit: Towards Appropriate NSAID Prescribing](#)
- AWMSG (2017) [CEPP National Audit: Medicines Management for CKD](#)

8.0 YELLOW CARDS

Purpose: To encourage an increase in the number of Yellow Cards submitted by GP practices in Wales.

Unit of measure: Number of Yellow Cards submitted, per practice and per health board.

Target for 2017–2018: Target for GP practice – to submit one Yellow Card per 2,000 practice population.

Target for each health board – submit Yellow Cards in excess of one per 2,000 health board population.

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^{114,115}.

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.

Side effects 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.

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 adverse events and critical incidents from across all professions and healthcare settings, as well as from patients.

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 CEPP Local Comparator and in April 2014 it became an NPI. In 2015–2016, the number of Yellow Cards submitted by GPs in Wales increased by 36% compared to the previous financial year, to 851.

It is anticipated that continuing to monitor Yellow Card reporting per practice population as the first part of this NPI for 2017–2018 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 adverse events reporting by submitting reports and/or promoting a culture of safety and pharmacovigilance.

The second part of the NPI monitors the number of Yellow Cards submitted by all reporters per health board population.

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](#)

SECONDARY CARE

1.0 INSULIN

Purpose: Ensure long-acting analogue insulin prescribing in type 2 diabetes mellitus is in line with NICE guidance to maximise cost-effective prescribing within Wales.

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

Aim for 2017–2018: To reduce prescribing of long-acting insulin analogues and to achieve prescribing levels below the Welsh average.

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 regimen¹¹⁶. For most people with type 2 diabetes, long-acting insulin analogues offer no significant benefit over human NPH insulin, and are more expensive. Indeed, NICE considered the available evidence and concluded that, while there is support for insulin glargine and insulin detemir to lower the incidence of hypoglycaemic events, the use of these insulins as first-line insulins in type 2 diabetes could not be justified on health economic grounds¹¹⁷.

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 to NPH insulin in long-term metabolic control (measured by glycated haemoglobin [HbA_{1c}])¹¹⁸. 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 advised¹¹⁸.

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 treatment¹¹⁶. Therefore discussion with the patient about their preferred specific insulin type, specifying the comparative effectiveness of NPH insulin to the long-acting insulin analogues, should be made. When patients are commenced on an insulin therapy, a structured programme employing active dose titration should be employed. This programme should encompass injection technique, continuing telephone support, self-monitoring, dose titration to target levels, dietary understanding, DVLA guidance, management of hypoglycaemia, management of acute changes in plasma glucose control, and support from an appropriately trained and experienced healthcare professional¹¹⁶.

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 diabetes¹¹⁹. 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 diabetes¹²⁰, the prescribing data

indicate that long-acting insulin analogues are being widely used to manage type 2 diabetes.

Despite the recommendations outlined in NG28, the prescribing cost for long-acting insulin analogues was approximately £8.8 million across NHS Wales for the 2015–2016 financial year.

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 2015–2016 was 89.9%; this is a slight decrease from the previous year (90.6%).

For NHS Wales secondary care, the average quantity of long-acting insulin analogues prescribed as a percentage of total long- and intermediate-acting insulin was 77% (April 2015–March 2016). This was the same figure as for 2014–2015. See Appendix 2 for more information.

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 potential cost saving to NHS Wales is likely to be significant. A UK study by Holden and colleagues, published in the BMJ, concluded that the rise 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 medicines¹²¹.

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 insulins¹¹⁷. Holden and colleagues state that if guidelines for insulin prescribing had been followed between 2000 and 2009, the UK NHS would have saved £625 million¹²¹. Extra money spent on long-acting insulin analogues may be considered better spent on diabetes specialist nurses or dieticians to help educate and manage the growing population of diabetic patients¹¹⁷. In Wales, if the proportion of long-acting insulins could be reduced to 74% of the total long- and intermediate-acting insulins, a potential cost saving of at least £700,000 could be made⁴. See Appendix 2 for insulin data.

Useful resources

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

2.0 BIOSIMILARS

Purpose: Ensure prescribing of biological medicines is in line with AWMSG guidance and supports cost-effective prescribing within Wales.

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

Aim for 2017–2018: Increase the appropriate use of cost-effective biological medicines, including biosimilar medicines, in line with guidance¹²²⁻¹²⁵.

2.1 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')¹²⁶. The regulatory authority 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 differences¹²⁶⁻¹²⁸.

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 Wales^{126,127}.

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. The NHS England publication "What is a biosimilar medicine" provides supportive information for the use of biosimilar medicines.

In line with MHRA guidelines, biological medicines, including biosimilar medicines, must be prescribed by brand name to ensure automatic substitution does not take place and to support on-going pharmacovigilance of the individual products¹²⁹. At the time of dispensing a biological medicine, there should be no automatic substitution with a biosimilar medicine.

Where AWMSG or NICE have already recommended the 'reference' biological medicine, the same guidance will normally apply to a biosimilar of the 'reference'. However, in other circumstances, where a review of the evidence for a biosimilar medicine is considered necessary, AWMSG and/or NICE will consider undertaking a further review¹³⁰. Current biological medicines with biosimilar versions for use within NHS Wales are:

- Infliximab – Inflectra[®]▼
- Filgrastim – Nivestim[®], Zarzio[®]
- Insulin glargine – Abasaglar[®]▼
- Etanercept – Benepali[®]▼

2.2 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 medicines¹²⁸.

The BNF listed prices for biosimilar medicines are currently lower than those of the 'reference' product³. Therefore the use of biosimilar medicines in place of the 'reference' biological medicine could be associated with cost savings. However, it should be noted that individual hospital contracting prices for biosimilar medicines and reference products may vary, which will affect 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.

For filgrastim and infliximab the total spends across Wales in secondary care were £439,472 and £9.08 million respectively, in the period April 2015–March 2016. The proportion of filgrastim prescribed as a biosimilar medicine was 98.8%.

For infliximab, £873,182 was spent on the biosimilar medicine Inflectra® in 2015–2016. This is approximately 10% of the total infliximab spend. However, data for quarter one of 2016–2017 has shown this percentage to be increasing, with some health boards significantly increasing biosimilar infliximab use. See Appendix 2 for biosimilar data.

Abasaglar®, a biosimilar of insulin glargine, was given a positive AWMSG recommendation in December 2015. Although the 2015–2016 usage data are of limited use, as with the biosimilar infliximab, data for quarter one 2016–2017 are showing an increasing percentage usage.

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?](#)

3.0 ANTIBIOTICS

Purpose: To encourage the appropriate prescribing of antibiotics. The development of NPIs for antibiotic prescribing supports one of the key elements of the Welsh Antimicrobial Resistance Programme: to inform, support and promote the prudent use of antimicrobials⁷⁵.

Unit of measure: Proportion of elective colorectal patients receiving surgical prophylaxis for more than 24 hours.

Aim for 2017–2018: Maintain performance below the Welsh average (Point Prevalence Survey [PPS] data) or show a reduction towards the Welsh average.

3.1 Background and evidence

The administration of antibiotic prophylaxis to surgical patients is intended to reduce the incidence of surgical site infection, use antibiotics in a manner that is supported by evidence of effectiveness and minimise adverse effects to the patient¹³¹. 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 infection¹³¹.

Antibiotic prophylaxis should be given to patients before:

- clean surgery involving the placement of a prosthesis or implant
- clean-contaminated surgery
- contaminated surgery¹³²

Antibiotic prophylaxis is not routinely recommended for clean non-prosthetic uncomplicated surgery¹³².

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 cases¹³¹⁻¹³³. 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^{133,134}. A repeat dose of prophylaxis antibiotic is recommended when the operation is longer than the half-life of the antibiotic given¹³³. 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 recommended¹³¹. Any additional prophylactic antibiotic doses should be confirmed and justified within the patient's notes.

There is, however, a tendency to continue antibiotic prophylaxis for longer than necessary¹³¹. The PPS for 2015 reports that the proportion of surgical prophylaxis administered for greater than 24 hours ranged from 15% to 38% across health boards¹³⁵, though the Wales average is reducing. Data from the PPS indicate that the proportion of surgical prophylaxis administered for more than 24 hours has reduced from 42% in 2012 to 26% in 2015¹³⁵.

In common with therapeutic use, the use of antibiotics for prophylaxis carries a risk of adverse effects (including *Clostridium 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 effects¹³⁶. Therefore, antibiotic choice should minimise *C. difficile* risk whilst ensuring adequate coverage of the expected pathogens for the operative site¹³¹. Antibiotic choice should reflect local, disease-specific information about the common

pathogens and their antimicrobial susceptibility¹³¹. Narrow-spectrum, less expensive antibiotics should be the first choice¹³¹.

The most recent data within the first quarter of 2016–2017 indicate that across Wales around 16% of colorectal patients received antimicrobial prophylaxis duration for greater than 24 hours. See Appendix 2 for antibiotic data.

Useful resources

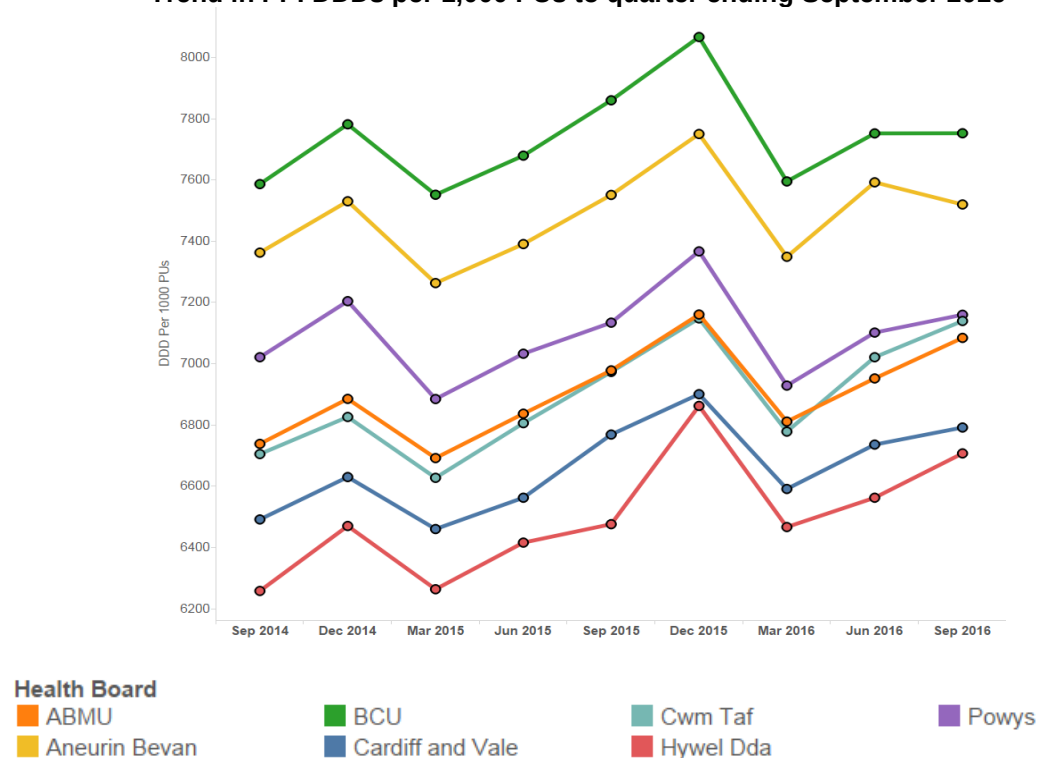
- Public Health Wales (2016) [Antimicrobial Usage in Secondary Care in Wales](#)
- Public Health Wales (2016) [Report on the Point Prevalence Survey of Antimicrobial Prescribing in Secondary Care in Wales](#)
- Public Health Wales (2016) [Antibacterial Resistance in Wales](#)

