All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

National Prescribing Indicators 2016–2017

February 2016

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).

Please direct any queries to AWTTC:

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

awttc@wales.nhs.uk
029 2071 6900

This document should be cited as:
All Wales Medicines Strategy Group, National Prescribing Indicators 2016–2017. February 2016.

NHS WALES GIG CYMRU

All Wales Medicines Strategy Group
Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

CONTENTS

INTRODUCTION

Prescribing indicators are used to compare the way in which different prescribers and organisations use a particular medicine or group 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.

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 are applicable to both primary and secondary care. Although it is not currently possible to set targets for NPIs in secondary care, ongoing comparative monitoring is undertaken to identify differences in prescribing practice.

Secondary Care Indicators, which aim to highlight therapeutic priorities for NHS Wales in secondary care, are expected to be published by AWMSG in early 2016.

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 2015–2016 NPIs, to ensure they were still valid and reflected best practice.

Prior to the NPI Task and Finish Group meeting, Health Board Chief Pharmacists, their medicines management teams, Medicines and Therapeutics Committees and Assistant Medical Directors were invited to comment on the continued relevance of the 2015–2016 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.

The proposed NPIs for 2016–2017, accompanied by the supporting evidence, were presented to AWPAG for their comment. The NPIs for 2016–2017 have been distributed for wider consultation prior to their endorsement by AWMSG.

Key changes:

- Introduce two new NPIs:
  - Lipid-regulating medicines: Items of bile acid sequestrants, fibrates, nicotinic acid and omega-3 fatty acid compounds (BNF 2.12 sub-set) as a percentage of total lipid-regulating items
  - Gabapentin and pregabalin use (defined daily doses [DDDs] per 1,000 patients)
- Retire two NPIs (continue to monitor as Local Comparators):
  - Lipid-regulating medicines: Items of LAC statins as a percentage of all statin, ezetimibe and simvastatin/ezetimibe combination prescribing
  - Opioids: Items of morphine as a percentage of strong opioid prescribing

Measures

- Where possible, measures used should be accessible to all medicines management teams through CASPA.net.
- The average daily quantity (ADQ) and specific therapeutic group age–sex related prescribing unit (STAR-PU) measurements are used for certain indicators instead of the DDD measurement and prescribing unit (PU) weighting, despite not being available on CASPA.net, in order to benchmark with the 'Quality, innovation, productivity and prevention' (QIPP) comparators in England. These data are available on a quarterly basis through the NHS Wales Shared Services Partnership: Primary Care Services.
- Yellow Card Centre (YCC) Wales will monitor Yellow Card reporting by GP practice, providing feedback at health board and practice level.

Targets

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 2015.
- 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 – total antibiotic prescribing. 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.
- One NPI has been included using alternative monitoring methods – Yellow Card reporting. This will be monitored by YCC Wales, who will provide data to the Welsh Analytical Prescribing Support Unit (WAPSU) and individual Health Board Chief Pharmacists on a quarterly basis.
- 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 2016–2017, with the evidence and supporting prescribing messages within the text that follows. Data to support the proposed NPIs for 2016–2017 are contained within Appendix 2.

Please note:
The NPIs constitute guidance only, and this document, either in isolation or as part of wider policy, is not associated with any financial incentive scheme, and does not offer any medical practice and/or practitioner any financial incentive to prescribe a specific named medicine.

Implementation of the recommended NPIs does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer. This is supported by the prudent healthcare agenda, which encourages the creation of a prescribing partnership where the process of prescribing, dispensing and administering medicines puts the patient at its centre and encourages shared decision making[1].

Table 1. AWMSG NPIs 2016–2017

Indicator	BNF chapter	Unit of measure	Target for 2016–2017
Proton pump inhibitors (PPIs)	1.3.5	PPI DDDs per 1,000 PUs	Maintain performance levels within the lower quartile, or show a reduction towards the quartile below
Lipid-regulating drugs	2.12	Items of bile acid sequestrants, fibrates, nicotinic acid and omega-3 fatty acid compounds (BNF 2.12 sub-set) as a percentage of total lipid-regulating items	Maintain performance levels within the lower quartile, or show a reduction towards the quartile below
Inhaled corticosteroids (ICS)	3.2	Low strength ICS items as a percentage of all ICS prescribing	Maintain performance levels within the upper quartile, or show an increase towards the quartile above
Hypnotics and anxiolytics	4.1	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	4.7.2	Tramadol DDDs per 1,000 patients	Maintain performance levels within the lower quartile, or show a reduction towards the quartile below
	4.8.1	Gabapentin and pregabalin DDDs per 1,000 patients	Maintain performance levels within the lower quartile, or show a reduction towards the quartile below
Antibiotics	5.1	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
	5.1.1	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
	5.1.2	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
	5.1.12	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
Non-steroidal anti-inflammatory drugs (NSAIDs)	10.1.1	NSAID ADQs per 1,000 STAR-PUs	Maintain performance levels within the lower quartile, or show a reduction towards the quartile below
	10.1.1	Ibuprofen and naproxen items as a percentage of NSAID prescribing	Maintain performance levels within the upper quartile, or show an increase towards the quartile above
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.

ADQ = average daily quantity; DDD = defined daily dose;
PU = prescribing unit; STAR-PU = specific therapeutic group age–sex related prescribing unit

1.0 PROTON PUMP INHIBITORS

***Purpose*:** To encourage appropriate use of PPIs.

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

Target for 2016–2017: 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]. In addition, they are used for a number of unlicensed indications (more common in hospital settings), including the reduction of re-bleeding episodes after treatment of severe peptic ulcer bleeding, prophylaxis of acid aspiration during general anaesthesia and stress ulcer prophylaxis[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 6% per year[4]. In the financial year 2014–2015, nearly 4.3 million prescriptions for PPIs were dispensed in Wales[4]. Assuming each patient received 13 (28-day) prescriptions during the year, this amounts to 328,400 patients (10.3% of the population) receiving PPIs[4]. 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]. Additionally, recommendations on the importance of gastroprotection, particularly for patients on combinations of high-risk medicines, e.g. NSAIDs for the treatment of osteoarthritis[6] and rheumatoid arthritis (RA)[7], 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 helpful[2]. 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” basis[2].

PPIs are generally well tolerated, with side-effects that are usually mild and reversible, including headache, diarrhoea, nausea, abdominal pain, constipation, dizziness and skin rashes. There are, however, growing concerns about a variety of serious adverse effects with long-term PPI use, particularly *Clostridium difficile* infection, increased risk of bone fractures, community-acquired pneumonia and increased mortality in older patients[8].

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 infection[9].

Medicines and Healthcare Products Regulatory Agency (MHRA) advice issued in April 2012 stated that there is "recent epidemiological evidence of an increased risk of fracture with long-term use of PPIs. Patients at risk of osteoporosis should be treated according to current clinical guidelines to ensure they have an adequate intake of vitamin D and calcium"[10].

Other possible serious adverse effects include acute intestinal nephritis, hypomagnesaemia, vitamin B_{12} deficiency and rebound hypersecretion syndrome[11]. Although there is a lack of strong evidence to support the association between these adverse effects and long-term PPI use, the association is biologically plausible, and has been shown in observational studies[11].

Advice in a 2012 Drug Safety Update highlighted reports of patients developing hypomagnesaemia following long-term use of PPIs[12]. 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 arrhythmia[12].

NICE confirms that long-term PPI use has also been linked to rebound hypersecretion, and states that: "This 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"[2].

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 appropriate[13,14]. Stepping down may involve a lower dose, as-required dosing, or changing to an antacid and/or alginate preparation[3]. 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 hypersecretion[13].

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 LIPID-REGULATING MEDICINES

***Purpose*:** To encourage prescribers to review and, if appropriate, revise prescribing of the lipid-regulating medicines – bile acid sequestrants, fibrates, nicotinic acid and omega-3 fatty acid compounds – to ensure it is in line with NICE guidance.

Unit of measure: Number of prescription items of bile acid sequestrants, fibrates, nicotinic acid and omega-3 fatty acid compounds (UDG) as a percentage of the total number of lipid-regulating items.

Target for 2016–2017: Maintain performance levels within the lower quartile, or show a reduction towards the quartile below.

Specific basket of medicines to be monitored, in this document referred to as a user-defined group (UDG).

UDG: Acipimox, bezafibrate, ciprofibrate, colesevelam hydrochloride, colestipol hydrochloride, cholestyramine, fenofibrate, gemfibrozil, nicotinic acid, nicotinic acid/laropiprant, omega-3 marine triglycerides, omega-3-acid ethyl esters.

Background and evidence

NICE issued Clinical Guideline (CG) 181 in July 2014, which updated the guidance relating to lipid modification in adults both with and without diabetes. The guidance recommends the use of atorvastatin 20 mg for the primary prevention of cardiovascular disease for people, with or without type 2 diabetes, who have a 10% or greater 10-year risk of developing cardiovascular disease[15]. Atorvastatin 20 mg is also recommended for primary prevention in patients with type 1 diabetes in specific circumstances[15]. Atorvastatin 80 mg is recommended for patients with established cardiovascular disease[*]. Lower doses should be used if there are potential drug interactions, if the patient is at high risk of adverse effects, or if patient preference is for a lower dose[15].

NICE CG181 recommends against the routine prescribing of fibrates, and against offering nicotinic acid, bile acid sequestrants and omega-3 fatty acid compounds, for the prevention of cardiovascular disease in the following: people who are being treated for primary prevention, people being treated for secondary prevention, people with chronic kidney disease (CKD), people with type 1 diabetes and people with type 2 diabetes, either as monotherapy or in combination with a statin.

NICE CG71 on the management of familial hypercholesterolaemia (FH) recommends using the maximum licensed or tolerated dose of statin first line to achieve a recommended reduction in low-density lipoprotein cholesterol (LDL-C) concentration of greater than 50% from baseline[16]. However, if a patient cannot tolerate such intensive treatment, ezetimibe can be added to statin therapy or initiated as monotherapy[16]. NICE CG71 states that 'adults with FH with intolerance or contraindications to statins or ezetimibe should be offered a referral to a specialist with expertise in FH for consideration for treatment with either a bile acid sequestrant, nicotinic acid, or a fibrate to reduce their LDL-C concentration. The decision to offer treatment with a bile acid sequestrant, nicotinic acid or a fibrate in addition to initial statin therapy should be taken by a specialist with expertise in FH'[16].

[*]NICE CG181: At the time of publication (July 2014), atorvastatin did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented[15].

NICE CG71 also states that 'people with FH should not routinely be recommended to take omega-3 fatty acid supplements'[16]. NICE CG172, however, does state that if a person chooses to take these products, there is no evidence of any harm associated with them[17].

In addition to their use in cardiovascular disease, omega-3 fatty acid supplements have been studied in boys with dyslexia[18], in children with behavioural or learning problems to improve concentration[19] and also in photosensitivity disorder[20]. Whilst there is some evidence of benefit in these situations, there is insufficient evidence to support the routine use.

These guidelines would therefore suggest minimal use of bile acid sequestrants, fibrates, nicotinic acid, and omega-3 fatty acid compounds as lipid-regulating medicines, and where used, this should be under the recommendation of a specialist.

Useful resources

- NICE (2014) CG181: Cardiovascular disease: risk assessment and reduction, including lipid modification.
- NICE (2014) Cardiovascular disease prevention overview – includes section on lipid modification therapy.
- NICE (2014) CG181: Lipid modification: patient decision aid.
- NICE (2008) CG71: Familial hypercholesterolaemia: identification and management.
- NICE (2007) TA132: Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia.

3.0 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: Low strength ICS* items as a percentage of all ICS prescribing.

Target for 2016–2017: Maintain performance levels within upper quartile, or show an increase towards the quartile above.

*Low strength ICS: Any inhaler device which when used at the usual dose provides a dose of ICS < 800 microgram of beclometasone or equivalent (see Appendix 1 for the specific basket of medicines to be monitored [UDG]).

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 2014–2015 show that the prevalence of asthma in Wales is 7.1%, and the prevalence of COPD is 2.2%[21]. Low strength (< 800 microgram of beclometasone or equivalent) combination ICS therapy and ICS monotherapy are not licensed for use in COPD. The limited place of ICS in the management of COPD and the prevalence data therefore suggest that the majority of ICS prescribed in Wales should be for the management of asthma.

In Wales, nearly 1.7 million primary care ICS prescriptions were dispensed in the financial year to the end of March 2015, costing NHS Wales £56.7 million. This group of medicines accounts for the highest spend in primary care in Wales[4]. Of the 1.7 million prescriptions, 62% are for inhalers classed as high strength (i.e. likely to be providing a daily dose of ICS equivalent to beclometasone ≥ 800 microgram)[4].

The *British guideline on the management of asthma* advocates a stepwise approach for the treatment of asthma[22]. An ICS is the first-choice regular preventer therapy for adults and children with asthma for achieving overall treatment goals[22]. An ICS should be considered for patients (adults and children, aged 5 years and older) with any of the following asthma-related features: exacerbations of asthma in the last two years, using inhaled beta-2 agonists three times a week or more, symptomatic three times a week or more, waking one night a week[22]. 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 maintained[22]. They recommend that dose reduction should be considered every 3 months, decreasing the dose by approximately 25–50% each time[22]. Where it is essential that a patient remains on the same device, prescribe by brand or refer to the British National Formulary (BNF), MHRA and/or local guidance.

An ICS is the first choice preventer medicine; however, a proportion of patients may not be adequately controlled on an ICS, and additional preventer therapy may be appropriate. There is no exact dose of ICS at which it can be deemed appropriate to add on another therapy[22]. A meta-analysis studying the dose-response relation of fluticasone propionate in adolescents and adults with asthma suggests that most of the therapeutic benefit is achieved with a total daily dose of 100–250 microgram[23]; a second meta-analysis supports this, suggesting that most therapeutic benefit is achieved with a total daily dose of 200 microgram fluticasone propionate, with minimal further clinical benefit achieved with higher doses[24].

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 appropriate[25]. The *British guideline on the management of asthma* recommends that before starting a new medicine, adherence and inhaler technique should be checked. Although no exact dose of ICS can be deemed the correct dose in adults and children aged 5 years and over, the guideline states that a LABA should be considered before going above a dose of 400 micrograms beclometasone dipropionate (BDP) or equivalent per day[22].

A retrospective prescribing analysis of 685 people with asthma in 46 general practice surgeries in Scotland found initiating combination ICS plus LABA therapy resulted in widespread increases in ICS dose[26]. 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 care[26]. The study also raises the question of whether there is sufficient awareness regarding ICS doses in the different combination preparations.

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 bronchodilators[27].

There are safety issues relating to the use of high doses of ICS in asthma. Unpleasant local side effects, including oral candidiasis and dysphonia, can occur with ICS at standard doses, but are more common with higher doses. Potentially serious systemic side effects, such as adrenal suppression, growth failure, decrease in bone mineral density, cataracts and glaucoma, may be associated with ICS particularly at high doses (above 800 micrograms beclometasone or equivalent per day in adults and above 400 micrograms beclometasone or equivalent per day in children)[22,28]. 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)[29]. The Committee on Safety of Medicines (CSM) issued warnings about the use of high-dose ICS, particularly in children and in relation to fluticasone propionate[30].

Use of ICS has been associated with increased risk of pneumonia, but the magnitude of risk and how this varies among different types of ICS remains unclear[31]. A review of clinical trials suggested that budesonide and fluticasone (fluticasone furoate and fluticasone propionate), delivered alone or in combination with a LABA, are associated with increased risk of serious adverse pneumonia events, but neither significantly affected mortality compared with controls[31]. The review concluded, however, that these safety concerns should be balanced with established randomised evidence of efficacy regarding exacerbations and quality of life[31].

Fluticasone furoate/vilanterol (Relvar® Ellipta® 92 micrograms/22 micrograms or 184 micrograms/22 micrograms) was launched in January 2014 for the treatment of asthma. Fluticasone furoate/vilanterol has received a positive recommendation from AWMSG as an option for use in both asthma and COPD[32,33]. According to the summary of product characteristics, in patients with asthma, fluticasone furoate 92 micrograms once a day is approximately equivalent to fluticasone propionate 250 micrograms twice a day[34]. Healthcare professionals should be aware of the high potency of fluticasone furoate compared with other types of ICS. Because a lower strength is not available, the ability to step down treatment is limited. Therefore, for the purposes of this NPI, fluticasone furoate/vilanterol appears in the denominator.

