All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

National Prescribing Indicators 2014–2015

January 2014

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

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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 should 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 size 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 is 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 and reported to identify differences in prescribing practice.

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 2013–2014 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 and Assistant Medical Directors were asked to complete a short feedback form to review the continued relevance of the 2013–2014 NPIs, whether any of the local comparators should be considered as new NPIs and other priority areas that may be appropriate to monitor through an NPI. This information then fed into the discussions of the NPI Task and Finish Group.

The proposed NPIs for 2014–2015, accompanied by the supporting evidence, were presented to AWPAG for their comment. The NPIs for 2014–2015 were also distributed for wider consultation prior to their endorsement by AWMSG.

MEASURES

- Where possible, measures used should be accessible to all medicines management teams through CASPA.net.
- The specific therapeutic group age–sex related prescribing unit (STAR-PU) measurement is used for certain indicators instead of the 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. This data is 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 general practitioners, providing feedback at health board level and, if available, at practice level, using practice postcodes (still to be confirmed).

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 2013.
- The target may be to achieve movement to the highest prescribing quartile or the lowest prescribing quartile depending on the aim of the NPI.
- The threshold may be retained from a previous year if considered appropriate by the NPI Task and Finish Group.
- Three NPIs have been included without a target:
    - Antidepressant prescribing – This is considered an extremely important area for review; however, there is little evidence to demonstrate what an appropriate level of prescribing is. The NPI has therefore been introduced to encourage review of prescribing in outlying practices and further analysis of factors that could contribute to the variation seen in prescribing between regions.
    - Total opioid prescribing – This is intended to allow benchmarking of the other NPIs in this section, and also to ensure that review of prescribing of one opioid does not lead to a significant increase in prescribing of other inappropriate opioid analgesics.
    - Total antibiotic prescribing – Seasonal variation prevents a target being set based on prescribing in any one particular quarter.
- 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.

Table 1 details the NPIs for 2014–2015, with the evidence and supporting prescribing messages within the text that follows. Data to support the proposed NPIs for 2014–2015 are contained within Appendices 1 and 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.

Table 1. AWMSG NPIs 2014–2015

Indicator	Unit of measure	Target for 2014–2015
Lipid-modifying drugs	Items of LAC statins as a percentage of all statin, ezetimibe and simvastatin/ezetimibe combination prescribing	Maintain performance levels above the threshold set for 2013–2014 NPI, or show an increase towards this threshold.
Hypnotics and anxiolytics	ADQs per 1,000 STAR-PUs	Maintain performance levels within the lower quartile, or show a reduction towards the quartile below
Antidepressants	ADQs per 1,000 STAR-PUs	No performance target set
Opioid analgesics	Total items per 1,000 PUs	No performance target set
	Items of morphine as a percentage of strong opioid prescribing	Maintain performance levels within the upper quartile, or show an increase towards the quartile above
	Tramadol DDDs per 1,000 patients	Maintain performance levels within the lower quartile, or show a reduction towards the quartile below
Antibiotics	Total antibacterial items per 1,000 STAR-PUs	No performance target set
	Quinolones as a percentage of total antibacterial items	Maintain performance levels within the lower quartile, or show a reduction towards the quartile below
	Cephalosporins as a percentage of total antibacterial items	Maintain performance levels within the lower quartile, or show a reduction towards the quartile below
	Co-amoxiclav as a percentage of total antibacterial items	Maintain performance levels within the lower quartile, or show a reduction towards the quartile below
Insulin	Items of long-acting insulin analogues as a percentage of total long- and intermediate-acting insulin (excluding biphasics)	Maintain performance levels within the lower quartile, or show a reduction towards the quartile below
Non-steroidal anti-inflammatory drugs (NSAIDs)	ADQs per 1,000 STAR-PUs	Maintain performance levels within the lower quartile, or show a reduction towards the quartile below
	Ibuprofen and naproxen as a percentage of NSAID items	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 – GPs 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.