APPENDIX 1. NHS WALES HEALTH BOARDS PERFORMANCE AND COMPARISON WITH ENGLISH CCGS AGAINST PRIMARY CARE NPIS 2017–2018

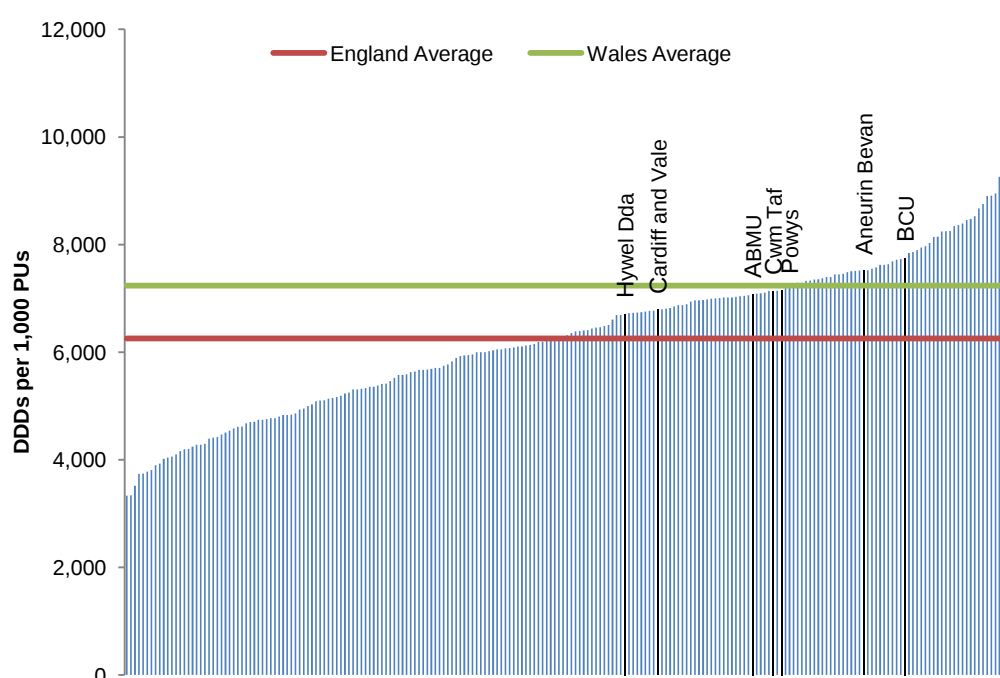
Data for each NPI are presented in two ways: a line graph/bar chart showing the trend in prescribing for each health board and a bar chart comparing prescribing of each health board with that of each CCG in England. The black bars represent the seven health boards in Wales; the blue bars represent the 209 CCGs in England.

1.0 PROTON PUMP INHIBITORS

Trend in PPI DDDs per 1,000 PUs to quarter ending September 2016

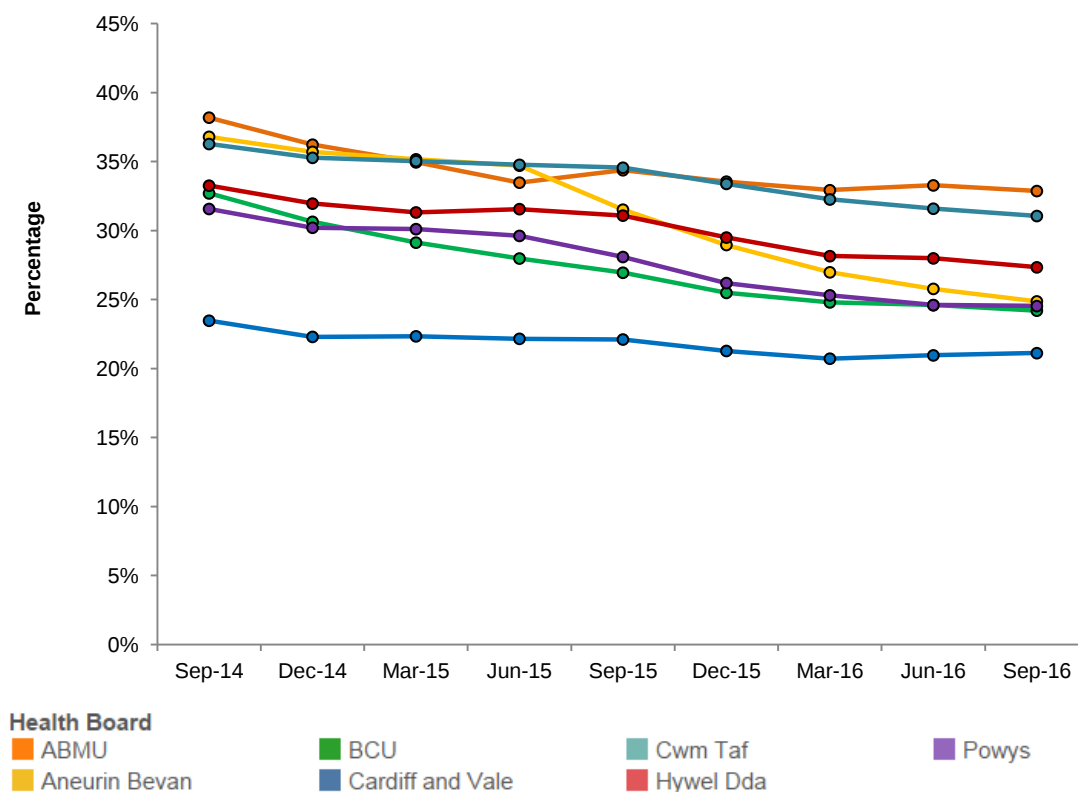


PPI DDDs per 1,000 PUs – Quarter ending September 2016

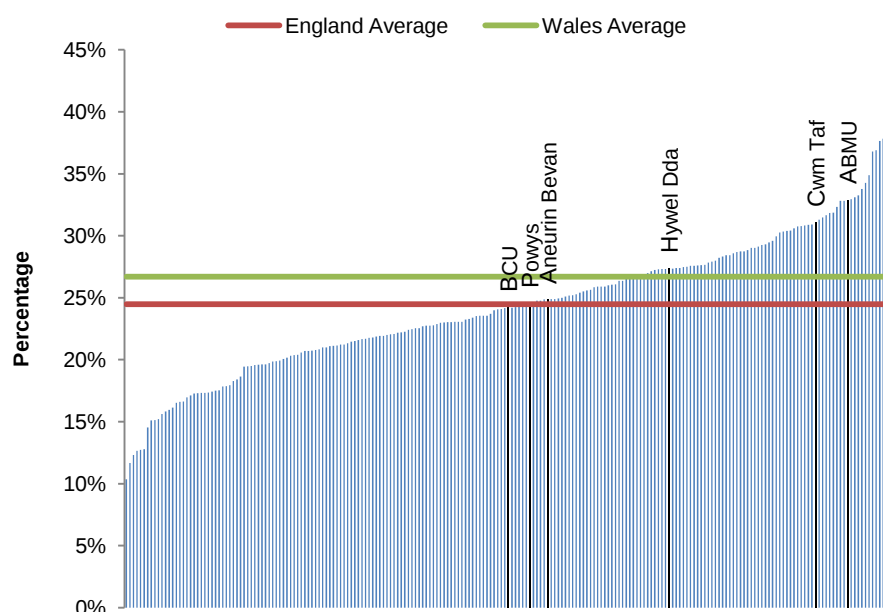


2.0 INHALED CORTICOSTEROIDS

Trend in high strength ICS items as a percentage of all ICS prescribing to quarter ending September 2016

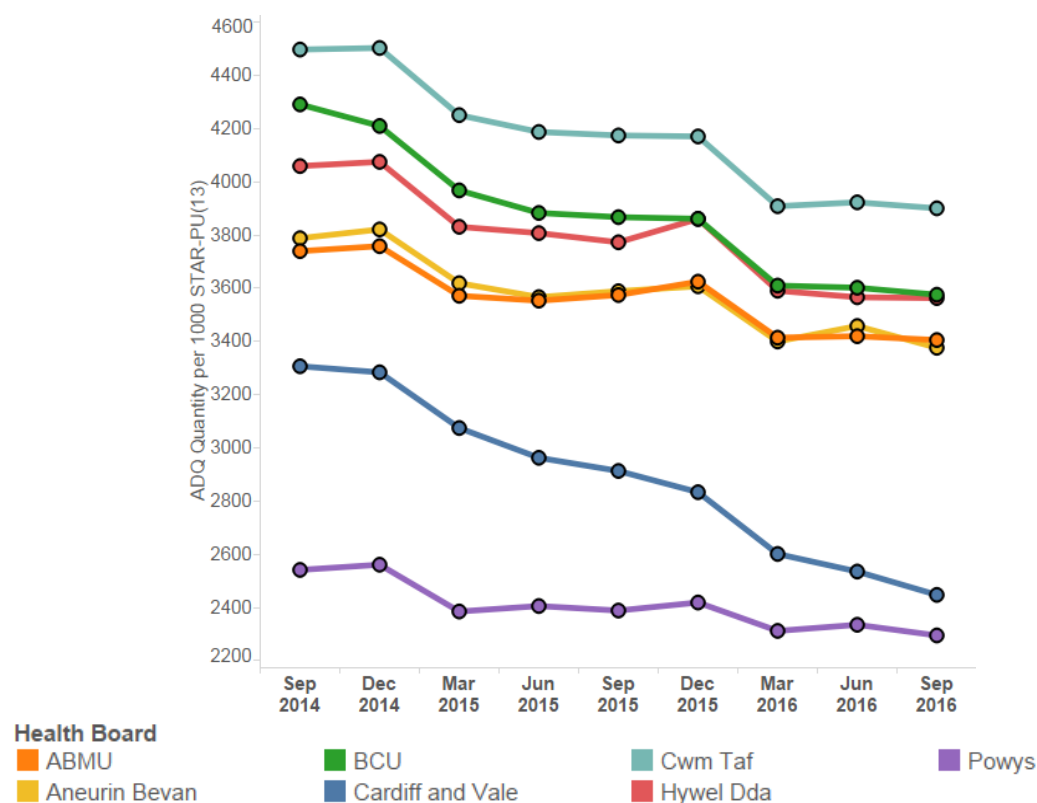


High strength ICS items as a percentage of all ICS prescribing – Quarter ending September 2016

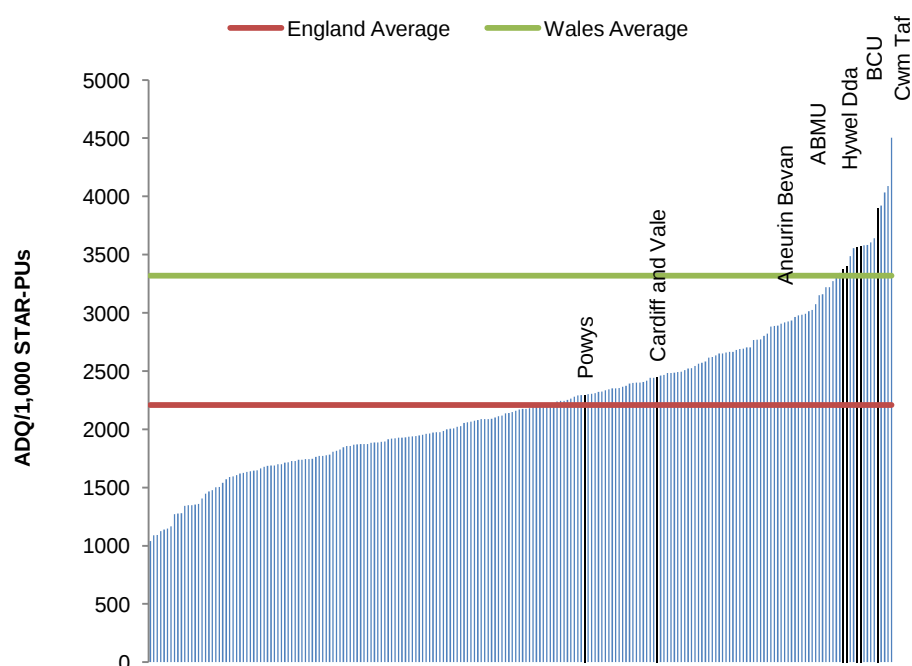


3.0 HYPNOTICS AND ANXIOLYTICS

Trend in hypnotic and anxiolytic ADQs per 1,000 STAR-PU's to quarter ending September 2016