Useful resources

SIGN (2014) SIGN 141: British guideline on the management of asthma.
NICE (2010) CG101: Chronic obstructive pulmonary disease in over 16s: diagnosis and management

4.0 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 (UDG).

Target for 2016–2017: Maintain performance levels within the lower quartile, or show a reduction towards the quartile below.

UDG: chlordiazepoxide, diazepam, flurazepam, loprazolam, lorazepam, lormetazepam, nitrazepam, oxazepam, temazepam, zaleplon, zolpidem, zopiclone

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 benzodiazepines[35]. Although the prescribing volume of hypnotics and anxiolytics (UDG) 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[4,36].

In the financial year 2014–2015, the number of items dispensed was 1,456,026, compared with 1,482,234 the previous year: a reduction of 1.8% (total quantity of tablets reduced by 4.4% from 41,145,680 to 39,322,721 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 distress[37]. NICE guidance on managing insomnia also advises that after non-drug therapies have been explored, hypnotics should be used in the lowest dose possible for the shortest duration possible in strict accordance with their licensed indications: no more than 4 weeks with benzodiazepines, maximum 2 weeks with zaleplon and 4 weeks with zopiclone and zolpidem[38,39]. NICE guidance on generalised anxiety disorder (GAD) in adults recommends that benzodiazepines should not be offered for the treatment of GAD in primary or secondary care except as a short-term measure during crises[40].

Benzodiazepine hypnotics and anxiolytics are known to significantly increase risk of falls[41]. Falls risk assessment tools advise reviewing sleeping tablets such as benzodiazepines and “Z” drugs in patients at high risk of falling[42].

More recently benzodiazepine use has been associated with an increase risk of Alzheimer’s disease. An observational study in Canada showed that the risk of Alzheimer’s disease was increased by 43–51% among those who had used benzodiazepines in the past. Risk increased with increased exposure and when long-acting benzodiazepines were used[43]. Another observational study suggested benzodiazepines increase the risk of dementia[44]. A further UK retrospective cohort study assessed the risk of death in people aged 16 years and over who were first prescribed anxiolytic or hypnotic drugs, or both, between 1998 and 2001. The study found that patients who had been prescribed anxiolytic and hypnotic medication had a

significantly increased risk of death from any cause over a 7-year period[45]. Whilst these are observational studies demonstrating association rather than causation, they reinforce guidance that anxiolytics and hypnotics should be prescribed only after consideration of non-drug therapies.

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 (2011) Educational Pack: Material to Support Appropriate Prescribing of Hypnotics and Anxiolytics Across Wales.
- AWMSG (2014) Polypharmacy: Guidance for Prescribing.

5.0 ANALGESICS

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

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

Target for 2016–2017: Maintain performance levels within lower quartile, or show a reduction towards the quartile below.

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

Target for 2016–2017: Maintain performance levels within lower quartile, or show a reduction towards the quartile below.

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 a common and distressing condition; acute pain can occur as a result of trauma, surgery or an acute illness. 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 chronic pain can present as a complex problem before this time[46]. Chronic pain is common, affecting around five million people in the UK[47].

Chronic non-malignant pain covers a wide range of painful conditions affecting patients physically, psychologically and socially. These conditions can have a significant impact on quality of life and the ability of patients to undertake everyday activities[48]. Opioid analgesics are increasingly used to treat chronic pain; however, their safety and efficacy in the long-term management of pain is uncertain, as is the propensity for these medicines to cause problems of tolerance, dependence and addiction[47].

Chronic pain becomes an increasingly significant problem as pain prevalence increases, for example with ageing and with more cancer survivors and trauma survivors[46]. Unrelieved chronic pain is a major socio-economic burden for the health service and the community[46].

5.1 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 pathways[38]. It has fewer of the typical opioid side effects, e.g. less respiratory depression and constipation, but psychiatric reactions have been reported. The unique dual-action pharmacological profile of tramadol increases the risk of adverse effects seen in overdose[49].

Tramadol has accounted for an increasing number of deaths and reports to the National Poisons Information Service[50]. It is subject to abuse and dependence and there are concerns with regard to interactions. Deaths related to the misuse of tramadol in England and Wales increased from 83 in 2008 to 240 in 2014[51]. In February 2013 the Advisory Council for the Misuse of Drugs (ACMD) proposed changes to the classification of tramadol intended to prevent its diversion and misuse[49] and, in June 2014, tramadol was placed within Schedule III to the Misuse of Drugs Regulations but with exemptions from safe custody.

Dizziness and nausea are the most commonly reported adverse effects of tramadol. Headache, drowsiness, vomiting, constipation, dry mouth, fatigue and sweating are other common side effects[52]. Hallucinations, confusion and convulsions, as well as rare cases of dependence and withdrawal symptoms, have been reported with tramadol at therapeutic doses[53].

To minimise the risk of convulsions, patients with a history of epilepsy or those susceptible to seizures should only be treated with tramadol if there are compelling reasons to do so[54]. 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)[54]. The use of tramadol is contra-indicated in uncontrolled epilepsy and in patients receiving, or who have recently discontinued (within the previous two weeks) monoamine oxidase inhibitors[52].

The NPI does not measure the prescribing of Tramacet® (tramadol/paracetamol combination) as there are no DDDs available. Tramacet® is a non-formulary item in all health boards in Wales and prescribing accounts for 1.9% of all tramadol prescribed. 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.

5.2 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 and pregabalin as first-line treatment options for neuropathic pain[55]. 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 patent[56]. Gabapentin is also licensed for use in epilepsy[57,58], and all brands of pregabalin are licensed for the treatment of generalised anxiety disorder and epilepsy in adults[59–61].

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 patient[55]. Pregabalin is less cost-effective than gabapentin and amitriptyline[55], 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 failed[62].

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 need[55]. 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 therapies[63].

NICE recommends considering gabapentin for the treatment of spasticity and oscillopsia in multiple sclerosis[64]. However, gabapentin does not have a UK marketing authorisation for this indication[65].

Both gabapentin and pregabalin have known psychiatric side effects[58,59,66,67]. For pregabalin, the incidence of euphoria is common (≥ 1/100 to < 1/10) and the incidence of hallucinations is uncommon (≥ 1/1,000 and < 1/100)[59]. The SPC for gabapentin lists hallucinations as a side effect, although the incidence is unknown[57].

Caution in prescribing pregabalin should be exercised in patients with a history of substance abuse[59–61]. Public Health England issued advice in 2014 highlighting the potential for misuse of gabapentin and pregabalin and providing suggestions for the balanced and rational use of these medicines[66]. Advice published by the Advisory Council on the Misuse of Drugs (ACMD) in January 2016, also highlighted the potential risk of dependence, misuse and diversion of gabapentin and pregabalin and the importance of the appropriate prescribing to minimise these risks[68]. The ACMD also 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 prescription[68].

Gabapentin and pregabalin have been mentioned on death certificates as adjunctive substances in patients dying of drug poisoning[66]; figures have increased from zero deaths for both gabapentin and pregabalin in 2008 to 26 and 38 respectively in 2014[69].

Prescribing of gabapentin and pregabalin in Wales is high in comparison to England (1,161 DDDs/1,000 patients compared to 883.8 DDDs/1,000 patients, for the quarter ending September 2015)[4,70], and primary care DDDs/1,000 patients are currently increasing at a rate of approximately 19% per year in Wales.

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

- WHO Pain Relief Ladder.
- SIGN (2013) SIGN 136. Management of chronic pain.
- AWMSG (2013) Tramadol Educational Resource Materials.
- PrescQIPP (2014) Pregabalin in neuropathic pain.
- Public Health England (2014) Advice for prescribers on the risk of the misuse of pregabalin and gabapentin.

6.0 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 antimicrobials[71].

Total items
Unit of measure:
Total antibacterial items per 1,000 STAR-PUs.

Target for 2016–2017:
No performance target set. Aim for reduction in prescribing year on year, measuring quarter to December only.

Co-amoxiclav
Units of measure:
Co-amoxiclav items per 1,000 patients.
Co-amoxiclav items as a percentage of total antibacterial items.

Target for 2016–2017:
Maintain performance levels within the lower quartile, or show a reduction towards the quartile below.

Cephalosporins
Units of measure:
Cephalosporin items per 1,000 patients.
Cephalosporin items as a percentage of total antibacterial items.

Target for 2016–2017:
Maintain performance levels within the lower quartile, or show a reduction towards the quartile below.

Fluoroquinolones
Units of measure:
Fluoroquinolone items per 1,000 patients.
Fluoroquinolone items as a percentage of total antibacterial items.

Target for 2016–2017:
Maintain performance levels within the lower quartile, or show a reduction towards the quartile below.

Notes
The above NPIs only include antibacterials that appear in Chapter 5 (Infections) of the British National Formulary (BNF)[38].

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

Background and evidence

6.1 Total antibacterial items
The Public Health Wales report *Antimicrobial Resistance in Wales (2005–2014)* presents the different prescribing and antimicrobial resistance (AMR) patterns across Wales[72]. The report shows Wales resistance rates for drug-bug combinations

compared to UK aggregate rates and find 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 areas[72]. For the year April 2014–March 2015, primary care prescribing rates varied from 691 to 856 items per 1,000 patients across Welsh health boards[4].

The *UK Five Year Antimicrobial Resistance Strategy 2013–2018* was published in September 2013[73]. This has been developed collaboratively with the UK devolved administrations and will provide surveillance and a coordinated plan of action needed to address this issue. The overarching goal of the strategy is to slow the development and spread of AMR. It focuses activities around three strategic aims:

- improve the knowledge and understanding of AMR,
- conserve and steward the effectiveness of existing treatments,
- stimulate the development of new antibiotics, diagnostics and novel therapies[73].

NICE guideline – *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 antimicrobial[74].

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”[75]. Broad-spectrum antibiotics need to be reserved to treat resistant disease, and should generally be used only when narrow-spectrum and less expensive antibiotics are ineffective. The guidance advises when it may be appropriate to consider a broad-spectrum antibiotic[75].

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 bacteraemias[76].

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* infection[77].

6.2 Co-amoxiclav

Co-amoxiclav is a broad-spectrum penicillin with activity against beta-lactamase-producing organisms such as *S. aureus* and *Escherichia coli*[78].

6.3 Cephalosporins

The cephalosporins are broad-spectrum antibiotics, which are used for the treatment of septicaemia, pneumonia, meningitis, biliary-tract infections, peritonitis and urinary tract infections[38] mainly in secondary care settings. Cephalosporins are not listed as first-line treatments in the public health report *Management of infection guidance for primary care for consultation and local adaption*[75].

6.4 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)[75].

Useful resources

- AWMSG (2013) CEPP National Audit: Focus on Antibiotic Prescribing.
- AWMSG (2015) Primary care antimicrobial guidelines.
- Welsh Medicines Resource Centre (WeMeReC) (2012) Bulletin: Appropriate antibiotic use – whose responsibility?
- Royal College of General Practitioners. TARGET Antibiotics toolkit.

7.0 NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

Purpose: Ensure that the risks associated with NSAIDs are minimised by appropriate choice and use.

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

Target for 2016–2017: Maintain performance levels within the lower quartile, or show a reduction towards the quartile below.

2. Unit of measure: Ibuprofen and naproxen items as a percentage of NSAID prescribing.

Target for 2016–2017: Maintain performance levels within the upper quartile, or show an increase towards the quartile above.

Background and evidence

All oral NSAIDs have analgesic effects of a similar magnitude[6,7]. 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 cylo-oxygenase-1 (COX-1) and cycloxygenase-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) toxicity[38].

There are long-standing and well recognised GI[79] and renal[80] safety concerns with all NSAIDs. Additionally, there have been increasing cardiovascular safety concerns with some NSAIDs, particularly COX-2 inhibitors and diclofenac[81].

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[6,7]. Gastroprotection, with a PPI, is recommended particularly for patients on NSAIDs with osteoarthritis or RA[6,7]. Ibuprofen and COX-2 inhibitors are associated with the lowest GI risk, but serious and fatal GI reactions have nevertheless been reported[82]. Co-prescription of SSRIs may be associated with a similar increase in the risk of GI complications as co-prescription of low-dose aspirin[83].

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 inhibitors[84]. Whilst in 2007, the MHRA raised concerns about the cardiovascular risks associated with diclofenac[79]. 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 inhibitors[81]. In 2013, an MHRA consultation concluded that diclofenac would no longer be available as a pharmacy (P) medicine[85]. 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 inhibitors[86]. In June 2015, the MHRA reported that an EMA review had confirmed the cardiovascular risk of high-dose ibuprofen (≥ 2400 mg/day) as being similar to that of a COX-2 inhibitor and diclofenac[87].

NSAIDs and renal events
NSAIDs, including COX-2 inhibitors, may rarely precipitate renal failure, and vulnerable (particularly elderly) patients may be at increased risk. 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 dehydration[88]. NSAIDs in combination with diuretics and angiotensin converting enzyme inhibitors or angiotensin receptor blockers are associated with an increased risk of AKI[89]. 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. It recommends exercising caution when treating people with CKD with NSAIDs over prolonged periods of time[90].

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).

7.1 All NSAIDs
Despite ongoing reductions in the usage of NSAIDs in Wales, total prescribing (ADQs/1,000 STAR-PUs) remains 26% higher than that seen in England. 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[6,7]. If an oral NSAID is indicated, 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[91].

7.2 Ibuprofen and naproxen
Naproxen and low-dose ibuprofen (≤ 1200 mg a day) are considered to have the most favourable cardiovascular safety profiles of all non-selective NSAIDs[81]. In the year to 31 March 2015, over 1.2 million prescriptions were dispensed for NSAIDs. Whilst the majority (80%) were for ibuprofen and naproxen, diclofenac still makes up 7% of all NSAID prescriptions dispensed.

Useful resources
- AWMSG (2015) CEPP All Wales Audit: Towards appropriate NSAID prescribing.

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 2016–2017*:** 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. ADRs are attributed to 6.5% of hospital admissions in adults and 2.1% in children[92,93].

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 2014–2015, the number of Yellow Cards submitted by GPs in Wales increased by 162% compared to the previous financial year, to 665.

It is anticipated that continuing to monitor Yellow Card reporting per practice population as the first part of this NPI for 2016–2017 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 website
- MHRA webpages
- WeMeReC (2013) Pharmacovigilance Bulletin
- YCC Wales website
- British Medical Journal Learning (2012) Pharmacovigilance – identifying and reporting adverse drug reactions
- NHS Scotland e-learning modules on ADRs

Download the Yellow Card App:

- Android:https://play.google.com/store/apps/details?id=uk.org.mhra.yellowcard&hl=en_GB
- Apple:https://itunes.apple.com/gb/app/yellow-card-mhra/id990237487?ls=1&mt=8

REFERENCES

1 Routledge P. Better health outcomes and safer care through prudent prescribing. 2014. Available at: http://www.prudenthealthcare.org.uk/prescribing/. Accessed Oct 2015.

2 National Institute for Health and Care Excellence. Clinical Guideline 184. Dyspepsia and gastro-oesophageal reflux disease: Investigation and management of dyspepsia, symptoms suggestive of gastro-oesophageal reflux disease, or both (CG184). 2014. Available at: http://www.nice.org.uk/guidance/cg184. Accessed Oct 2015.

3 Welsh Medicines Resource Centre. Stopping medicines – proton pump inhibitors. 2010. Available at: http://www.wemerec.org/Documents/enotes/StoppingPPIsenotes.pdf. Accessed Oct 2015.

4 NHS Wales Shared Services Partnership. Comparative Analysis System for Prescribing Audit (CASPA). 2015. Accessed Oct 2015.

5 McColl KEL, Gillen D. Evidence that proton-pump inhibitor therapy induces the symptoms it is used to treat. *Gastroenterology* 2009; 137 (1): 20-2. Available at: http://www.gastrojournal.org/article/S0016-5085(09)00780-X/abstract. Accessed: Oct 2015.

6 National Institute for Health and Care Excellence. Clinical Guideline 177. Osteoarthritis: Care and management (CG177). 2014. Available at: http://www.nice.org.uk/guidance/cg177. Accessed Oct 2015.

7 National Institute for Health and Care Excellence. Clinical Guideline 79. Rheumatoid arthritis in adults: management (CG79). 2009. Available at: http://www.nice.org.uk/guidance/CG79. Accessed Oct 2015.