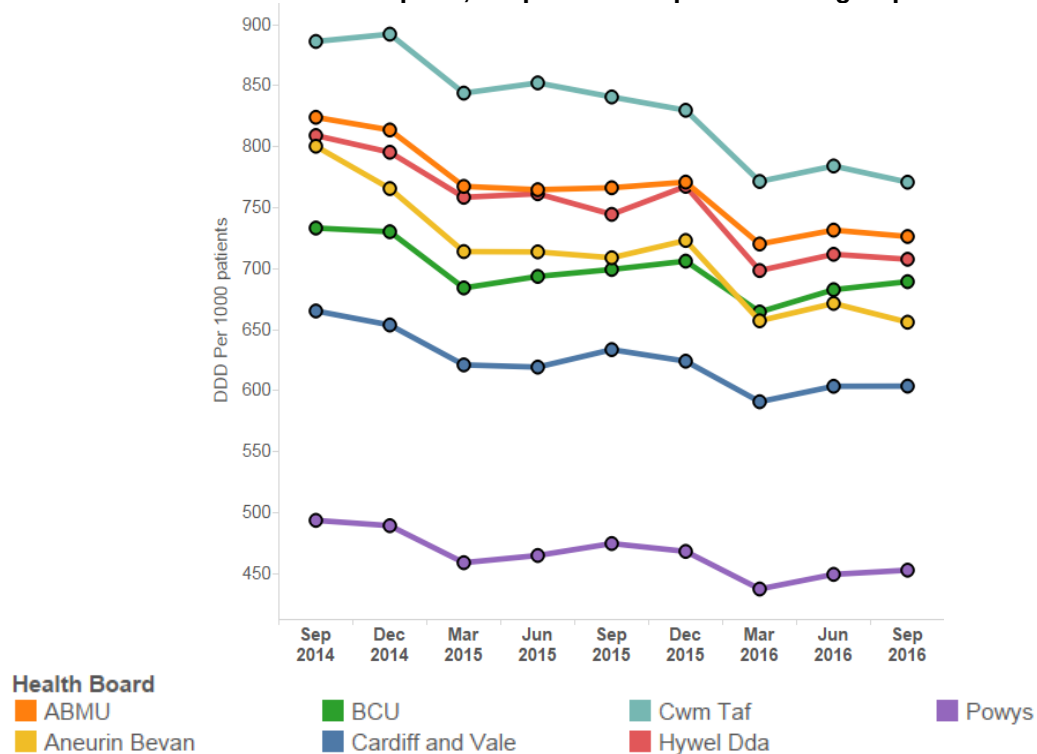
Hypnotic and anxiolytic ADQs per 1,000 STAR-PU's
Quarter ending September 2016



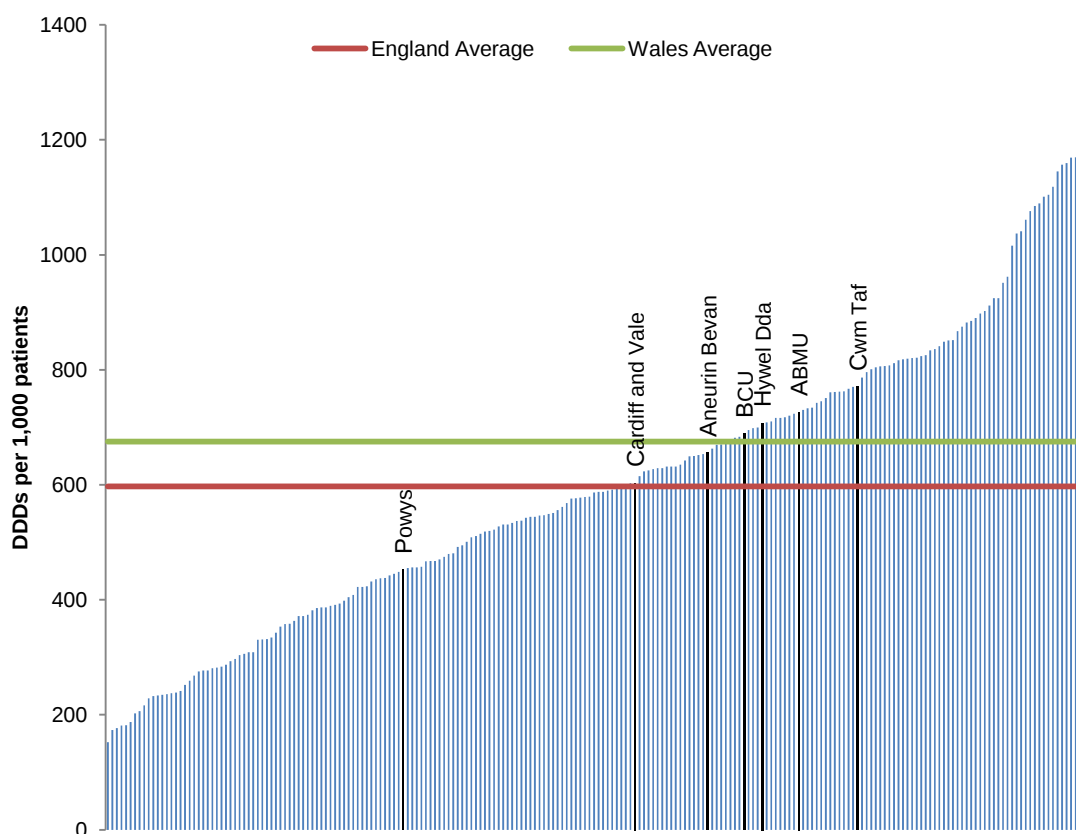
4.0 ANALGESICS

4.1 Tramadol

Trend in tramadol DDDs per 1,000 patients to quarter ending September 2016

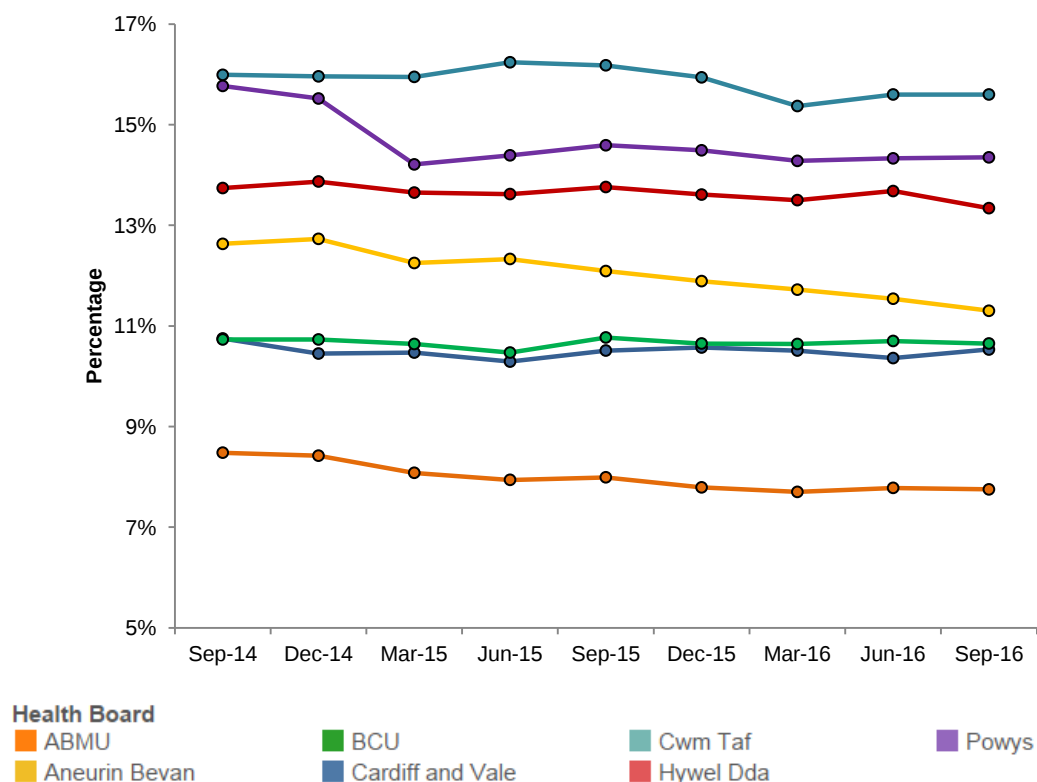


Tramadol DDDs per 1,000 patients – Quarter ending September 2016

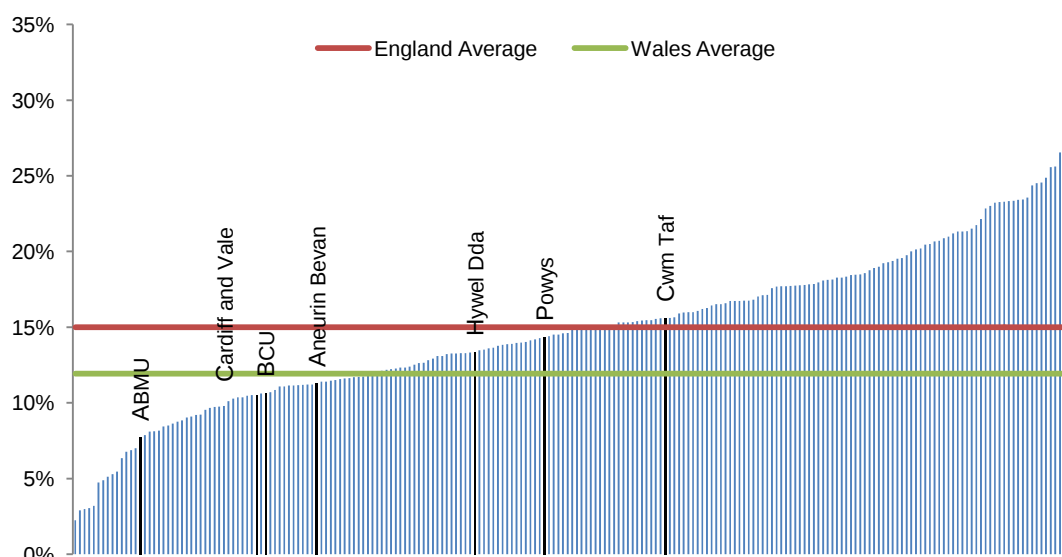


4.2 Opioid patches

Trend in opioid patch items as a percentage of all opioid analgesics to quarter ending September 2016

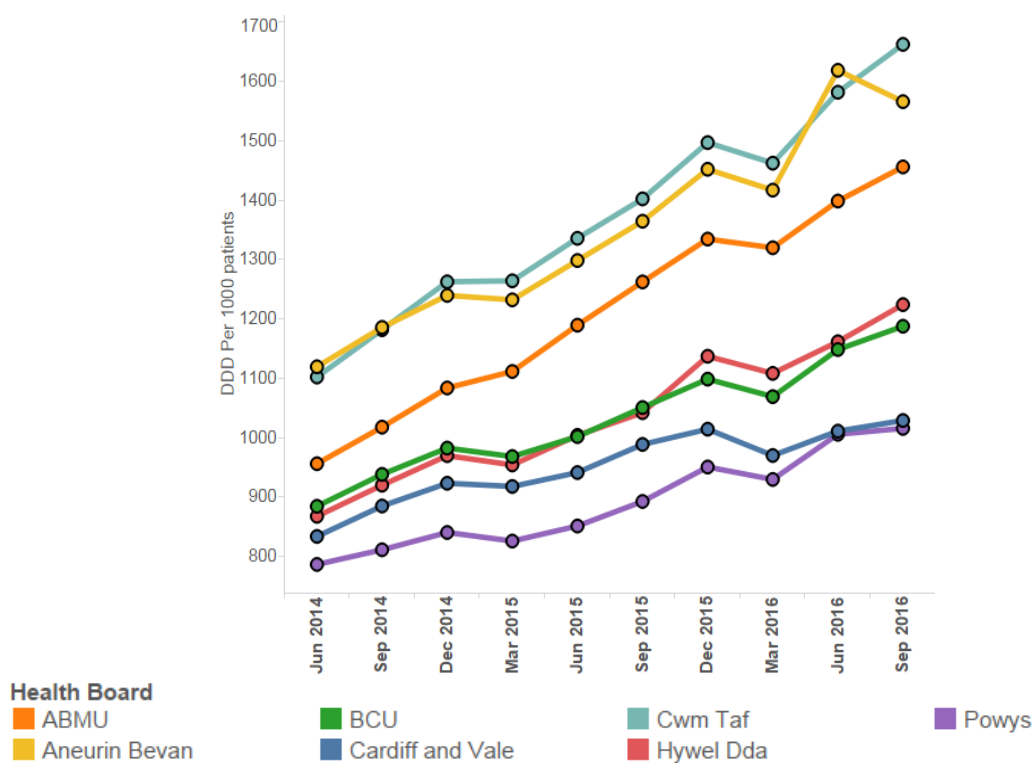


Opioid patch items as a percentage of all opioid analgesics
Quarter ending September 2016