8 National Institute for Health and Care Excellence. Eyes on Evidence: Use of proton pump inhibitors (PPIs) on discharge from hospital and 1-year mortality in older patients. 2013. Available at: http://arms.evidence.nhs.uk/resources/hub/1027935/attachment. Accessed Oct 2015.

9 National Prescribing Centre. MeReC Rapid Review: Increased risk of C. difficile infections and of fractures: two more good reasons to review PPI prescribing. 2010. Available at: http://webarchive.nationalarchives.gov.uk/20110927231944/http:/www.npc.nhs.uk/rapidreview/?p=1494. Accessed Oct 2015.

10 Medicines and Healthcare products Regulatory Agency. Drug Safety Update. Proton pump inhibitors in long-term use: increased risk of fracture. 2012. Available at: https://www.gov.uk/drug-safety-update/proton-pump-inhibitors-in-long-term-use-increased-risk-of-fracture. Accessed Oct 2015.

11 Abraham NS. Proton pump inhibitors: potential adverse effects. *Current Opinion in Gastroenterology* 2015; 28 (6): 615-20. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23010681. Accessed: Oct 2015.

12 Medicines and Healthcare products Regulatory Agency. Drug Safety Update: Proton pump inhibitors in long-term use: reports of hypomagnesaemia. 2012. Available at: https://www.gov.uk/drug-safety-update/proton-pump-inhibitors-in-long-term-use-reports-of-hypomagnesaemia. Accessed Oct 2015.

13 All Wales Medicines Strategy Group. Polypharmacy: Guidance for Prescribing. 2014. Available at: http://www.awmsg.org/docs/awmsg/medman/Polypharmacy%20-%20Guidance%20for%20Prescribing.pdf. Accessed Oct 2015.

14 Gallagher P, Ryan C, Byrne S et al. STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. *International Journal of Clinical Pharmacology and Therapeutics* 2008; 46: 72-83. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18218287.

15 National Institute for Health and Care Excellence. Clinical Guideline 181. Cardiovascular disease: risk assessment and reduction, including lipid modification (CG181). 2014. Available at: http://www.nice.org.uk/guidance/cg181. Accessed Oct 2015.
16 National Institute for Health and Care Excellence. Clinical Guideline 71. Familial hypercholesterolaemia: identification and management (CG71). 2008. Available at: http://www.nice.org.uk/guidance/cg71. Accessed Oct 2015.
17 National Institute for Health and Care Excellence. Clinical Guideline 172. Myocardial infarction: cardiac rehabilitation and prevention of further MI (CG172). 2013. Available at: https://www.nice.org.uk/guidance/cg172. Accessed Oct 2015.
18 UK Medicines Information. Fish oil supplements in dyslexia - is there evidence of benefit? 2014. Available at: http://www.medicinesresources.nhs.uk/GetDocument.aspx?pageId=504124. Accessed Oct 2015.
19 UK Medicines Information. Fish oil supplements - is there evidence that they improve concentration and behaviour in children? 2013. Available at: http://www.medicinesresources.nhs.uk/upload/documents/Evidence/Medicines%20Q%20&%20A/NW_QA_146_4_Fish_oils_and_ADHD.doc. Accessed Oct 2015.
20 UK Medicines Information. Can fish oils protect against photosensitivity disorders? 2014. Available at: http://www.medicinesresources.nhs.uk/GetDocument.aspx?pageId=504084. Accessed Oct 2015.
21 Welsh Government. General medical services contract: Quality and outcomes framework. 2015. Available at: http://wales.gov.uk/statistics-and-research/general-medical-services-contract/?lang=en. Accessed Oct 2015.
22 Scottish Intercollegiate Guidelines Network. SIGN 141. British guideline on the management of asthma. 2014. Available at: http://www.sign.ac.uk/pdf/SIGN141.pdf. Accessed Oct 2015.
23 Holt S, Suder A, Weatherall M et al. Dose-response relation of inhaled fluticasone propionate in adolescents and adults with asthma: meta-analysis. 2001. 323(253)Available at: http://www.bmj.com/content/323/7307/253.long. Accessed Oct 2015.
24 Masoli M, Weatherall M, Holt S et al. Clinical dose-response relationship of fluticasone propionate in adults with asthma. 2004. 59:16-20. Available at: http://thorax.bmj.com/content/59/1/16.full. Accessed Oct 2015.
25 National Institute for Health and Care Excellence. Technology Appraisal 138. Inhaled corticosteroids for the treatment of chronic asthma in adults and in children aged 12 years and over (TA138). 2008. Available at: https://www.nice.org.uk/guidance/ta138. Accessed Oct 2015.
26 Covvey JR, Johnston BF, Wood F et al. Changes to inhaled corticosteroid dose when initiating combination inhaler therapy in long-acting ß agonist-naïve patients with asthma: a retrospective database analysis. *Thorax* 2014; 1-3. Available at: http://thorax.bmj.com/content/early/2014/01/15/thoraxjnl-2013-204944.full.pdf+html. Accessed: Oct 2013.
27 National Institute for Health and Care Excellence. Clinical Guideline 101. Chronic obstructive pulmonary disease: Management of chronic obstructive pulmonary disease in adults in primary and secondary care (partial update). 2010. Available at: https://www.nice.org.uk/guidance/cg101. Accessed Oct 2014.
28 Medicines and Healthcare products Regulatory Agency. Current Problems in Pharmacovigilance. High dose inhaled steroids: new advice on supply of steroid treatment cards. 2006. Available at: http://webarchive.nationalarchives.gov.uk/20141205150130/http:/www.mhra.gov.uk/Publications/Safetyguidance/CurrentProblemsinPharmacovigilance/CON2023859. Accessed Oct 2015.

29 Medicines and Healthcare products Regulatory Agency. Drug Safety Update: Inhaled and intranasal corticosteroids: risk of psychological and behavioural side effects. 2010. Available at: https://www.gov.uk/drug-safety-update/inhaled-and-intranasal-corticosteroids. Accessed Oct 2015.

30 Committee on Safety of Medicines. Current Problems in Pharmacovigilance: Inhaled corticosteroids and adrenal suppression in children. 2002. Available at: http://webarchive.nationalarchives.gov.uk/20090724113803/http://mhra.gov.uk/Publications/Safetyguidance/CurrentProblemsinPharmacovigilance/CON007451. Accessed Oct 2014.

31 Kew KM, Seniukovich A. Inhaled steroids and risk of pneumonia for chronic obstructive pulmonary disease. 2014. Available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010115.pub2/abstract. Accessed Oct 2015.

32 All Wales Medicines Strategy Group. fluticasone furoate/vilanterol (as trifenatate) (Relvar® Ellipta®). 2014. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/1534. Accessed Oct 2015.

33 All Wales Medicines Strategy Group. fluticasone furoate/vilanterol (as trifenatate) (Relvar® Ellipta®). 2014. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/1216. Accessed Oct 2015.

34 Electronic Medicines Compendium. SPC: Relvar Ellipta 92 micrograms/22 micrograms inhalation powder, pre-dispensed. 2015. Available at: http://www.medicines.org.uk/emc/medicine/28496. Accessed Oct 2015.

35 Welsh Government. Working together to reduce harm: The substance misuse strategy for Wales 2008-2018. 2008. Available at: http://wales.gov.uk/dsjlg/publications/commmunitysafety/strategy/strategye.pdf?lang=en. Accessed Oct 2014.

36 NHS Business Services Authority. Electronic Prescribing Analysis and Cost (ePACT). 2015. Accessed Sep 2015.

37 Committee on Safety of Medicines. Current Problems in Pharmacovigilance: Benzodiazapines, dependence and withdrawal symptoms. Jan 1988. 21:1-2. Available at: http://webarchive.nationalarchives.gov.uk/20141205150130/http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con2024428.pdf. Accessed Oct 2015.

38 British Medical Association, Royal Pharmaceutical Society of Great Britain. *British National Formulary. No. 70*. London: BMJ Group; Pharmaceutical Press; 2015.

39 National Institute for Health and Care Excellence. Technology Appraisal 77. Guidance on the use of zaleplon, zolpidem and zopiclone for the short-term management of insomnia (TA77). 2004. Available at: https://www.nice.org.uk/guidance/ta77. Accessed Oct 2015.

40 National Institute for Health and Care Excellence. Clinical Guideline 113. Generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults. Jan 2011. Available at: http://www.nice.org.uk/cg113. Accessed Sep 2013.

41 Woolcott JC, Richardson KJ, Wiens MO et al. Meta-analysis of the impact of 9 medication classes on falls in elderly persons. *Arch Intern Med* 2009; 169 (21): 1952-60. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19933955. Accessed: Oct 2015.

42 1000 Lives Plus. Assessment of falls risk in older people. 2014. Available at: http://www.1000livesplus.wales.nhs.uk/sitesplus/documents/1011/FRATtool.pdf. Accessed Oct 2014.

43 Billioti de Gage S, Moride Y, Ducruet T et al. Benzodiazepine use and risk of Alzheimer's disease: case-control study. *BMJ* 2014; 349. Available at: http://www.bmj.com/content/349/bmj.g5205. Accessed: Oct 2015.

44 Gallacher J, Elwood P, Pickering J et al. Benzodiazepine use and risk of dementia: evidence from the Caerphilly Prospective Study (CaPS). *J Epidemiol Community Health* 2012; 66: 869-73. Available at: http://jech.bmj.com/content/66/10/869. Accessed: Oct 2015.

45 Weich S, Pearce HL, Croft P et al. Effect of anxiolytic and hypnotic drug prescriptions on mortality hazards: retrospective cohort study. *BMJ* 2014; 348. Available at: http://www.bmj.com/content/348/bmj.g1996?etoc. Accessed: Oct 2015.

46 Rowbotham DJ, Collett BJ. Guidelines for the Provision of Anaesthetic Services. 2014. Available at: http://www.rcoa.ac.uk/system/files/GPAS-2014-12-CHRONICPAIN.pdf. Accessed Oct 2015.

47 British Pain Society. *Opioids for persistent pain: Good practice*. London: The British Pain Society; 2010.

48 Welsh Assembly Government. Service Development and Commissioning Directives. Chronic Non-Malignant Pain. 2008. Available at: http://gov.wales/dhss/publications/health/strategies/chronicpain/chronicpaine.pdf%3Bjsessionid=zJkSTybfkLzsKzTPpgPMgPC7B4FhfJpDrhC0Ltr6t3nCvBhJH8q3!-124502640?lang=en. Accessed Oct 2015.

49 Advisory Council on the Misuse of Drugs. ACMD consideration of tramadol. Feb 2013. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/144116/advice-tramadol.pdf. Accessed Jul 2013.

50 Directorate for Public Health Welsh Government. Chief Medical Officer for Wales Update 61. 2013. Available at: http://www.wales.nhs.uk/sites3/Documents/428/CMO%20Update%2061.pdf. Accessed Oct 2014.

51 Office for National Statistics. Statistical bulletin: Deaths related to drug poisoning in England and Wales, 2014 registrations. 2015. Available at: http://www.ons.gov.uk/ons/rel/subnational-health3/deaths-related-to-drug-poisoning/england-and-wales---2014/deaths-related-to-drug-poisoning-in-england-and-wales--2014-registrations.html#tab-Other-opiates--including-tramadol-and-methadone. Accessed Oct 2015.

52 Electronic Medicines Compendium. SPC: Zydol 50 mg capsules. 2014. Available at: http://www.medicines.org.uk/emc/medicine/16371/SPC/Zydol+50mg+Capsules/#UNDESIRABLE_EFFECTS. Accessed Oct 2014.

53 Committee on Safety of Medicines. Current Problems in Pharmacovigilance: In focus: Tramadol (Zydol, Tramake and Zamadol). Oct 1996. 22:11. Available at: http://webarchive.nationalarchives.gov.uk/20141205150130/http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con2023218.pdf. Accessed Oct 2015.

54 Electronic Medicines Compendium. SPC: Tramadol Hydrochloride 50mg Capsules. 2015. Available at: http://www.medicines.org.uk/EMC/medicine/24186/SPC. Accessed Jan 2016.

55 National Institute for Health and Care Excellence. Clinical Guideline 173. Neuropathic pain in adults: pharmacological management in non-specialist settings (CG173). 2013. Available at: https://www.nice.org.uk/guidance/cg173. Accessed Oct 2015.

56 National Institute for Health and Care Excellence. Clinical Guideline 173. Neuropathic pain in adults: pharmacological management in non-specialist settings. 2013. Available at: http://www.nice.org.uk/Guidance/CG173. Accessed Nov 2015.

57 Electronic Medicines Compendium. SPC: Neurontin 100mg Hard Capsules. 2015. Available at: https://www.medicines.org.uk/emc/medicine/17095. Accessed Nov 2015.

58 Electronic Medicines Compendium. SPC: Gabapentin 100mg capsules. 2015. Available at: https://www.medicines.org.uk/emc/medicine/26529. Accessed Oct 2015.
59 Electronic Medicines Compendium. SPC: Lyrica Capsules. 2015. Available at: https://www.medicines.org.uk/emc/medicine/14651. Accessed Oct 2015.
60 Electronic Medicines Compendium. SPC: Alzain 100 mg Capsules, Hard. 2015. Available at: https://www.medicines.org.uk/emc/medicine/30054. Accessed Oct 2015.
61 Electronic Medicines Compendium. SPC: Pregabalin 150mg Capsules. 2015. Available at: https://www.medicines.org.uk/emc/medicine/30924. Accessed Jan 2016.
62 Scottish Intercollegiate Guidelines Network. SIGN 136. Management of chronic pain. 2013. Available at: http://sign.ac.uk/pdf/SIGN136.pdf. Accessed Nov 2014.
63 PrescQIPP. Bulletin 50 - Pregabalin in Neuropathic Pain Now Available to All PrescQIPP Users. 2014. Available at: http://www.prescqipp.info/newsfeed/bulletin-50-pregabalin-in-neuropathic-pain-now-available-to-all-prescqipp-users. Accessed Nov 2015.
64 National Institute for Health and Care Excellence. Clinical Guideline 186. Multiple sclerosis in adults: management (CG186). 2014. Available at: https://www.nice.org.uk/guidance/cg186. Accessed Oct 2015.
65 EMC. Electronic Medicines Compendium. 2016. Available at: https://www.medicines.org.uk/emc/. Accessed Feb 2016.
66 Public Health England, NHS England. Advice for prescribers on the risk of the misuse of pregabalin and gabapentin. 2014. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/385791/PHE-NHS_England_pregabalin_and_gabapentin_advice_Dec_2014.pdf. Accessed Oct 2015.
67 Electronic Medicines Compendium. SPC: Gabapentin 100mg Hard Capsules (Arrow). 2014. Available at: https://www.medicines.org.uk/emc/medicine/27864. Accessed Jan 2016.
68 Advisory Council on the Misuse of Drugs. Pregabalin and Gabapentin advice. Jan 2016. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/491854/ACMD_Advice_-_Pregabalin_and_gabapentin.pdf. Accessed Jan 2016.
69 Office for National Statistics. Deaths involving gabapentin and pregabalin in England and Wales, 1999 to 2014. 2015. Available at: http://www.ons.gov.uk/ons/search/index.html?newquery=pregabalin. Accessed Oct 2015.
70 NHS Business Services Authority. Electronic Prescribing Analysis and Cost (ePACT). Oct 2012. Accessed Sep 2013.
71 Public Health Wales. Welsh Antimicrobial Resistance Programme. Apr 2010. Available at: http://www.wales.nhs.uk/sites3/page.cfm?orgid=457&pid=28418. Accessed Oct 2014.
72 Public Health Wales. Antibacterial Resistance in Wales 2005-2014. 2015. Available at: http://www.wales.nhs.uk/sites3/Documents/457/Antimicrobial%20Resistance%20in%20Wales%202005-2014.pdf. Accessed Oct 2015.
73 Department of Health, Department for Environment FaRA. UK Five Year Antimicrobial Resistance Strategy 2013-2018. 2013. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/244058/20130902_UK_5_year_AMR_strategy.pdf. Accessed Oct 2014.
74 National Institute for Health and Care Excellence. NICE Guideline 15. Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (NG15). 2015. Available at: http://www.nice.org.uk/guidance/ng15. Accessed Oct 2015.