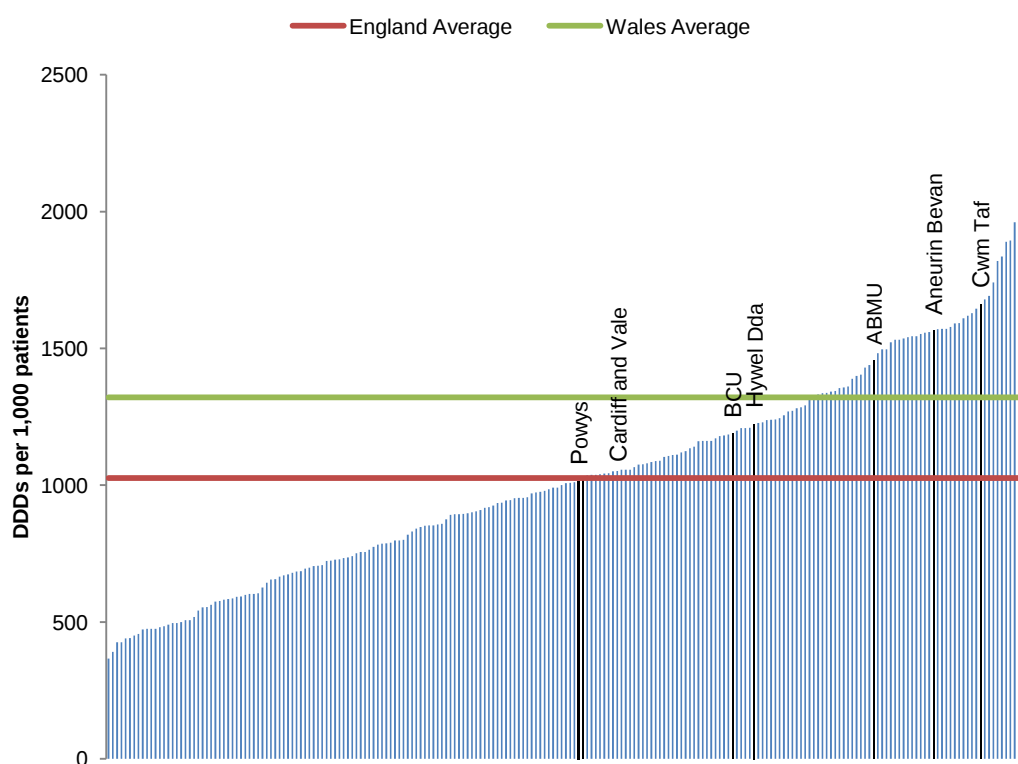


4.3 Gabapentin and pregabalin

Trend in gabapentin and pregabalin DDDs per 1,000 patients to quarter ending September 2016



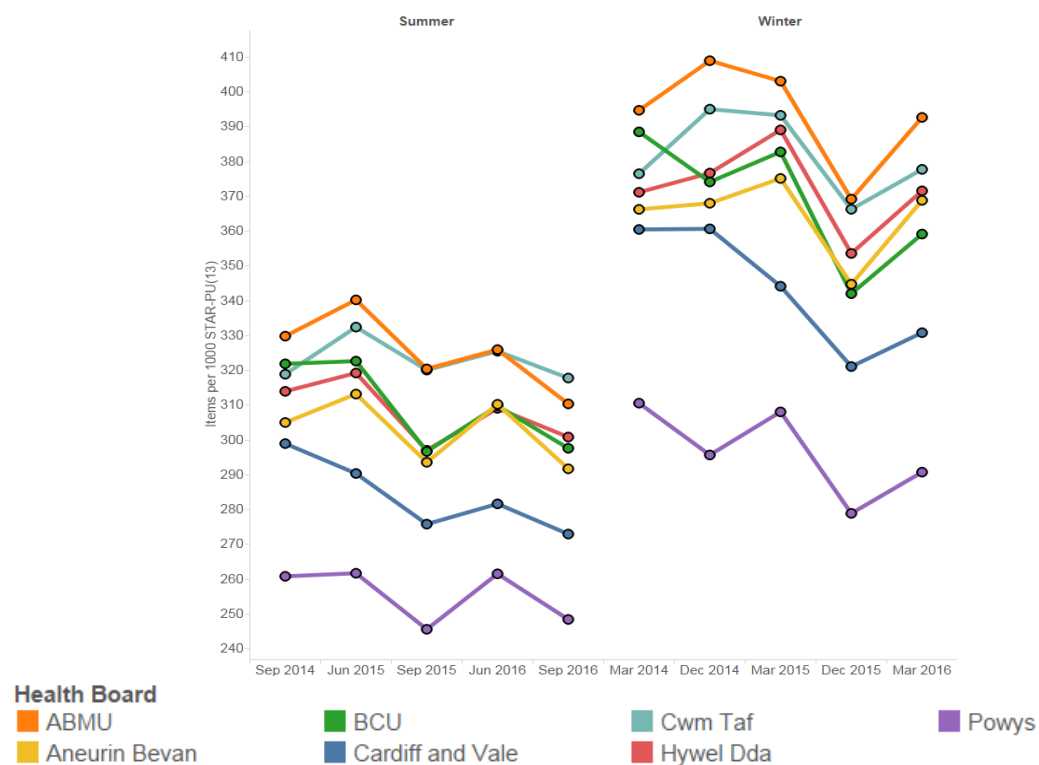
Gabapentin and pregabalin DDDs per 1,000 patients – Quarter ending September 2016



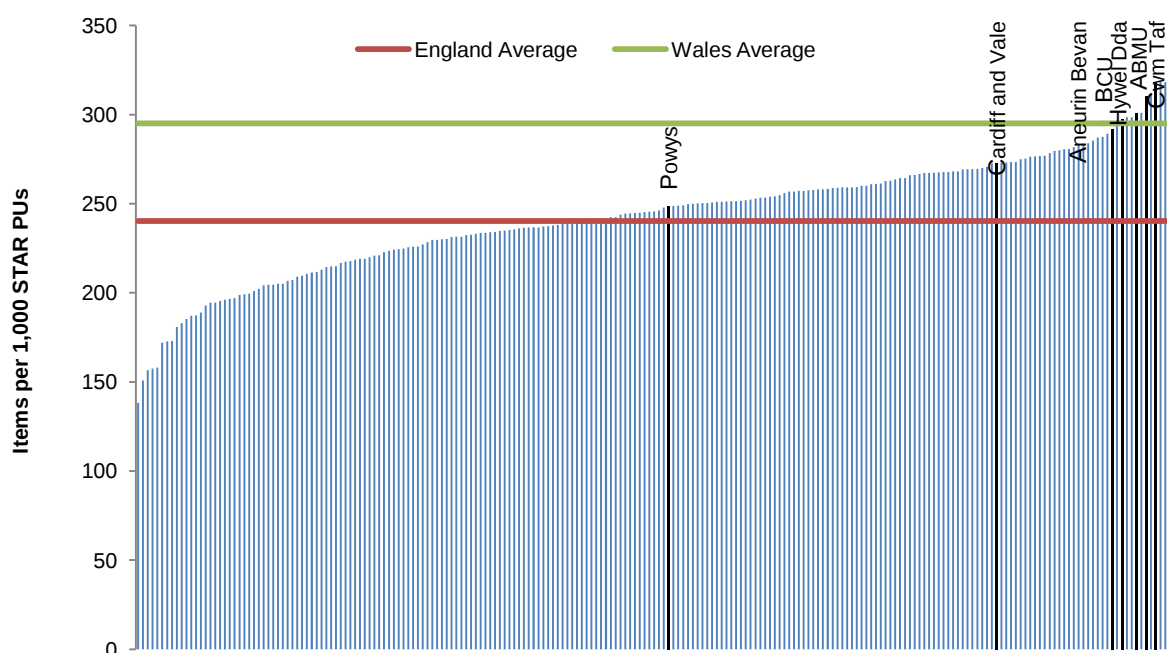
5.0 ANTIBIOTICS

5.1 Total antibiotics

Trend in total antibacterial items per 1,000 STAR-PUs to quarter ending September 2016

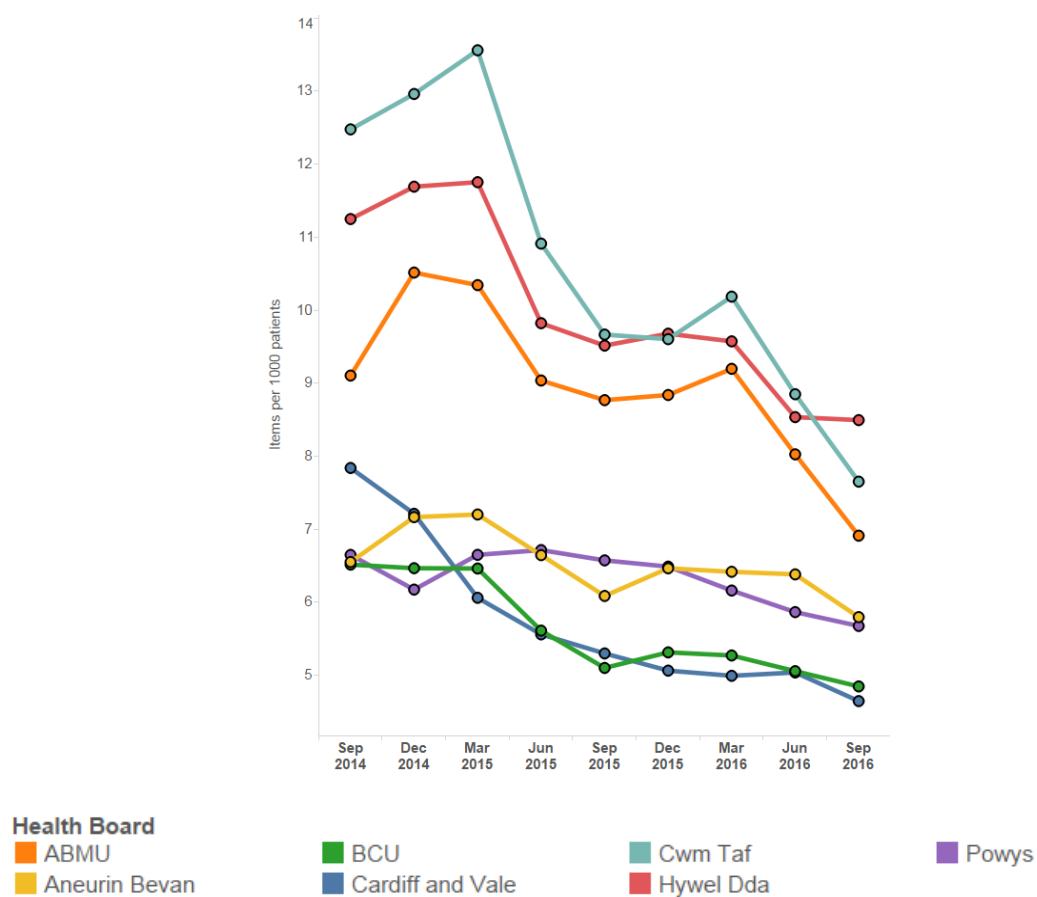


Total antibacterial items per 1,000 STAR-PUs – Quarter ending September 2016

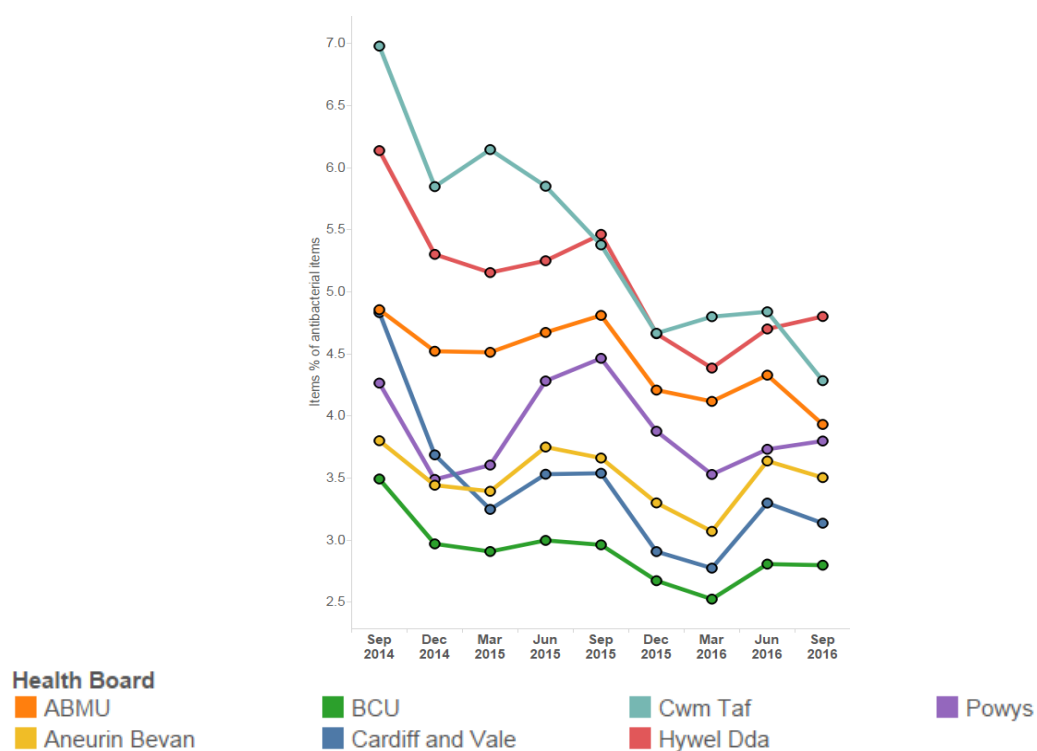


5.2 Co-amoxiclav

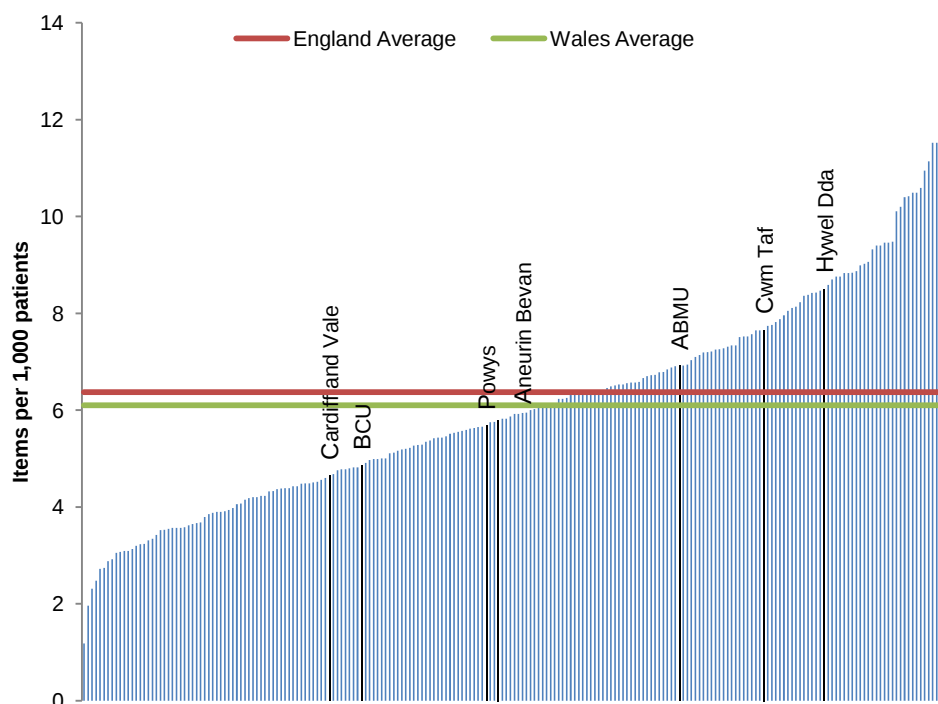
Trend in co-amoxiclav items per 1,000 patients to quarter ending September 2016



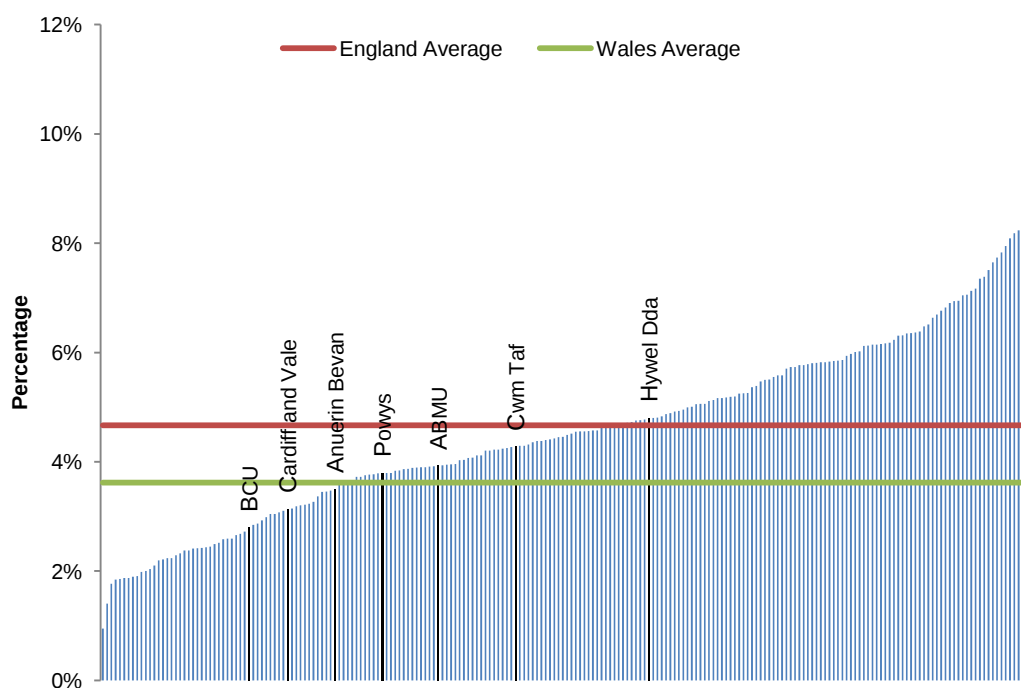
Trend in co-amoxiclav items as a percentage of total antibacterial items to quarter to September 2016



Co-amoxiclav items per 1,000 patients – Quarter ending September 2016

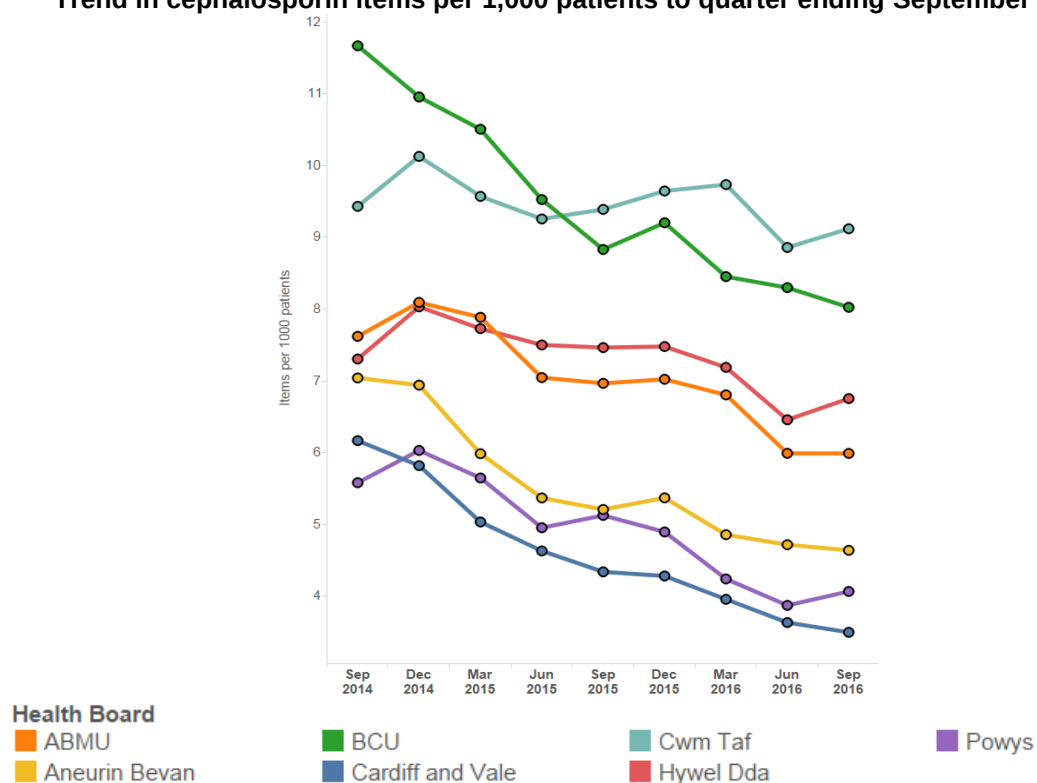


Co-amoxiclav items as a percentage of total antibacterial items – Quarter ending September 2016