75 Public Health England. Management of infection guidance for primary care for consultation and local adaptation. 2015. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/377509/PHE_Primary_Care_guidance_14_11_14.pdf. Accessed Oct 2015.
76 Chief Medical Officer, Chief Nursing Officer. Code of practice for the prevention and control of healthcare associated infections. 2014. Available at: http://gov.wales/topics/health/cmo/publications/cmo/2014/cmo-june14/?lang=en. Accessed Oct 2015.
77 Monaghan T, Boswell T, Mahida YR. Recent advances in *Clostridium difficile*-associated disease. *Gut* 2008; 57 (6): 850-60. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18252748. Accessed: Oct 2015.
78 Committee on Safety of Medicines, Medicines and Healthcare products Regulatory Agency. Current Problems in Pharmacovigilance: Revised indications for co-amoxiclav (Augmentin). 1997. 23:8. Available at: http://webarchive.nationalarchives.gov.uk/20141205150130/http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con2023230.pdf. Accessed Oct 2015.
79 Medicines and Healthcare products Regulatory Agency. Drug Safety Update. NSAIDs and coxibs: balancing of cardiovascular and gastrointestinal risks. 2007. Available at: https://www.gov.uk/drug-safety-update/nsaids-and-coxibs-balancing-of-cardiovascular-and-gastrointestinal-risks. Accessed Oct 2015.
80 Medicines and Healthcare products Regulatory Agency. Drug Safety Update. Non-steroidal anti-inflammatory drugs (NSAIDs): reminder on renal failure and impairment. 2009. Available at: https://www.gov.uk/drug-safety-update/non-steroidal-anti-inflammatory-drugs-nsaids-reminder-on-renal-failure-and-impairment. Accessed Oct 2015.
81 Medicines and Healthcare products Regulatory Agency. Drug Safety Update. Non-steroidal anti-inflammatory drugs (NSAIDs): cardiovascular risks. 2012. Available at: https://www.gov.uk/drug-safety-update/non-steroidal-anti-inflammatory-drugs-nsaids-cardiovascular-risks. Accessed Oct 2015.
82 Medicines and Healthcare products Regulatory Agency, Committee on Safety of Medicines. Current Problems in Pharmacovigilance: Reminder: Gastrointestinal toxicity of NSAIDs. 2003.Report No.: 29. Available at: http://webarchive.nationalarchives.gov.uk/20141205150130/http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con007450.pdf. Accessed Oct 2015.
83 Loke YK, Trivedi AN, Singh S. Meta-analysis: gastrointestinal bleeding due to interaction between selective serotonin uptake inhibitors and non-steroidal anti-inflammatory drugs. *Aliment Pharmacol Ther* 2008; 27 (1): 31-40. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17919277. Accessed: Oct 2015.
84 European Medicines Agency. European Medicines Agency concludes action on COX-2 inhibitors. 2005. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2010/01/news_detail_000969.jsp&mid=WC0b01ac058004d5c1. Accessed Oct 2015.
85 Medicines and Healthcare products Regulatory Agency. Press release. Diclofenac tablets now only available as a prescription medicine. 2015. Available at: https://www.gov.uk/government/news/diclofenac-tablets-now-only-available-as-a-prescription-medicine. Accessed Oct 2015.
86 Medicines and Healthcare products Regulatory Agency. Drug Safety Update. Aceclofenac (Preservex): updated cardiovascular advice in line with diclofenac and COX-2 inhibitors. 2015. Available at: https://www.gov.uk/drug-safety-update/aceclofenac-preservex-updated-cardiovascular-advice-in-line-with-diclofenac-and-cox-2-inhibitors. Accessed Oct 2015.
87 Medicines and Healthcare products Regulatory Agency. Drug Safety Update. High-dose ibuprofen (=/>2400mg/day): small increase in cardiovascular risk.

2015. Available at: https://www.gov.uk/drug-safety-update/high-dose-ibuprofen-2400mg-day-small-increase-in-cardiovascular-risk. Accessed Oct 2015.

88 National Institute for Health and Care Excellence. Clinical Guideline 169. Acute kidney injury: Prevention, detection and management. 2013. Available at: https://www.nice.org.uk/guidance/CG169. Accessed Oct 2015.

89 Lapi F, Azoulay L, Yin H et al. Concurrent use of diuretics, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers with non-steroidal anti-inflammatory drugs and risk of acute kidney injury: nested case-control study. *BMJ* 2013; 346. Available at: http://www.bmj.com/content/346/bmj.e8525. Accessed: Oct 2015.

90 National Institute for Health and Care Excellence. Clinical Guideline 182. Chronic kidney disease in adults: assessment and management. 2014. Available at: http://www.nice.org.uk/guidance/cg182. Accessed Oct 2015.

91 Medicines and Healthcare products Regulatory Agency. Drug Safety Update. Diclofenac: new contraindications and warnings. 2013. Available at: https://www.gov.uk/drug-safety-update/diclofenac-new-contraindications-and-warnings. Accessed Oct 2015.

92 Pirmohamed M, James S, Meakin S et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *BMJ* 2004; 329 (7456): 15-9. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15231615. Accessed: Oct 2014.

93 Impicciatore P, Choonara I, Clarkson A et al. Incidence of adverse drug reactions in paediatric in/out-patients: a systematic review and meta-analysis of prospective studies. *Br J Clin Pharmacol* 2001; 52 (1): 77-83. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2014499/. Accessed: Oct 2014.

GLOSSARY

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 Organisation is a unit of measurement whereby each medicine is assigned a value within its recognised dosage range. The value is the assumed average maintenance dose per day for a medicine when used for its main indication in adults. A medicine can have different DDDs depending on the route of administration.

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

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

APPENDIX 1. USER-DEFINED GROUP OF LOW-STRENGTH ICS

The list below is the user-defined group being monitored as low-strength ICS, i.e. any inhaler device, which when used at the usual dose provides < 800 microgram of beclometasone or equivalent

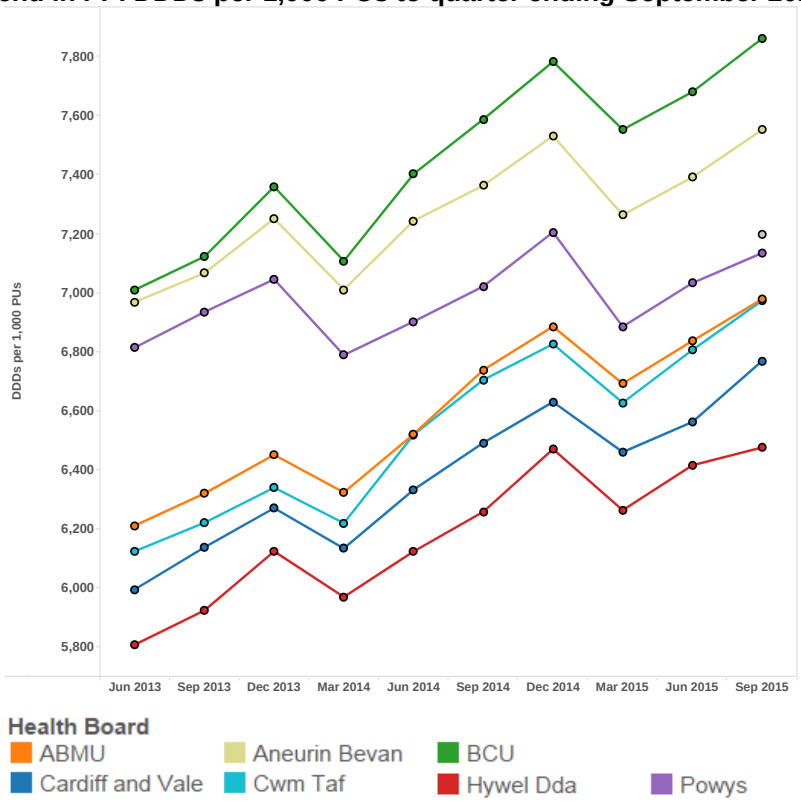
BNF name	BNF code
Beclomet Diprop_Inha 50mcg (200d)	0302000C0AAAAAA
Beclomet Diprop_Inha 100mcg (200d)	0302000C0AAABAB
Beclomet Diprop_Inha B/a 50mcg (200 D)	0302000C0AAASAS
Beclomet Diprop_Inha B/a 100mcg (200 D)	0302000C0AAATAT
Gppe Inha_Qvar 50 (200d) Cff	0302000C0AABEBE
Gppe Inha_Qvar 100 (200d) Cff	0302000C0AABFBF
Gppe Inha_Qvar 50 Autohaler (200d) Cff	0302000C0AABGBG
Gppe Inha_Qvar 100 Autohaler (200d) Cff	0302000C0AABHBH
Beclomet Diprop_Pdr For Inh 100mcg(200 D	0302000C0AABJBJ
Beclomet Diprop_Inha B/a 100mcg (100 D)	0302000C0AABQBQ
Beclomet Diprop_Inha B/a 200mcg (100 D)	0302000C0AABRBR
Beclomet Diprop/formoterol_Inh100/6(120d	0302000C0AABXBX
Beclomet/formoterol_Inh 100/6 (120d) Dry	0302000C0AABYBY
Beclazone 100 E-Breathe_Inha 100mcg(200d	0302000C0BFAEAT
Asmabec Clickhaler_D/p Inh 50mcg (200 D)	0302000C0BIADBI
Asmabec Clickhaler_D/p Inh 100mcg (200d)	0302000C0BIAEBJ
Qvar 50_Inha 50mcg (200 D)	0302000C0BJAABE
Qvar 50_Autohaler 50mcg (200 D)	0302000C0BJACBG
Qvar 50 E-Breathe_Inha 50mcg (200 D)	0302000C0BJAEBG
Pulvinal Beclomet_Inha 200mcg (100 D)	0302000C0BLAABM
Pulvinal Beclomet_Inha 100mcg (100 D)	0302000C0BLABBN
Clenil Modulite_Inha 50mcg (200d)	0302000C0BPAABE
Clenil Modulite_Inha 100mcg (200d)	0302000C0BPABBF
Fostair_Inh 100mcg/6mcg (120d) Cff	0302000C0BQAABX
Fostair Nexthaler_Inh 100mcg/6mcg (120d)	0302000C0BRAABY
Budesonide_Pdr For Inh 200mcg (100 D)	0302000K0AAAGAG
Budesonide_Pdr For Inh 100mcg (200 D)	0302000K0AAAKAK
Gppe Pdr For Inhb/a_Symbicort 100/6(120d	0302000K0AAALAL
Gppe Pdr For Inhb/a_Symbicort 200/6(120d	0302000K0AAAMAM
Budesonide_Pdr For Inh 200mcg (100d)+dev	0302000K0AAAVAV
Budesonide_Pdr For Inh 200mcg (100d) Ref	0302000K0AAAWAW
Budesonide_Pdr For Inh 200mcg (200 D)	0302000K0AAAXAX
Pulmicort_Turbohaler 200mcg (100 D)	0302000K0BBAHAG
Pulmicort_Turbohaler 100mcg (200 D)	0302000K0BBAKAK
Symbicort_Turbohaler 100mcg/6mcg (120 D)	0302000K0BDAAAL
Symbicort_Turbohaler 200mcg/6mcg (120 D)	0302000K0BDABAM
Easyhaler_Budesonide 100mcg (200 D)	0302000K0BGAAAK
Easyhaler_Budesonide 200mcg (200 D)	0302000K0BGABAX
Duoresp Spiromax_Inh 160mcg/4.5mcg(120d)	0302000K0BHAAAM
Fluticasone Prop_Pdr For Inh 50mcg (60d)	0302000N0AAARAR
Fluticasone Prop_Pdr For Inh 100mcg(60d)	0302000N0AAASAS
Gppe Pdr For Inh_Seretide 100 (60 D)	0302000N0AAAXAX
Gppe Inha_Seretide 50 Evohaler (120d)cff	0302000N0AABEBE
Fluticasone Prop_Inha 50mcg (120 D) Cff	0302000N0AABHBH
Fluticasone/formoterol_Inh 50/5mcg 120 D	0302000N0AABLBL
Flixotide_Accuhaler 50mcg (60 D)	0302000N0BBARAR
Flixotide_Accuhaler 100mcg (60 D)	0302000N0BBASAS
Flixotide_Evohaler 50mcg (120 D)	0302000N0BBBBBH
Seretide 100_Accuhaler 100mcg/50mcg(60d)	0302000N0BCAAAX
Seretide 50_Evohaler 50mcg/25mcg (120 D)	0302000N0BCADBE
Flutiform_Inha 50/5mcg (120 D)	0302000N0BDACBL
Mometasone Fur_Pdr For Inh 200mcg (30 D)	0302000R0AAAAAA
Mometasone Fur_Pdr For Inh 200mcg (60 D)	0302000R0AAABAB
Asmanex Twisthaler_D/p Inh 200mcg (30 D)	0302000R0BBAAAA
Asmanex Twisthaler_D/p Inh 200mcg (60 D)	0302000R0BBABAB
Ciclesonide_Inh 80mcg (120 D) Cff	0302000U0AAAAAA
Alvesco 80_Inh 80mcg (120 D) Cff	0302000U0BBAAAA

APPENDIX 2. NHS WALES HEALTH BOARDS PERFORMANCE AND COMPARISON WITH ENGLISH CCGS AGAINST THE PROPOSED 2016–2017 NPIS

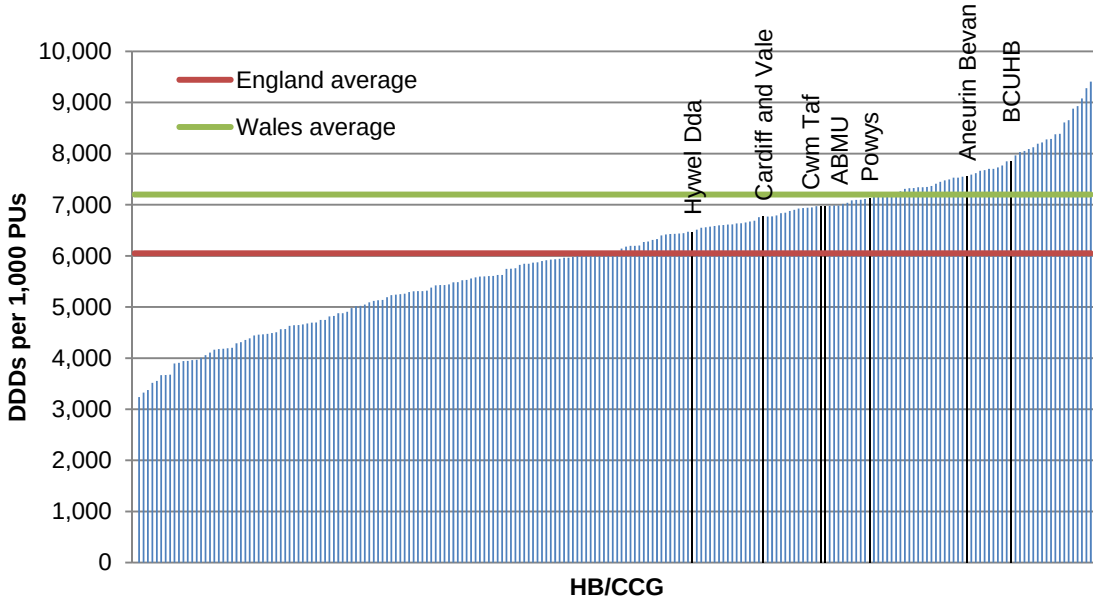
Data for each NPI are presented in two ways: a line graph/bar chart showing the trend in prescribing for each health board and a bar chart comparing prescribing of each health board with that of each CCG in England. The black bars represent the seven health boards in Wales; the blue bars represent the 211 CCGs in England.