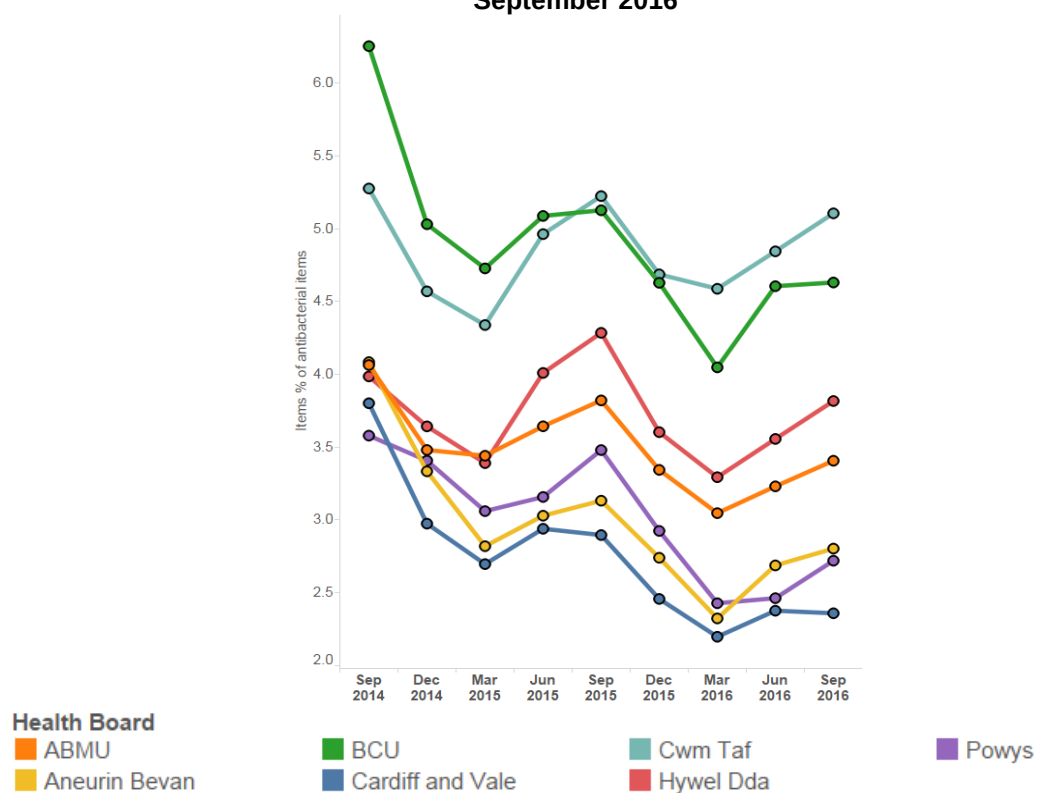


5.3 Cephalosporins

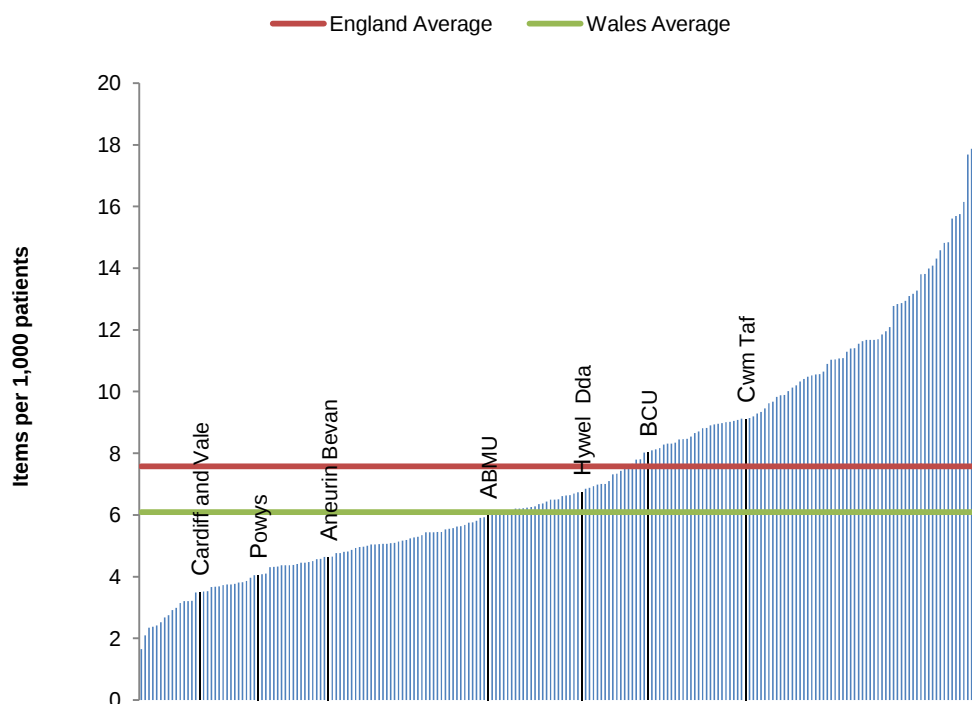
Trend in cephalosporin items per 1,000 patients to quarter ending September 2016



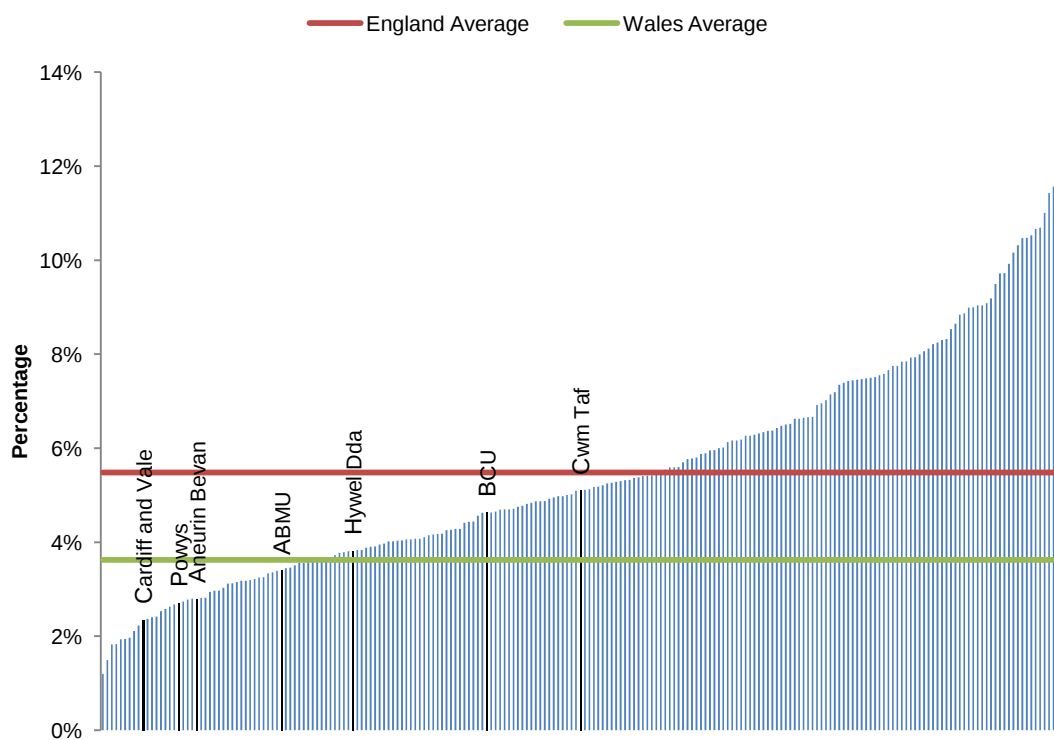
Trend in cephalosporin items as a percentage of total antibacterial items to quarter September 2016



Cephalosporin items per 1,000 patients – Quarter ending September 2016

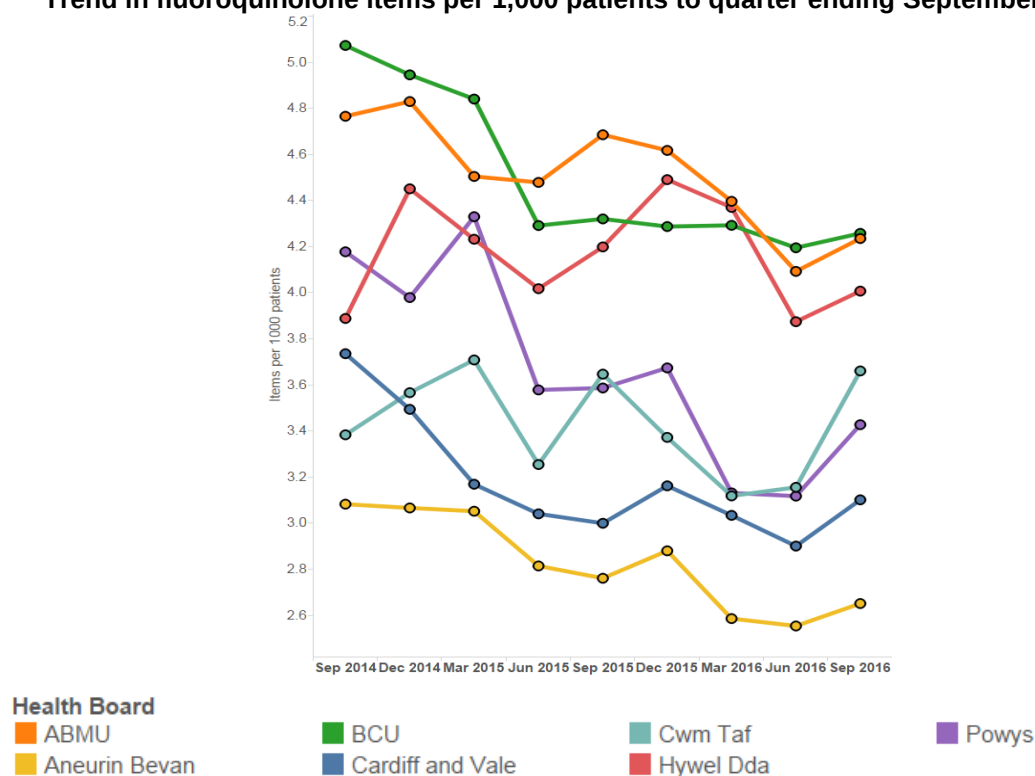


Cephalosporin items as a percentage of total antibacterial items – Quarter ending September 2016

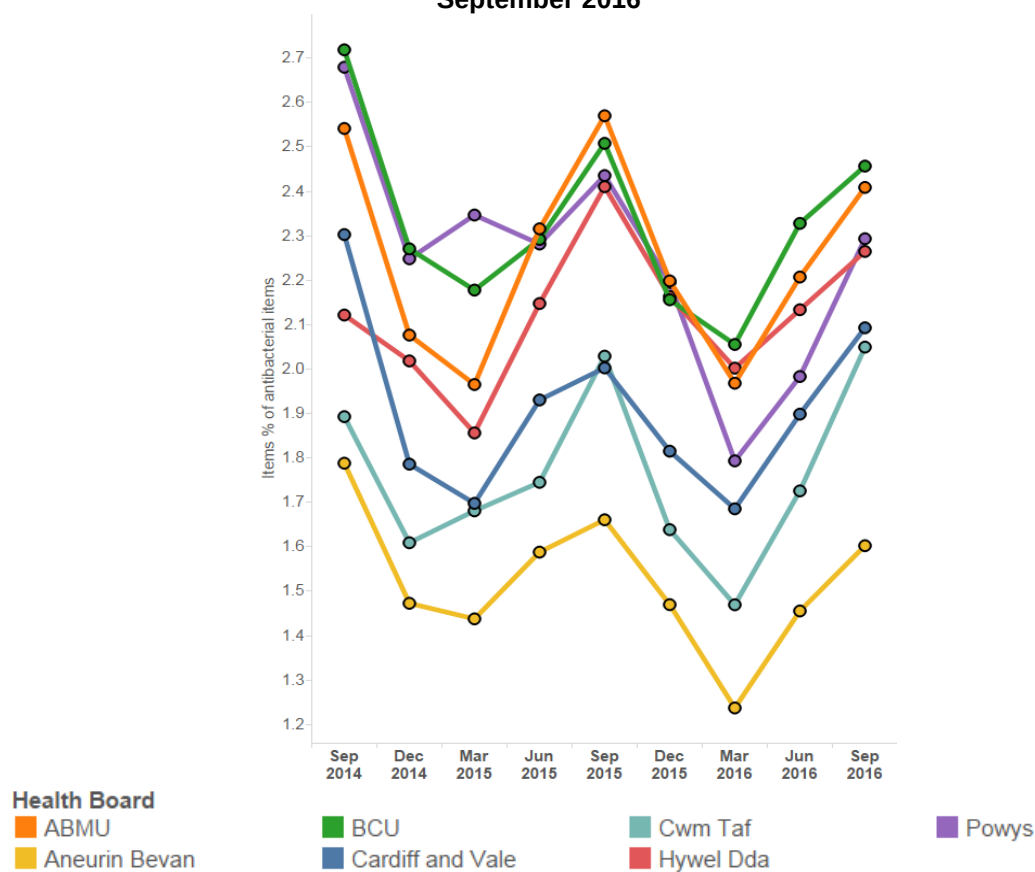


5.4 Fluoroquinolones

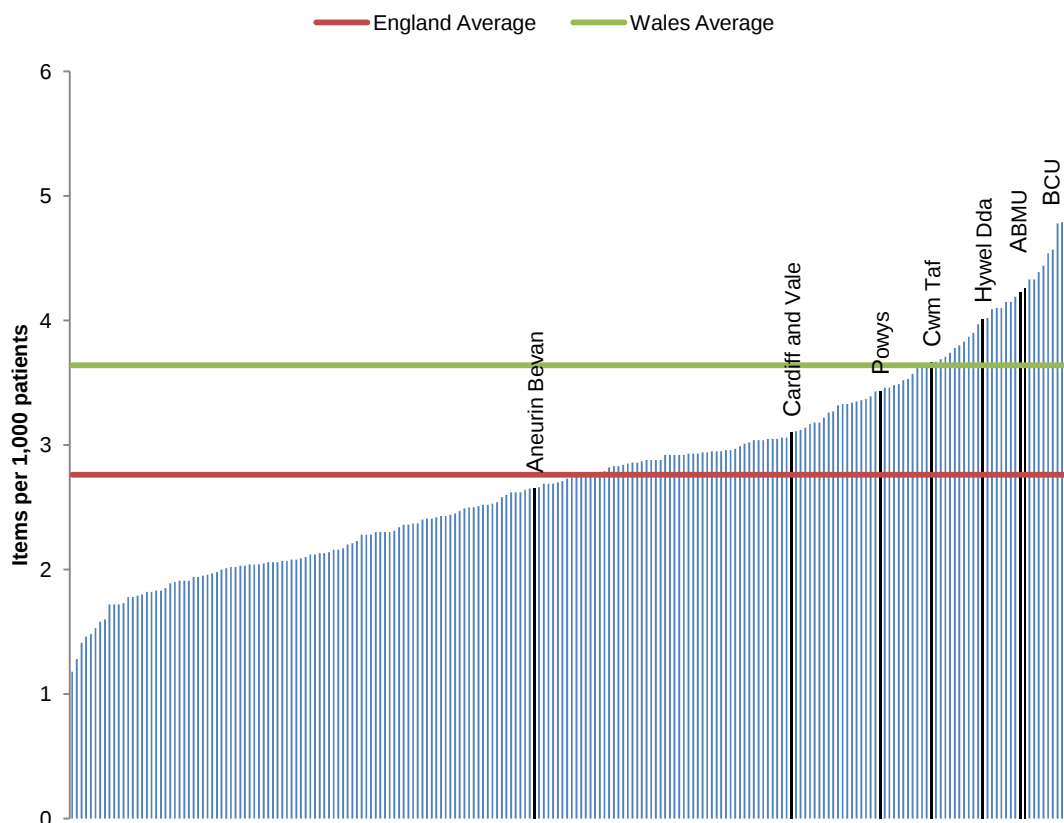
Trend in fluoroquinolone items per 1,000 patients to quarter ending September 2016



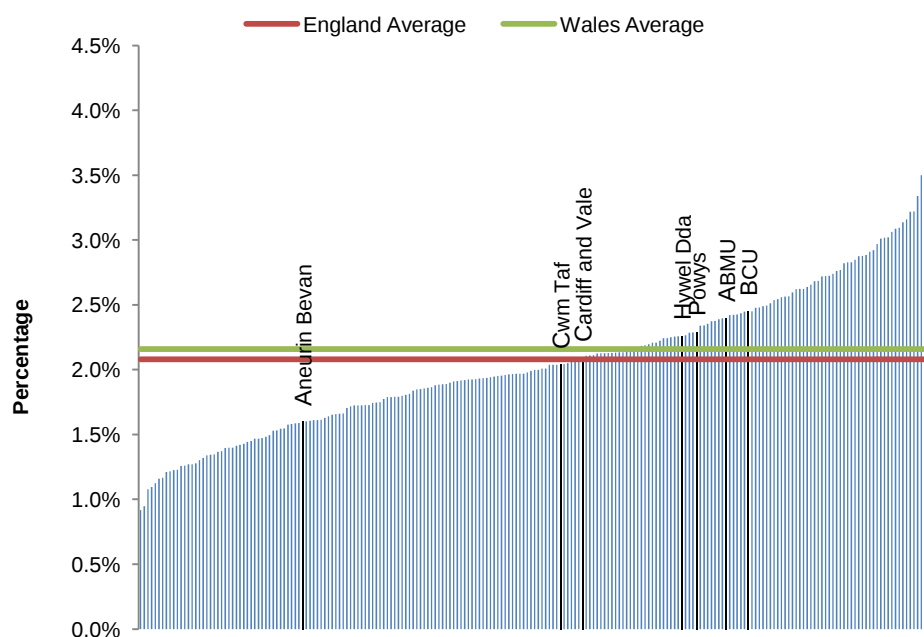
Trend in fluoroquinolone items as a percentage of total antibacterial items to quarter ending September 2016



Fluoroquinolone items per 1,000 patients – Quarter ending September 2016



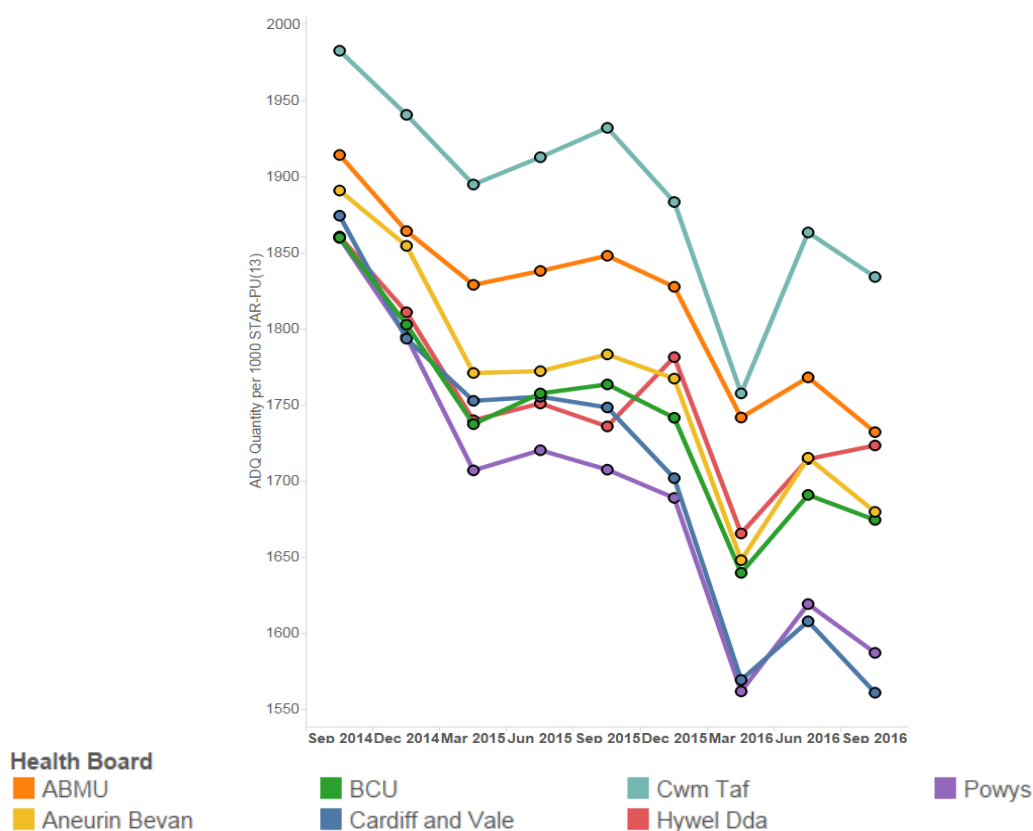
Fluoroquinolone items as a percentage of total antibacterial items – Quarter ending September 2016



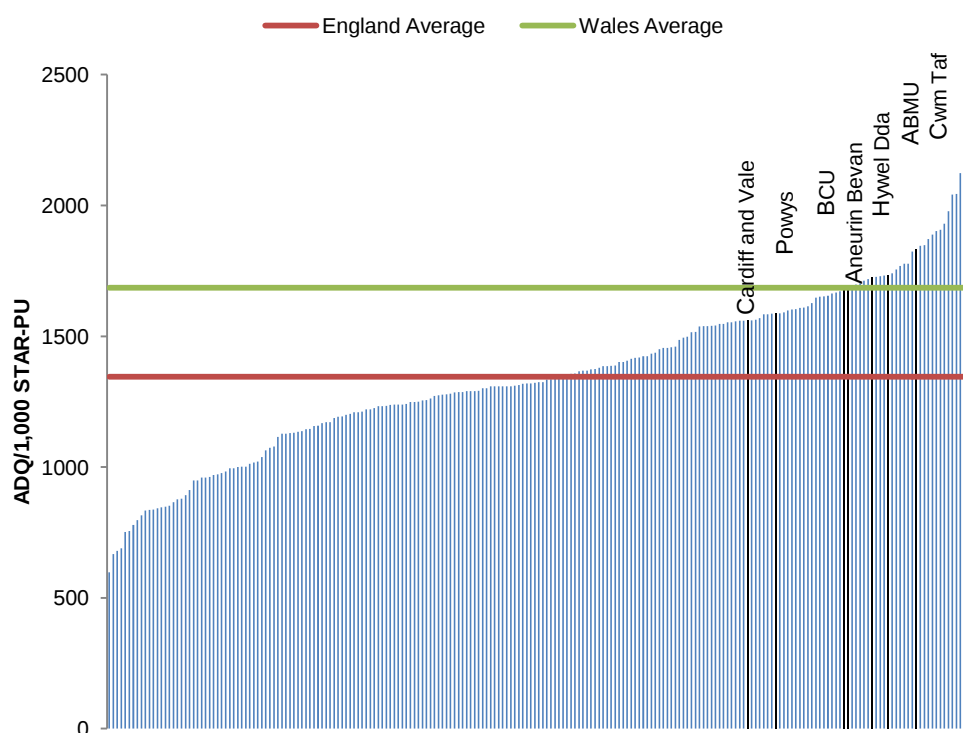
8.0 NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

8.1 Total NSAIDs

Trend in NSAID ADQs per 1,000 STAR-PU to quarter ending September 2016

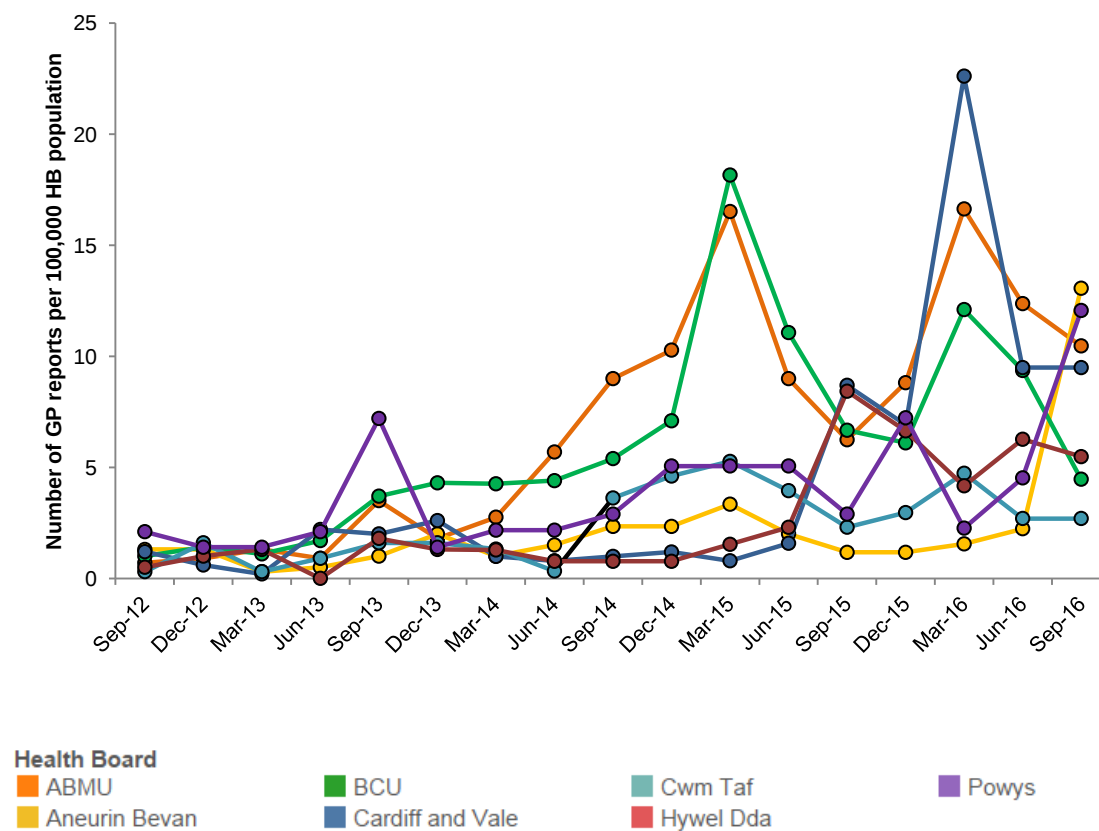


NSAID ADQs per 1,000 STAR-PU –Quarter ending September 2016



9.0 YELLOW CARDS

Trend in Yellow Card reporting to quarter ending September 2016



APPENDIX 2. NHS WALES HEALTH BOARD PRESCRIBING DATA FOR SECONDARY CARE NPIS 2017–2018

1.0 INSULIN

Table 1. Proportion of long-acting insulin analogue prescribing in primary care

Health Board	2014–2015	2015–2016	% change
ABMU	92.55	92.56	0.01
Aneurin Bevan	86.38	86.28	-0.12
BCU	94.68	94.17	-0.54
Cardiff and Vale	93.04	91.56	-1.59
Cwm Taf	79.61	79.10	-0.64
Hywel Dda	94.76	93.64	-1.18
Powys	88.61	86.78	-2.07
National average	90.55	89.91	-0.71