1.0 PROTON PUMP INHIBITORS

Trend in PPI DDDs per 1,000 PUs to quarter ending September 2015

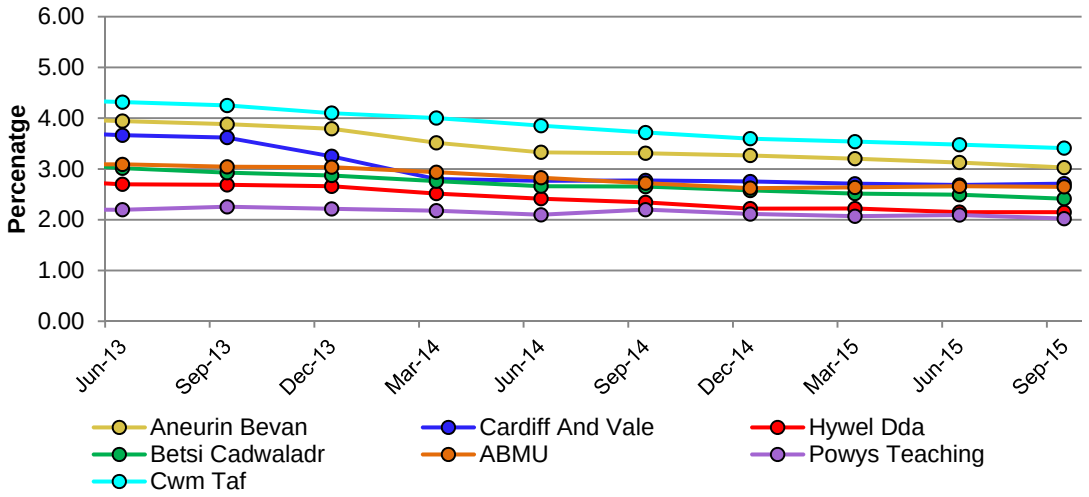


PPI DDDs per 1,000 PUs – Quarter ending September 2015

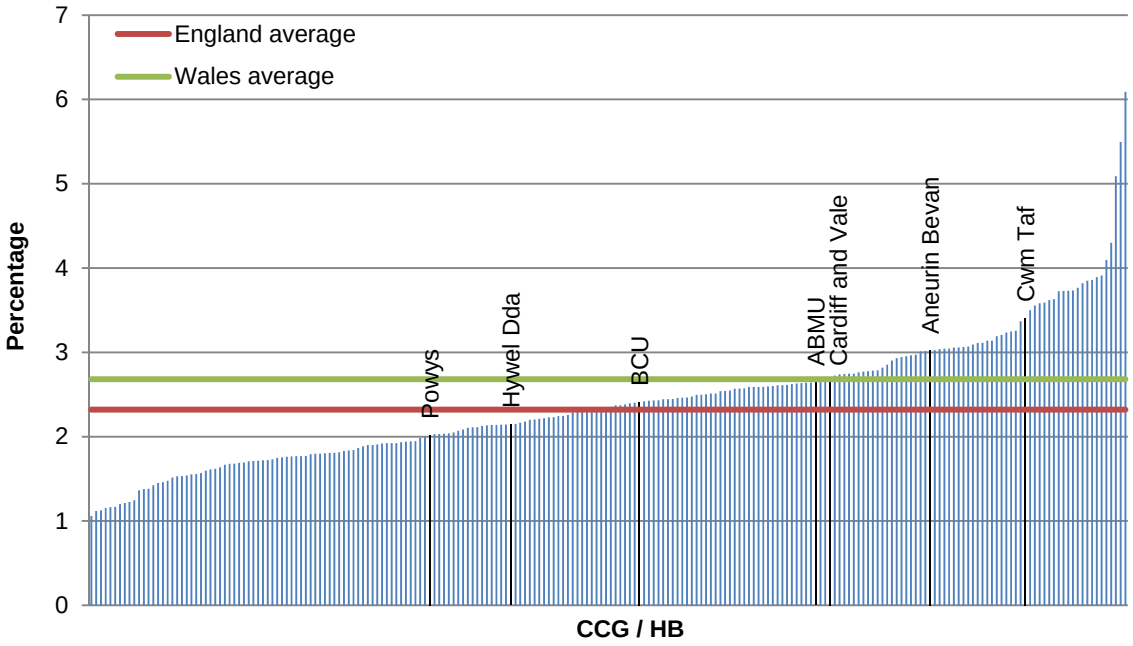


2.0 LIPID-REGULATING DRUGS

Trend in bile acid sequestrants, fibrates, nicotinic acid and omega-3 fatty acid compounds (BNF 2.12 sub-set) as a percentage of total items for lipid-regulating drugs to quarter ending September 2015

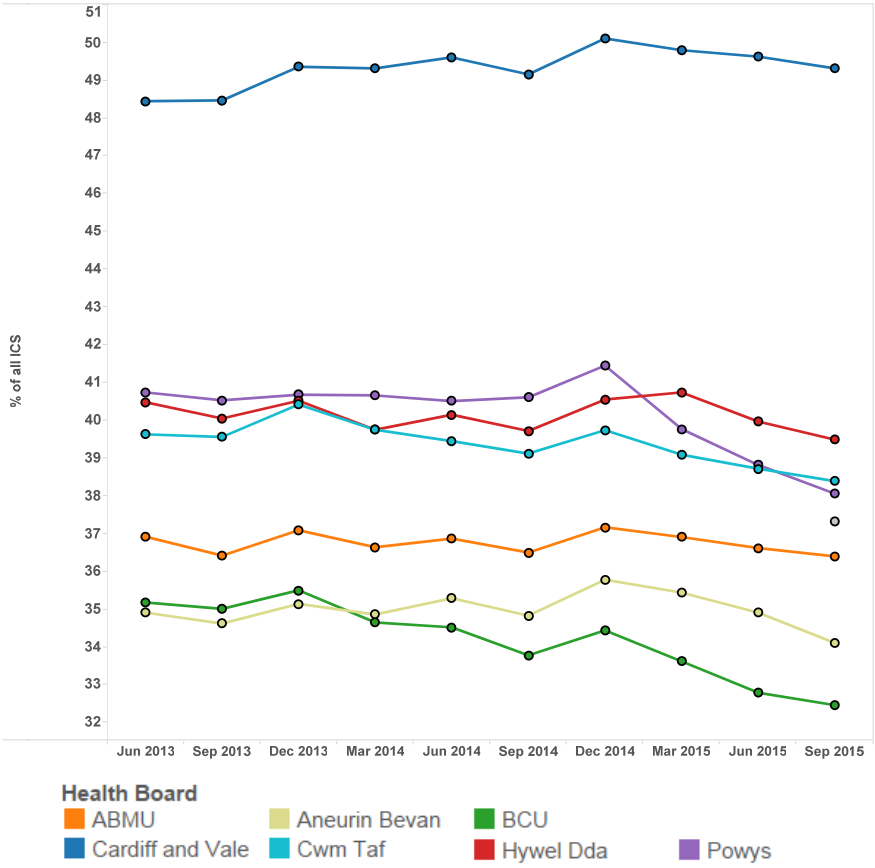


Bile acid sequestrants, fibrates, nicotinic acid and omega-3 fatty acid compounds (BNF 2.12 sub-set) as a percentage of total items for lipid-regulating drugs – Quarter ending September 2015

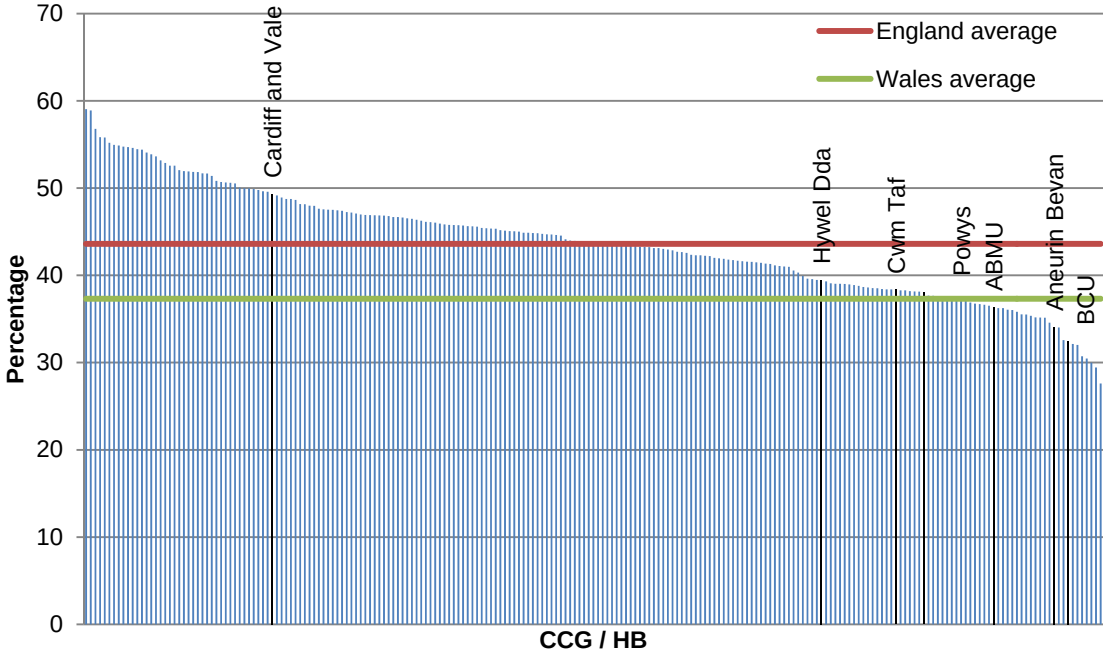


3.0 INHALED CORTICOSTEROIDS

Trend in low strength ICS items as a percentage of all ICS prescribing to quarter ending September 2015

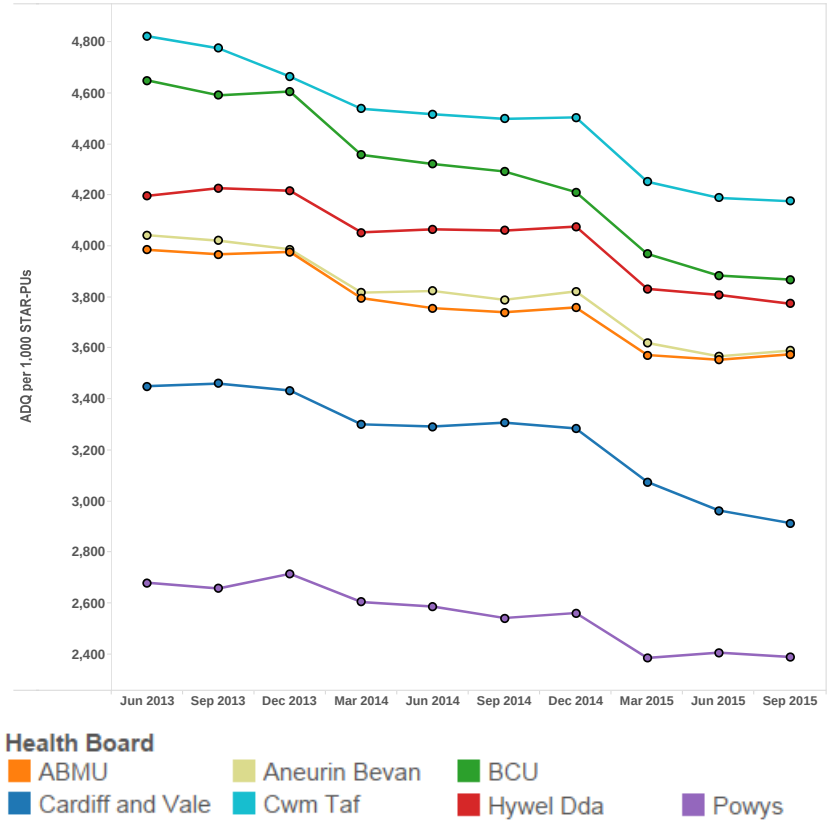


Low strength ICS items as a percentage of all ICS prescribing – Quarter ending September 2015

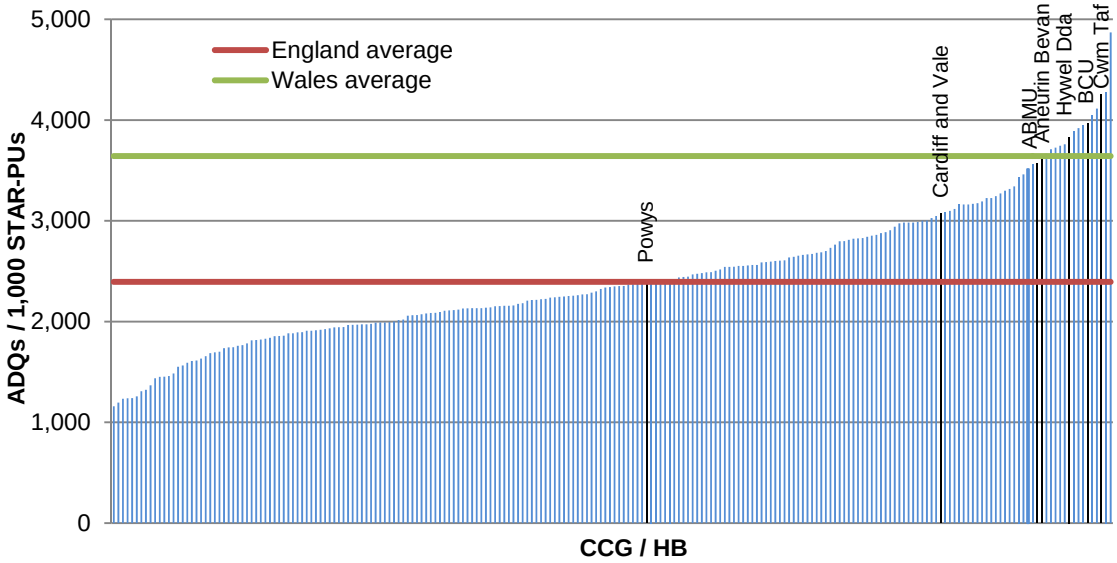


4.0 HYPNOTICS AND ANXIOLYTICS

Trend in hypnotic and anxiolytic ADQs per 1,000 STAR-PUs (13)† (2012–2013 UDG) to quarter ending September 2015



Hypnotic and anxiolytic ADQs per 1,000 STAR-PUs (13) (2012–2013 UDG) Quarter ending March 2015‡



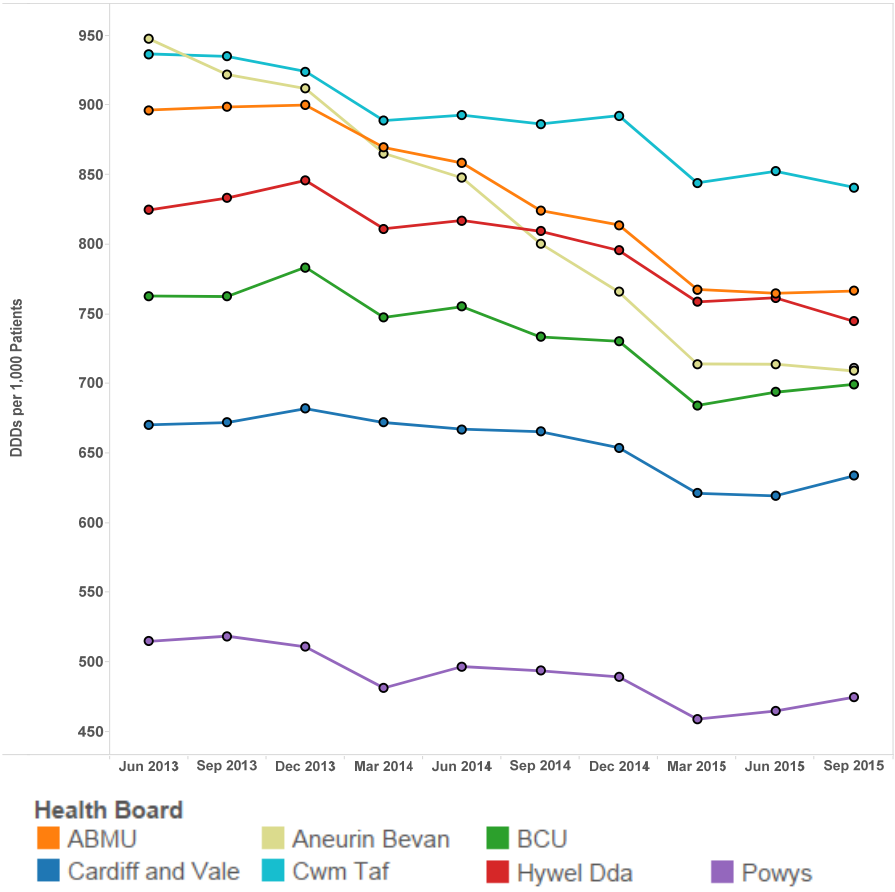
† STAR-PU weightings have been revised by the Health and Social Care Information Centre. STAR-PU (09) weightings have been updated to the STAR-PU (13) versions. These measures are routinely being used in data reported from April 2014. The data used in this document have been retrospectively calculated to provide comparisons dating back to April 2013.

‡ Data for March 2015 as data to September 2015 currently unavailable.

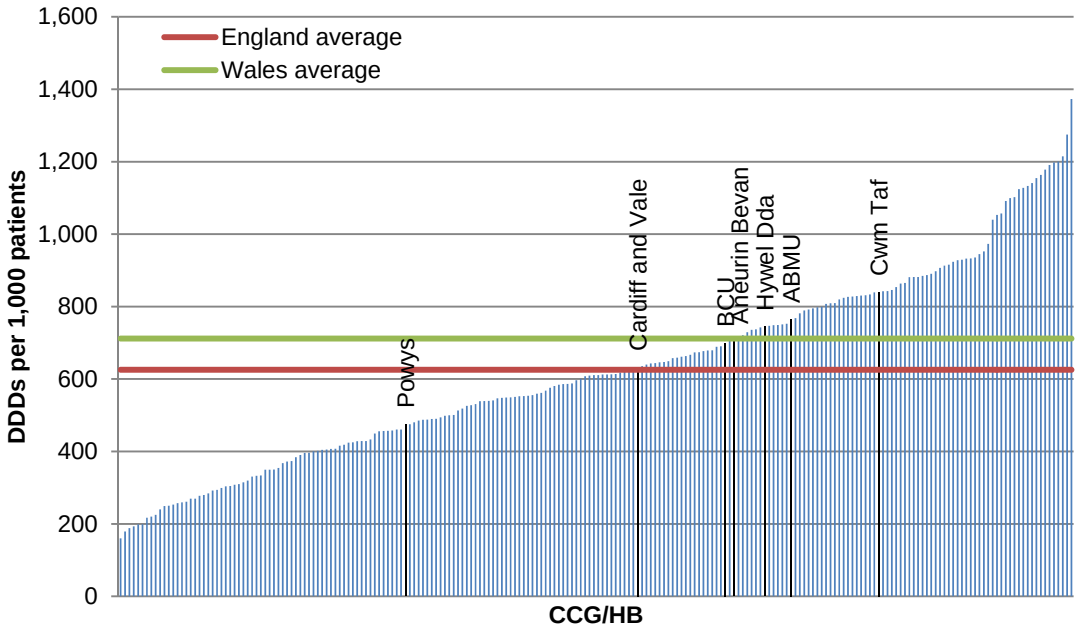
5.0 ANALGESICS

5.1 Tramadol

Trend in tramadol DDDs per 1,000 patients to quarter ending September 2015

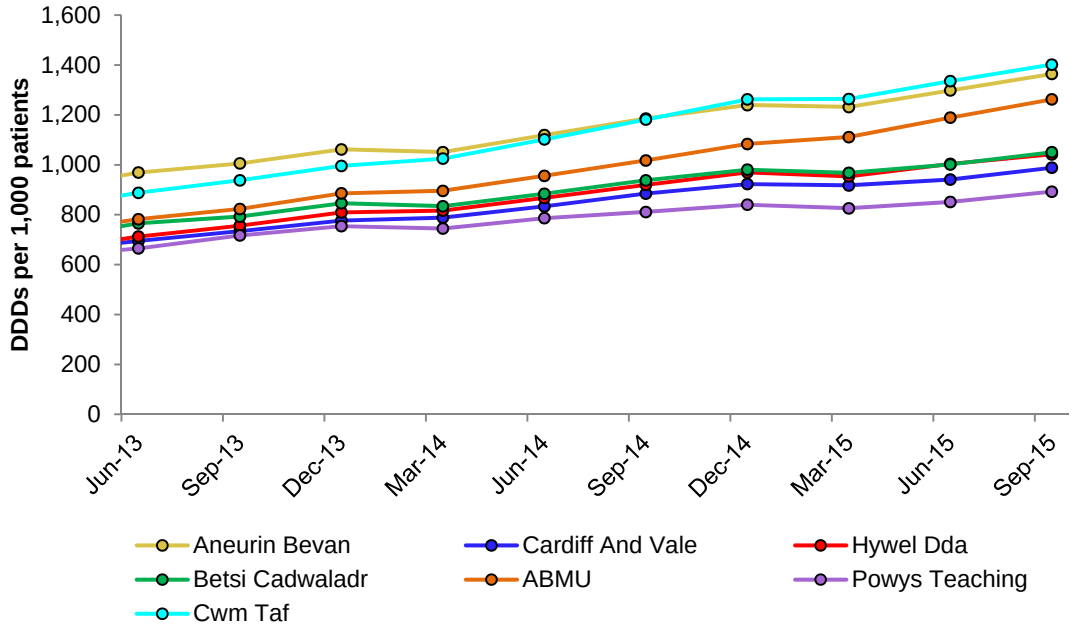


Tramadol DDDs per 1,000 patients – Quarter ending September 2015

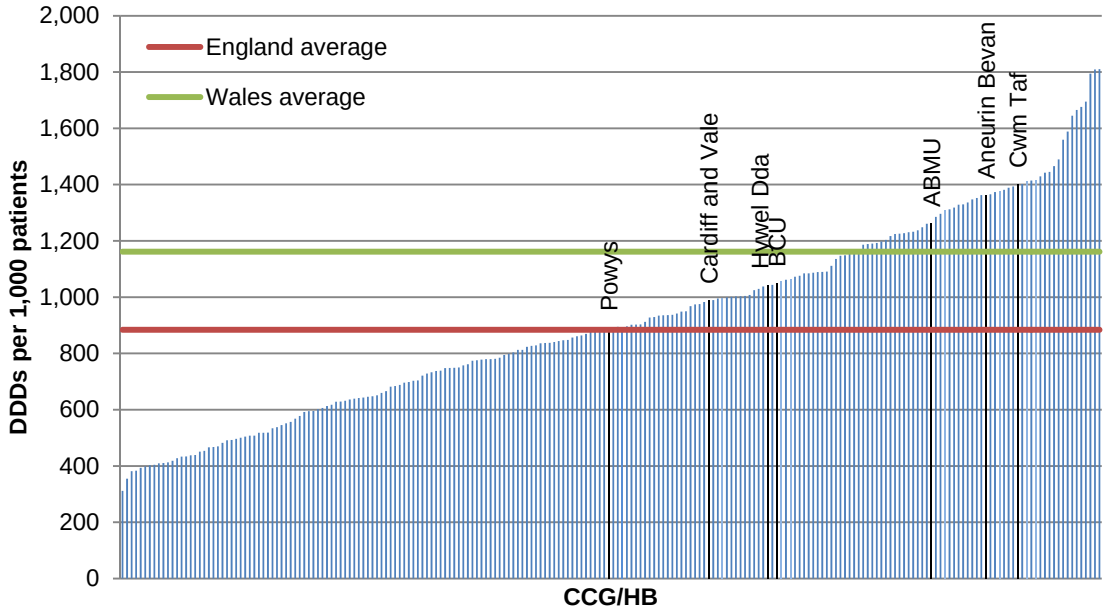


5.2 Gabapentin and pregabalin

Trend in gabapentin and pregabalin DDDs per 1,000 patients to quarter ending September 2015



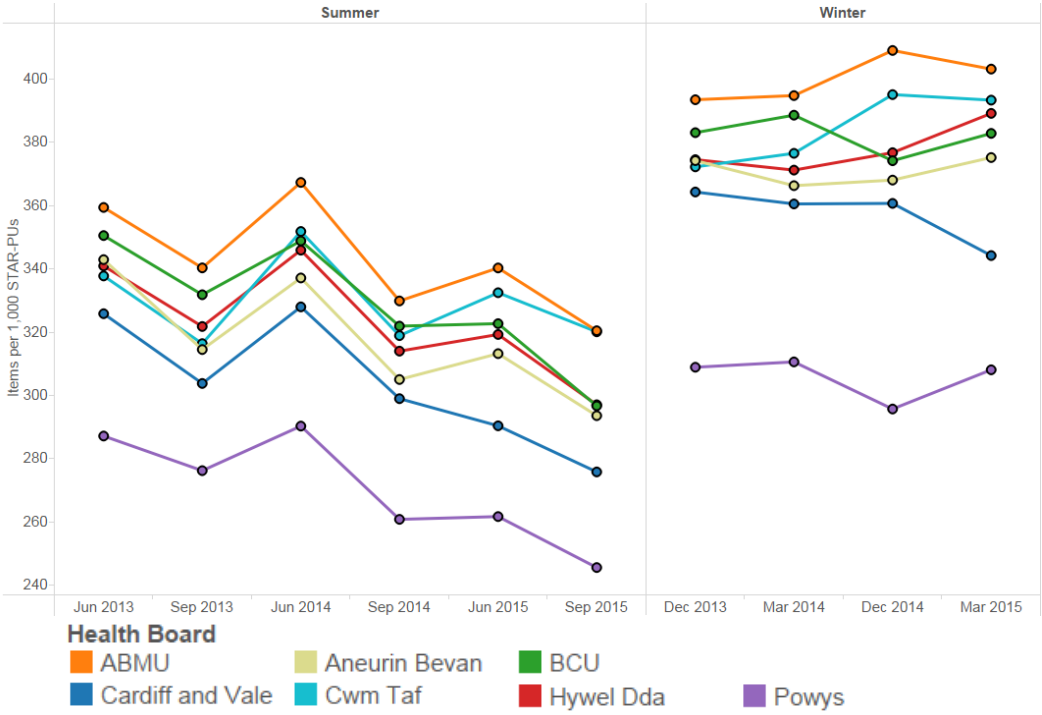
Gabapentin and pregabalin DDDs per 1,000 patients – Quarter ending September 2015



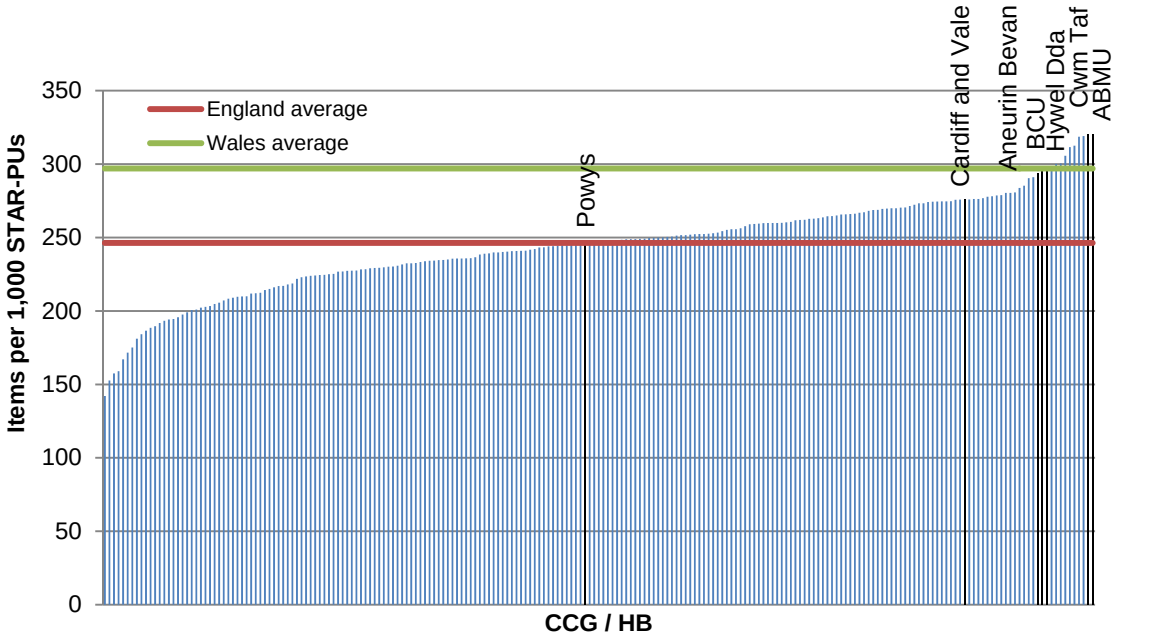
6.0 ANTIBIOTICS

6.1 Total antibiotics

Trend in total antibacterial items per 1,000 STAR-PUs (13) to quarter ending September 2015

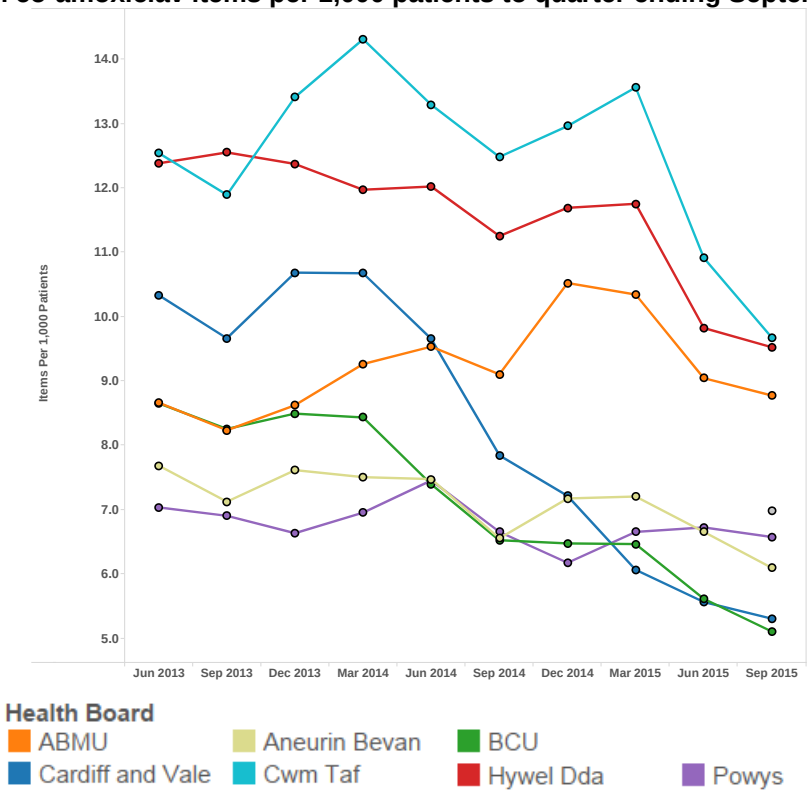


Total antibacterial items per 1,000 STAR-PUs (13) – Quarter ending September 2015