Figure 1. Trend in long-acting analogue prescribing as a percentage of total long and intermediate-acting insulin prescribing in primary care

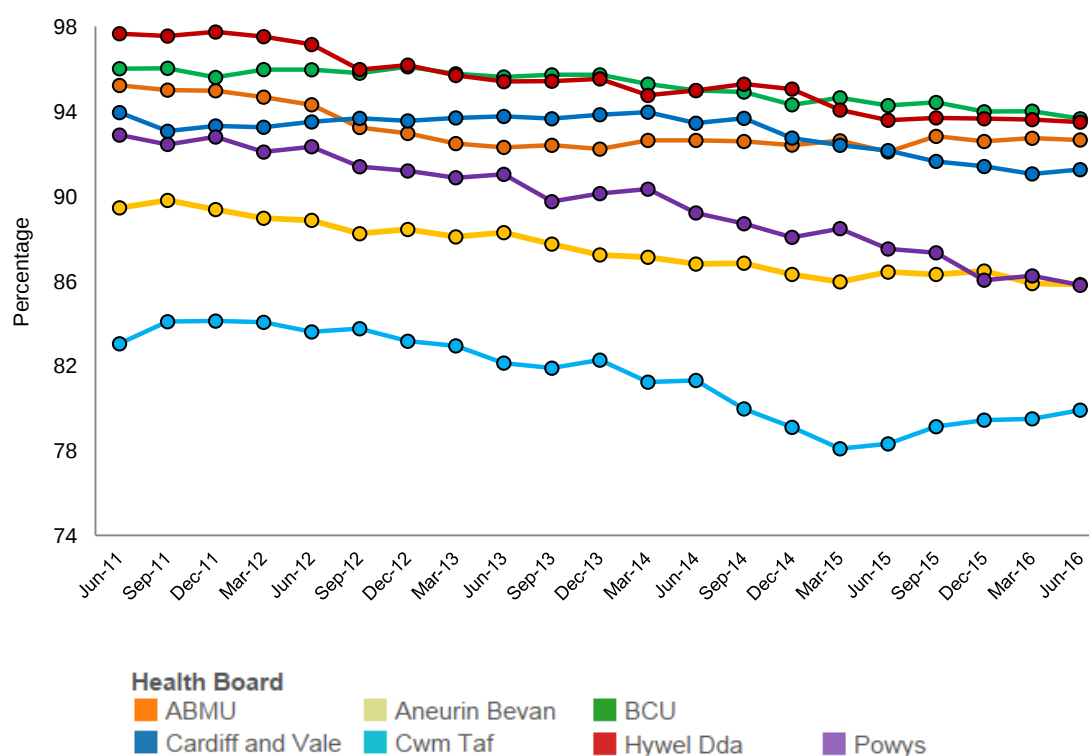


Table 2. Proportion of long-acting insulin analogue prescribing April 2015–March 2016

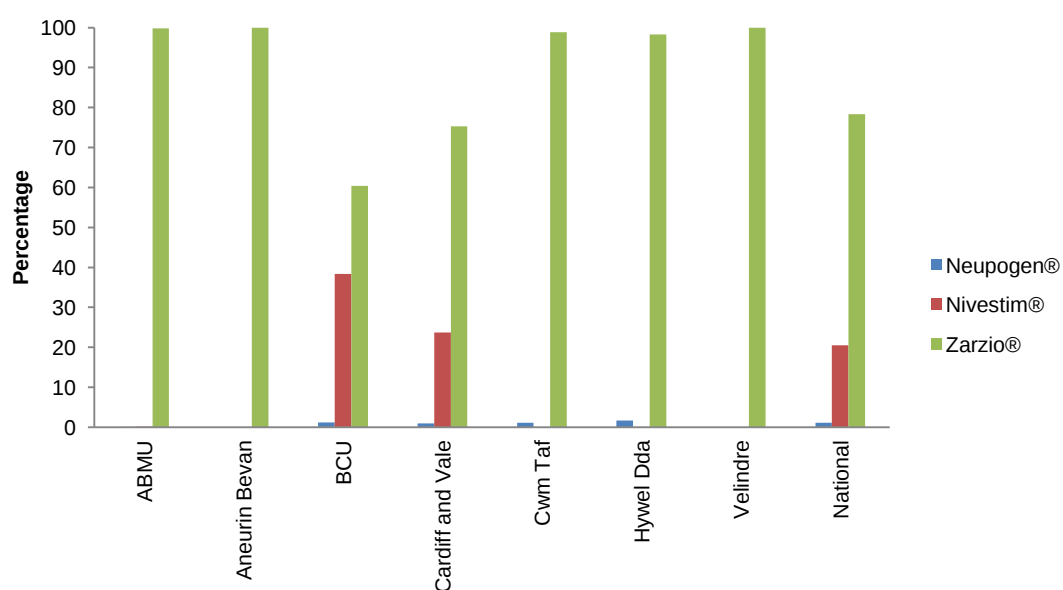
	ABMU	Aneurin Bevan	BCU	Cardiff and Vale	Cwm Taf	Hywel Dda	Powys	Velindre	National
Primary care (items)	93%	86%	94%	92%	79%	94%	87%	N/A	90%
Secondary care (number)	72%	72%	85%	81%	62%	81%	N/A	58%	77%

2.0 BIOSIMILARS

Table 3. Quantity and cost of filgrastim (Neupogen®) and filgrastim biosimilars prescribed within NHS Wales 2015–2016

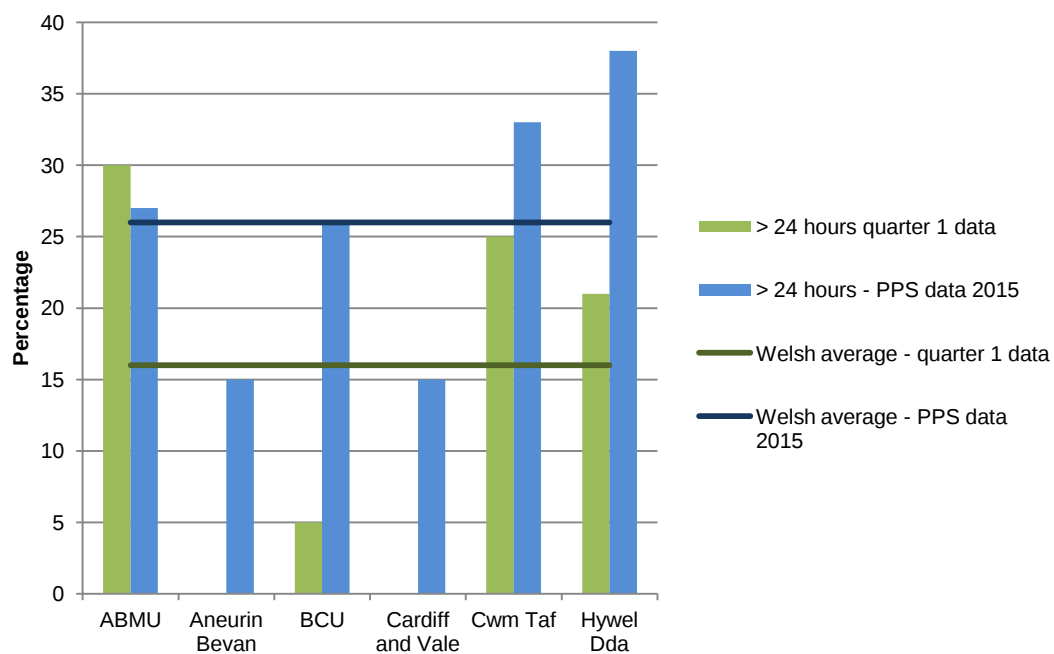
Medicine	Biosimilar	AWMSG Advice	Total quantity
Filgrastim (prescribed generically)	Unknown		107
Filgrastim (Neupogen®)			311
	Nivestim®	Recommended (March 2011)	5,160
	Zarzio®	Recommended (Sept 2010)	19,889
	TevaGrastim®	Recommended (Sept 2010)	0
	Ratiograstim®	Recommended (Sept 2009)	0

Figure 2. Filgrastim (Neupogen®) and filgrastim biosimilar medicines as a proportion of total filgrastim prescribed in secondary care 2015–2016



3.0 ANTIBIOTICS

Figure 3. Percentage of patients whose duration of colorectal surgical prophylaxis is > 24 hours (quarter one 2016–2017)



APPENDIX 3. USER-DEFINED GROUP OF HIGH-STRENGTH ICS

High-strength ICS	BNF code
Airflusal Forspiro_Inh 500/50mcg (60d)	0302000N0BGAAAZ
Beclomet Diprop/formoterol_Inh200/6(120d)	0302000C0AABZBZ
Beclomet Diprop_Inha 250mcg (200 D) Cff	0302000C0AABWBW
Beclomet/formoterol_Inh 200/6 (120d) Dry	0302000C0AACACA
Budesonide_Pdr For Inh 400mcg (100 D)	0302000K0AAAYAY
Budesonide_Pdr For Inh 400mcg (50 D)	0302000K0AAHAH
Clenil Modulite_Inha 250mcg (200d)	0302000C0BPADBW
Duoresp Spiromax_Inh 320mcg/9mcg (60 D)	0302000K0BHABAU
Easyhaler_Budesonide 400mcg (100 D)	0302000K0BGACAY
Flixotide_Accuhaler 500mcg (60 D)	0302000N0BBAUUAU
Flixotide_Evohaler 250mcg (120 D)	0302000N0BBAZBC
Fluticasone Prop_Inha 250mcg (120 D) Cff	0302000N0AABCBC
Fluticasone Prop_Pdr For Inh 500mcg(60d)	0302000N0AAAUUAU
Fluticasone/formoterol_Inh 250/10mcg120d	0302000N0AABKBK
Fluticasone/vilanterol_Inha 184/22mcg30d	0301011Y0AAAAAA
Flutiform_Inha 250/10mcg (120 D)	0302000N0BDABBK
Fostair Nexthaler_Inh 200mcg/6mcg (120d)	0302000C0BRABCA
Fostair_Inh 200mcg/6mcg (120d) Cff	0302000C0BQABBZ
Gppe Inha_Seretide 250 Evohaler(120d)cff	0302000N0AABGBG
Gppe Pdr For Inh_Seretide 500 (60 D)	0302000N0AAAZAZ
Gppe Pdr For Inhb/a_Symbicort 400/12(60d)	0302000K0AAAUUAU
Pulmicort_Turbohaler 400mcg (50 D)	0302000K0BBAIAH
Relvar Ellipta_Inha 184mcg/22mcg (30 D)	0301011Y0BBAAAA
Seretide 250_Evohaler 250mcg/25mcg(120d)	0302000N0BCAFBG
Seretide 500_Accuhaler 500mcg/50mcg(60d)	0302000N0BCACAZ
Sirdupla_Inh 250mcg/25mcg (120d)	0302000N0BFABBG
Symbicort_Turbohaler 400mcg/12mcg (60 D)	0302000K0BDACAU

APPENDIX 4. ANTICHOLINERGIC EFFECT ON COGNITION (AEC) SCORE⁹⁸

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	Metoprolol	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			
Levodopa	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

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