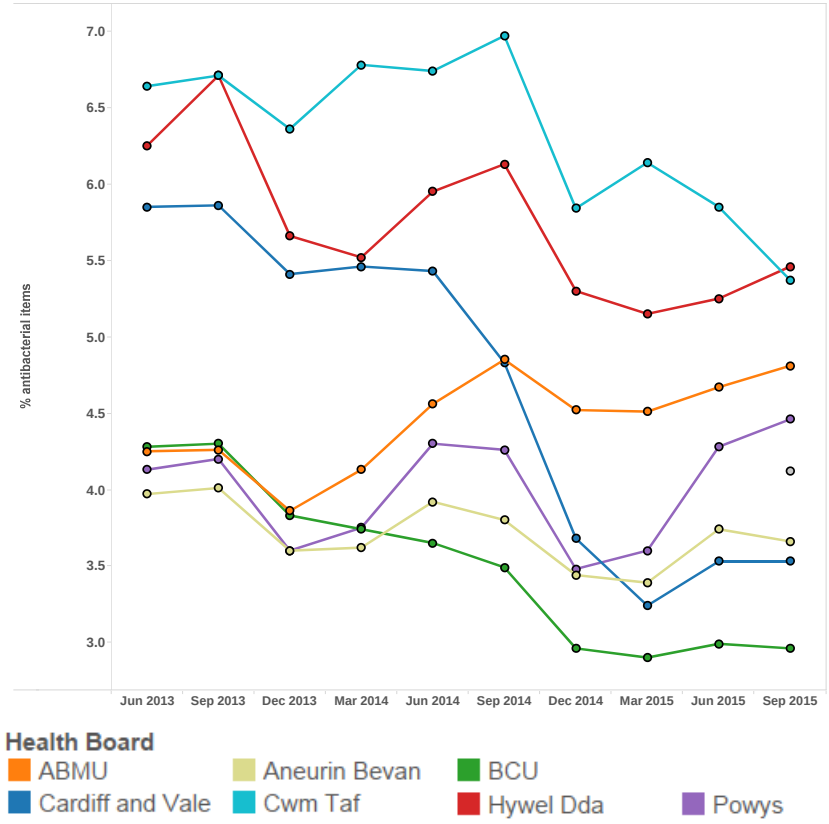


6.2 Co-amoxiclav

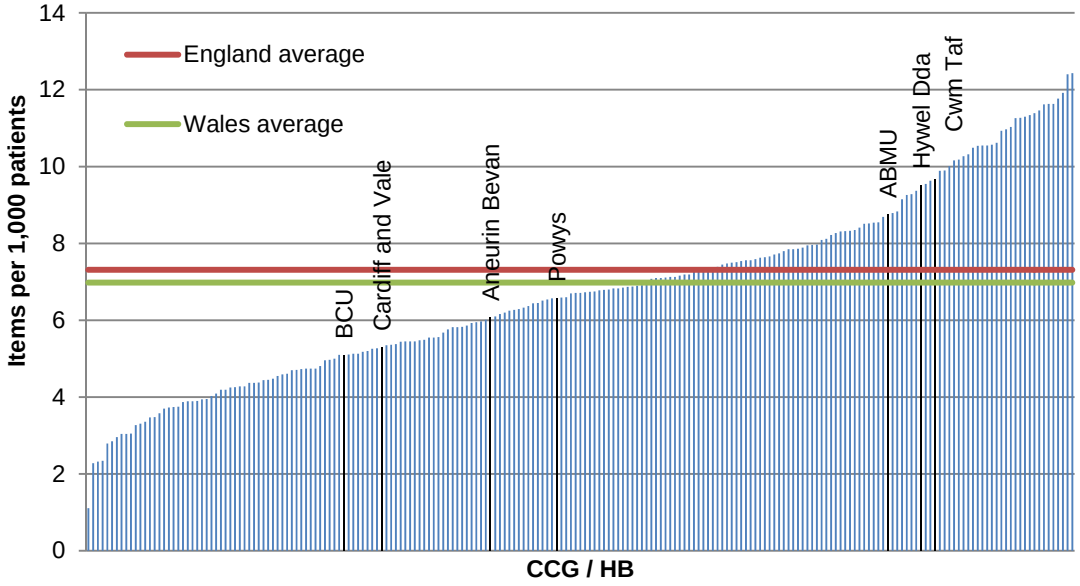
Trend in co-amoxiclav items per 1,000 patients to quarter ending September 2015



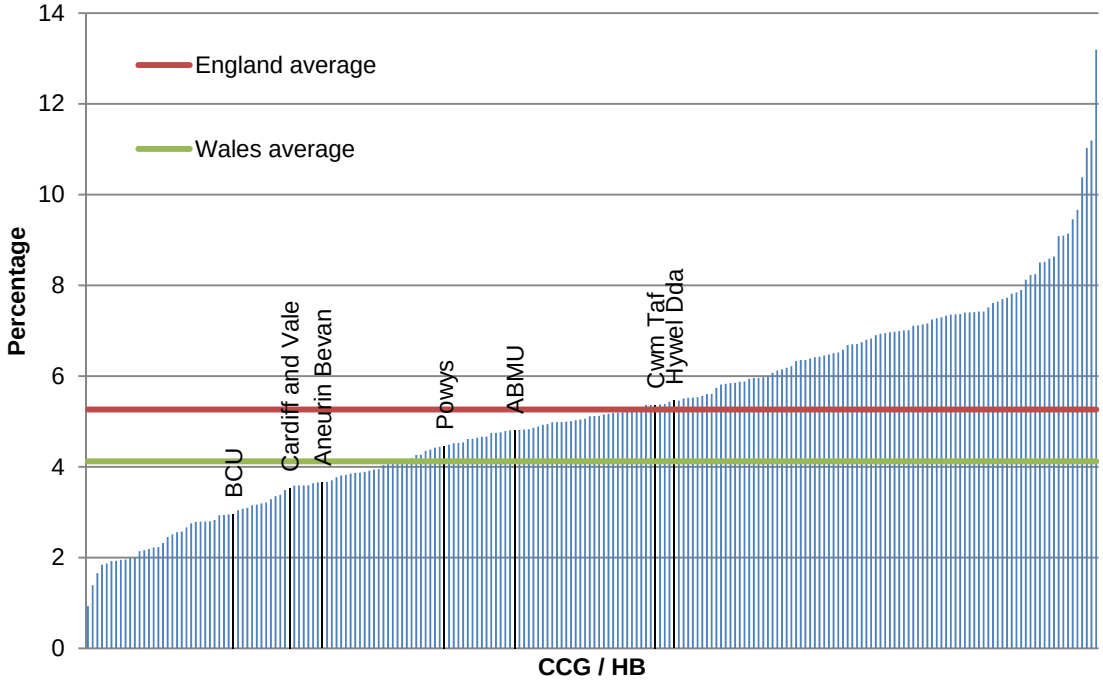
Trend in co-amoxiclav items as a percentage of total antibacterial items to quarter to September 2015



Co-amoxiclav items per 1,000 patients – Quarter ending September 2015

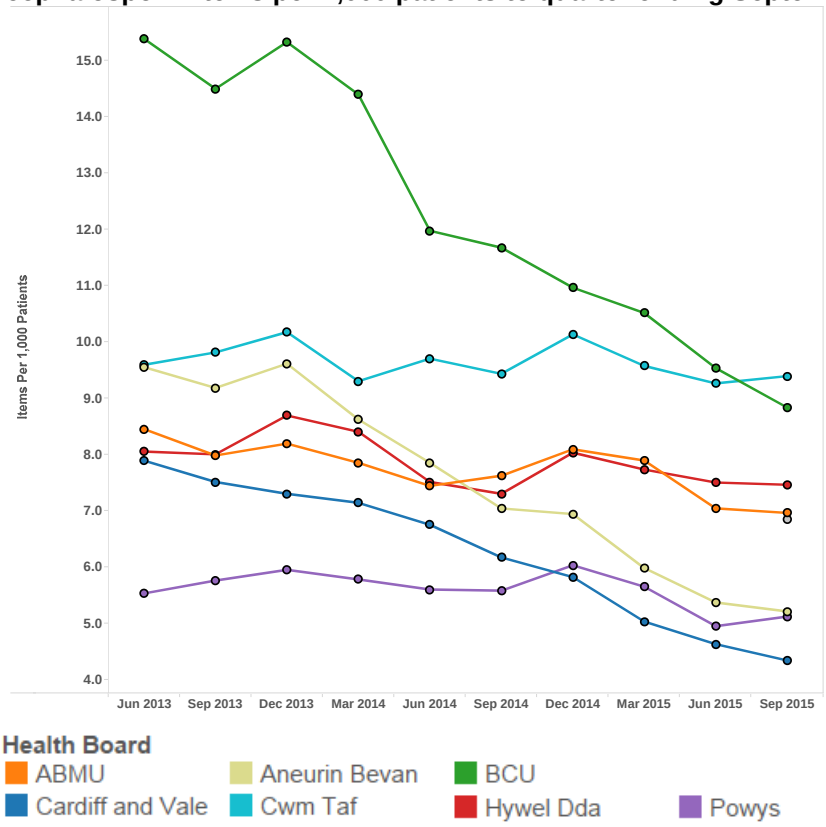


Co-amoxiclav items as a percentage of total antibacterial items – Quarter ending September 2015

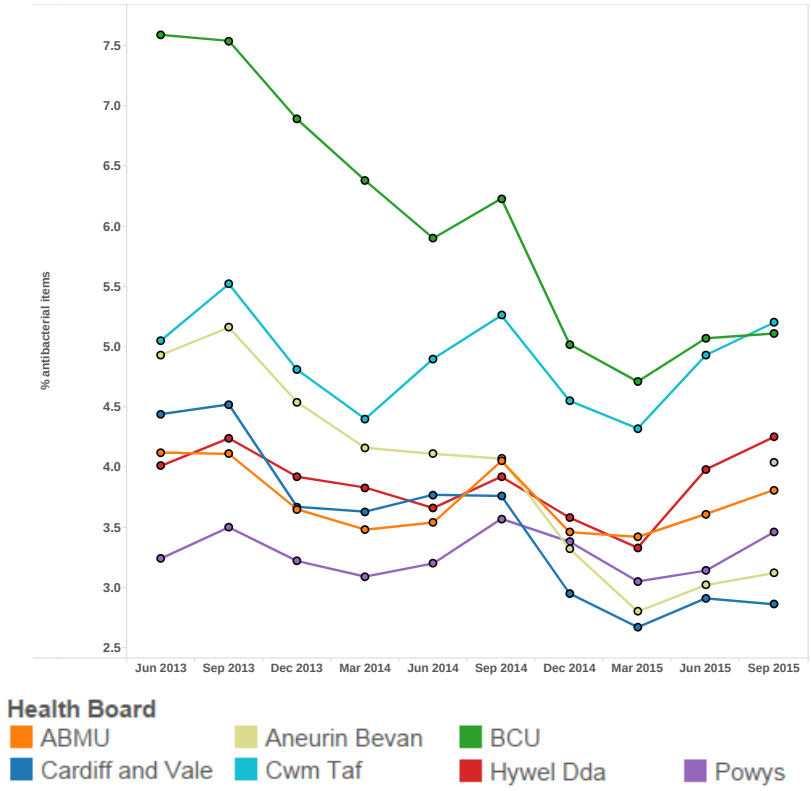


6.3 Cephalosporins

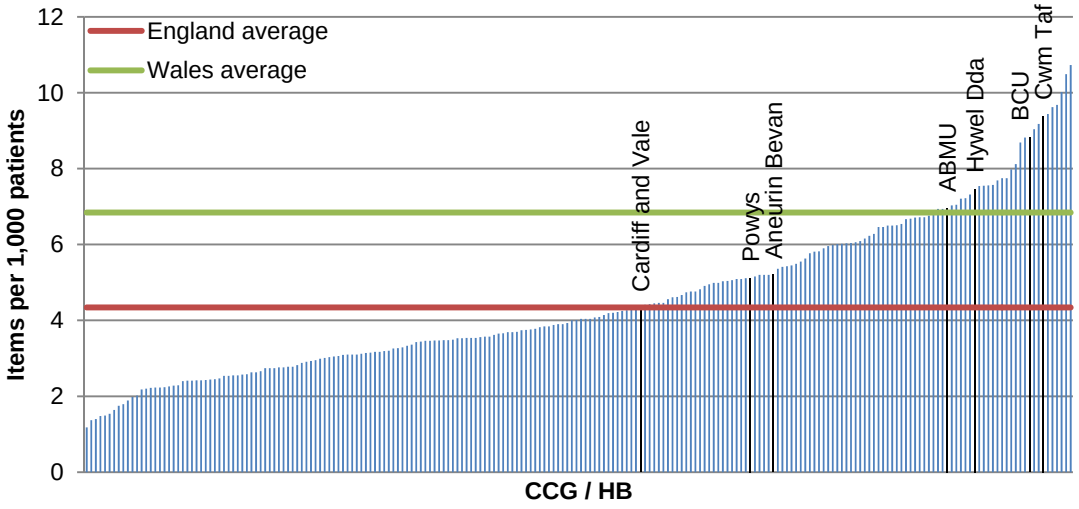
Trend in cephalosporin items per 1,000 patients to quarter ending September 2015



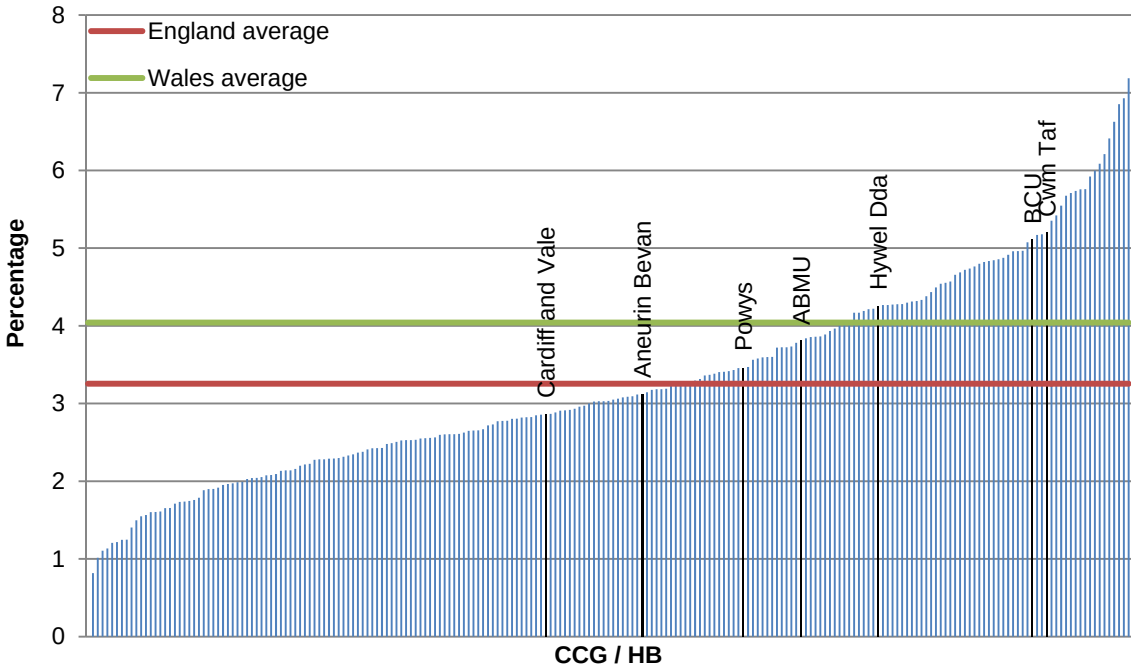
Trend in cephalosporin items as a percentage of total antibacterial items to quarter September 2015



Cephalosporin items per 1,000 patients – Quarter ending September 2015

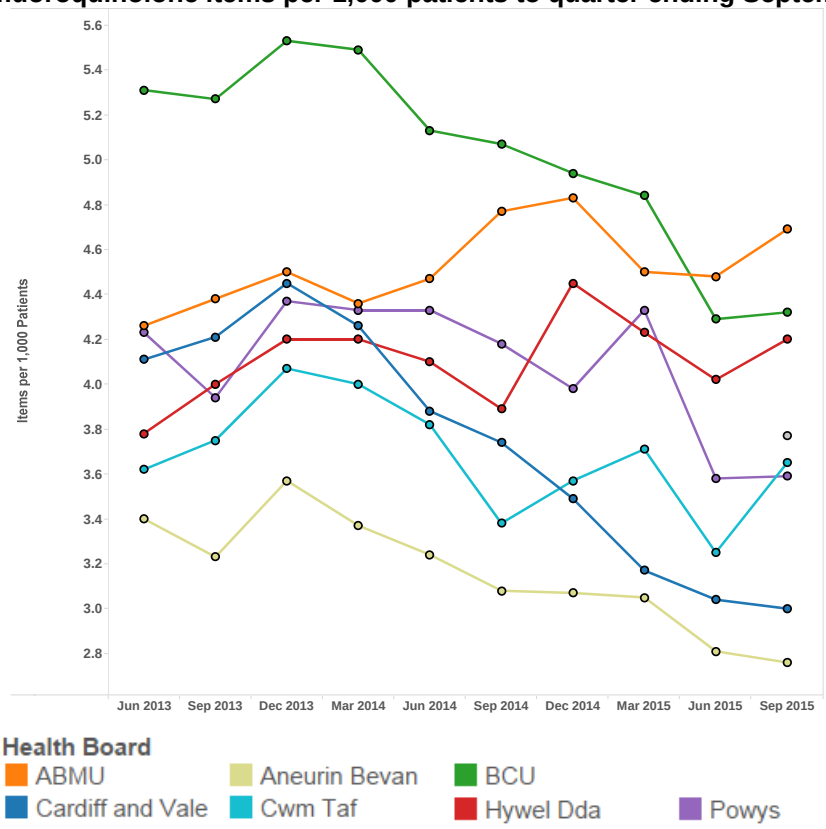


Cephalosporin items as a percentage of total antibacterial items – Quarter ending September 2015

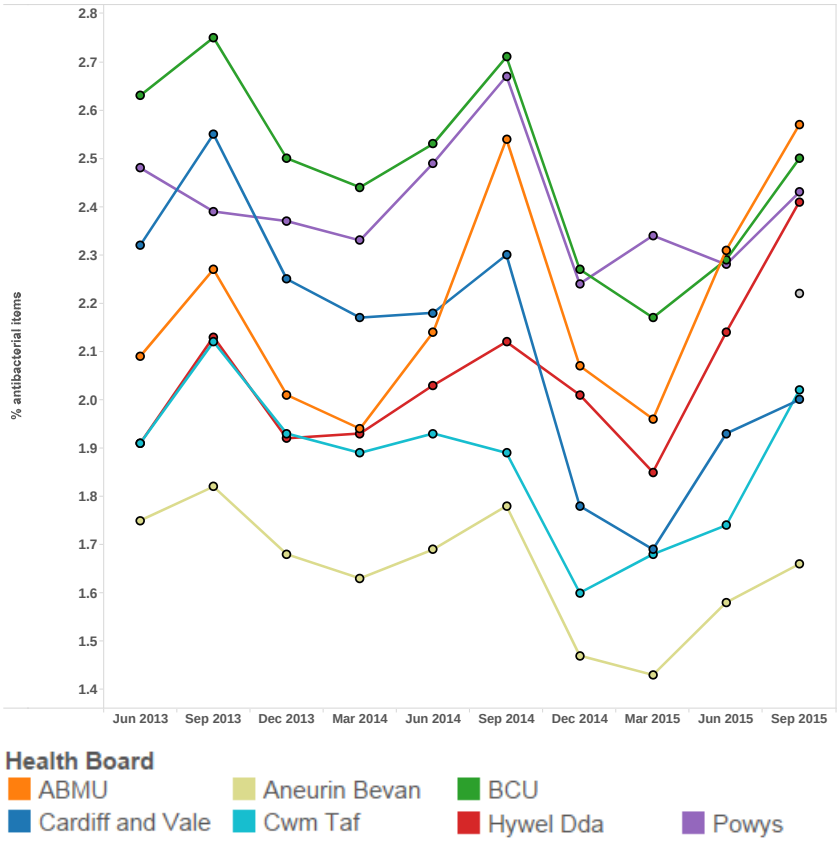


6.4 Fluoroquinolones

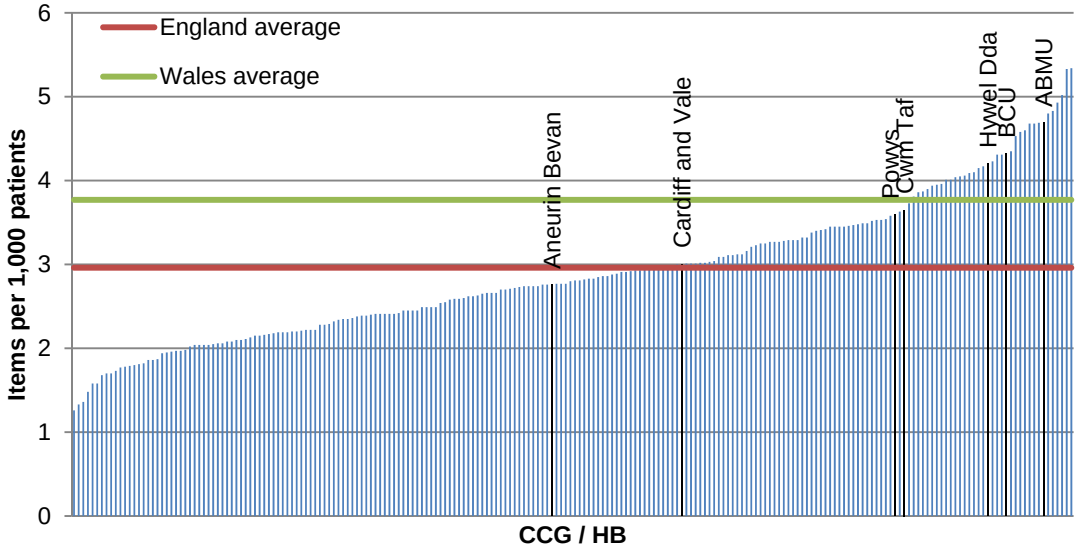
Trend in fluoroquinolone items per 1,000 patients to quarter ending September 2015



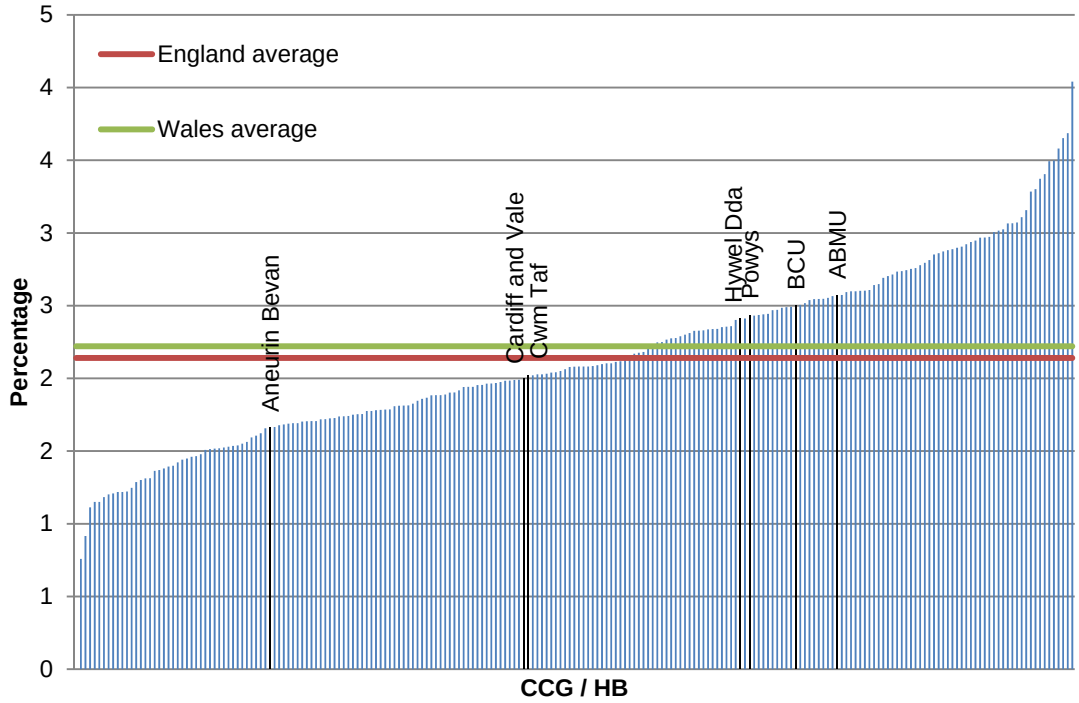
Trend in fluoroquinolone items as a percentage of total antibacterial items to quarter ending September 2015



Fluoroquinolone items per 1,000 patients – Quarter ending September 2015



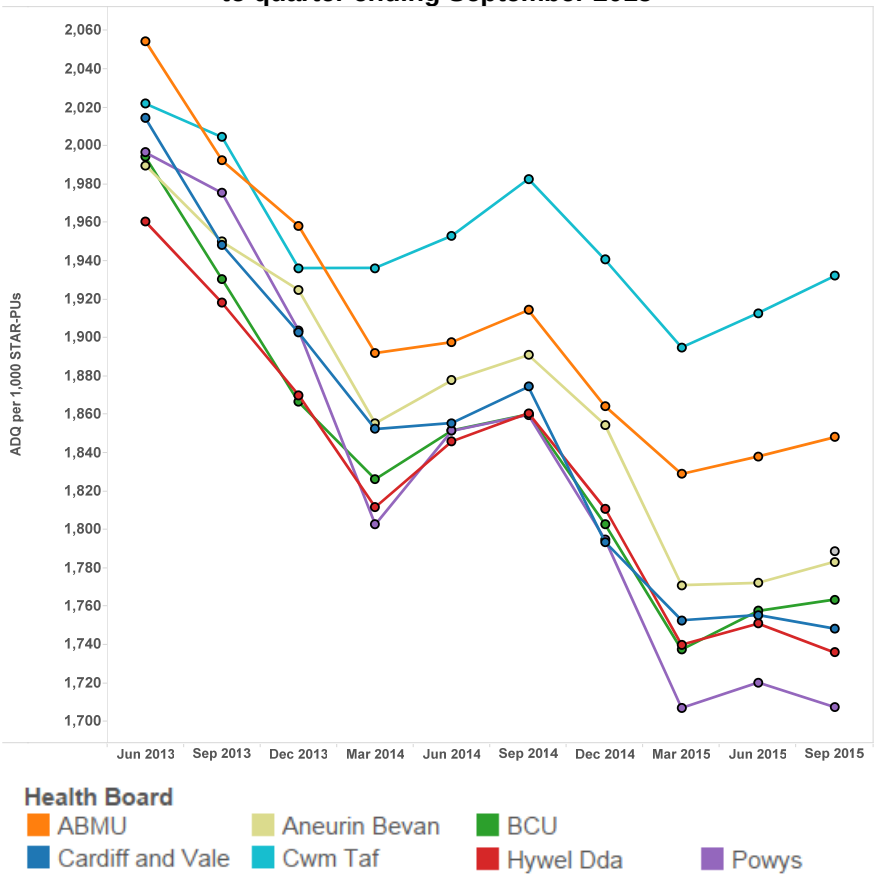
Fluoroquinolone items as a percentage of total antibacterial items – Quarter ending September 2015



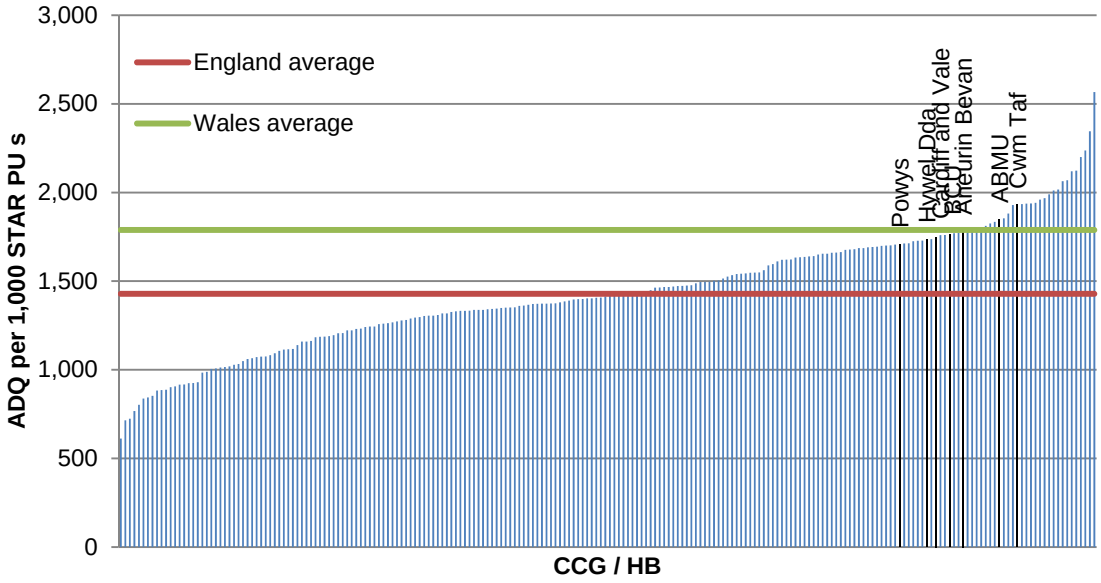
7.0 NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

7.1 Total NSAIDS

Trend in NSAID ADQs per 1,000 STAR-PUs (13) to quarter ending September 2015

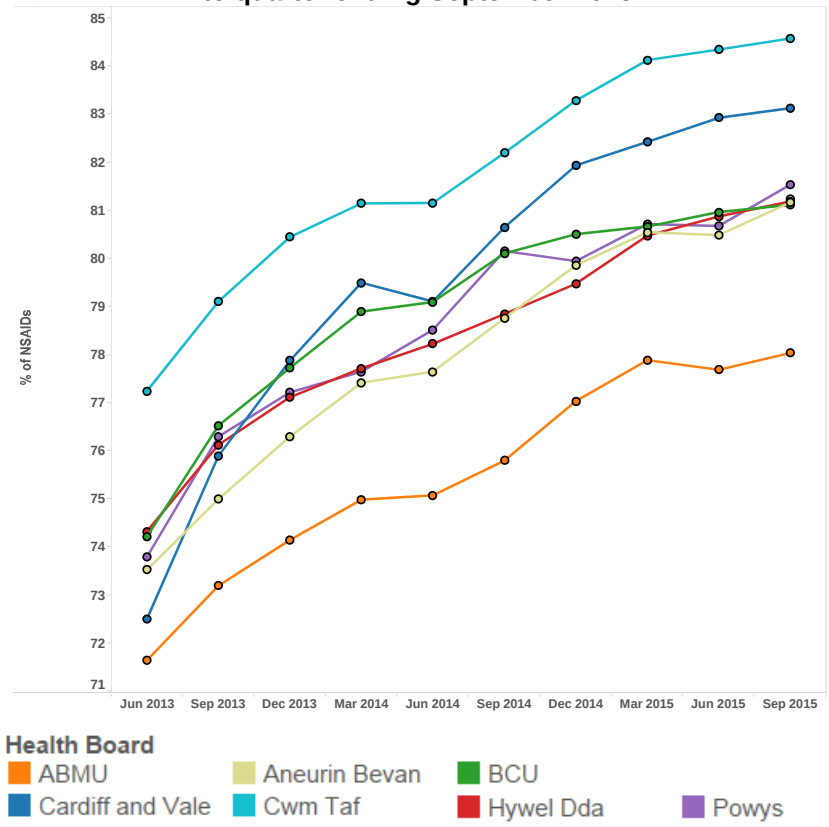


NSAID ADQs per 1,000 STAR-PUs (13) – Quarter ending September 2015

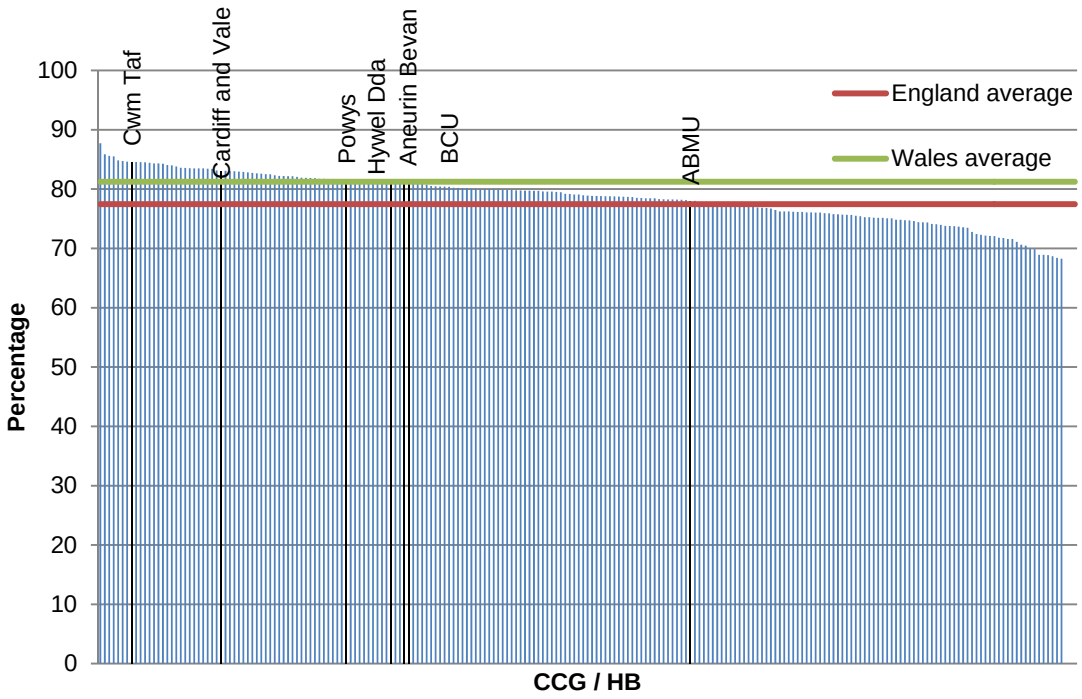


7.2 Ibuprofen and naproxen

Trend in ibuprofen and naproxen items as a percentage of NSAID prescribing to quarter ending September 2015



Ibuprofen and naproxen items as a percentage of NSAID prescribing Quarter ending September 2015



8.0 YELLOW CARDS