ADQ = average daily quantity; DDD = defined daily dosage; LAC = low acquisition cost; PU = prescribing unit; STAR-PU = specific therapeutic group age–sex related prescribing unit

1.0 LIPID-MODIFYING DRUGS

***Purpose*:** Ensure appropriate prescribing of lipid-modifying drugs with the lowest acquisition cost (LAC) in line with NICE guidance.

Unit of measure: Items of LAC statins as a percentage of all statin, ezetimibe and simvastatin/ezetimibe combination prescribing.
Target for 2014–2015: Maintain performance levels above the threshold set for 2013–2014 NPI, or show an increase towards this threshold.

Background and evidence
The use of LAC statins is promoted through the Department of Health "Better Care, Better Value" (BCBV) indicators[1]. The BCBV indicators are not targets, but are intended to provide useful comparative information to help NHS organisations to decide where and how to improve performance. There are still savings to be made by some NHS organisations through the use of LAC statins.

The basket of LAC statins comprises simvastatin, pravastatin and atorvastatin.

The National Institute for Health and Care Excellence (NICE) has issued several pieces of guidance relating to lipid modification in adults[2–5]. Clinical guideline (CG) 67 on lipid management in people without type 2 diabetes advises that simvastatin 40 mg daily should be prescribed for people for whom statins are indicated. If there are potential drug interactions or simvastatin 40 mg is contraindicated, a lower dose or alternative LAC preparation may be chosen[2]. NICE CG87 on lipid management in people with type 2 diabetes recommends simvastatin 40 mg daily as the usual choice and dose of statin, with an increase to 80 mg daily if appropriate[4].

A Medicines Resource Centre (MeReC) bulletin on lipid-modifying treatment is also available[6]. This:

- addresses the similarities and differences between NICE guidance for people with and without type 2 diabetes;
- provides clarification on NICE recommendations regarding thresholds for intensifying treatment;
- discusses the evidence base for high intensity statins and ezetimibe, the reliability of single cholesterol measurements, and the side effects of statins.

NICE provides guidance on the use of higher intensity statins. In people with type 2 diabetes with existing or newly diagnosed cardiovascular disease, or increased albumin excretion, NICE advises the consideration of intensifying lipid-lowering treatment to achieve total cholesterol of less than 4 mmol/L or low-density lipoprotein (LDL) cholesterol of less than 2 mmol/L[4]. NICE also advises that patients with acute coronary syndrome should be offered high intensity statins, and that for patients requiring secondary prevention, who do not have acute coronary syndrome, prescribers should consider intensifying statin treatment where total cholesterol is greater than 4 mmol/L, or LDL cholesterol is greater than 2 mmol/L[2]. However, all decisions should take into account the patient's informed preference, including the benefits and risks of treatment[2].

MeReC Rapid Review 1423 discusses the place in therapy of simvastatin 80 mg, which should be considered only in patients with severe hypercholesterolaemia at high risk of cardiovascular complications who have not achieved their treatment goals on lower doses, when the benefits are expected to outweigh the potential risks[7]. Advice from the Medicines and Healthcare Products Regulatory Agency (MHRA) also highlights the increased risk of myopathy associated with simvastatin 80 mg daily, as found in the study of the effectiveness of additional reductions in cholesterol and homocysteine (SEARCH)[8], discussed further in MeReC Rapid Review 2138[9].

A further large meta-analysis has confirmed the benefits of standard dose statin therapy on cardiovascular outcomes[10]; however, it comes to a different conclusion regarding more intensive statin therapy in selected populations. It suggests more intensive statin therapy to further reduce LDL cholesterol may reduce the risk of death from coronary heart disease or non-fatal myocardial infarction in people at particular high risk. However, it did not fully explore the potential harms associated with more intensive statin therapy, or examine the cost-effectiveness of this approach. This meta-analysis and its implications are discussed in MeReC Rapid Review 2127[11].

More recently, the MHRA has announced changes in prescribing advice relating to interactions between simvastatin and other drugs. The maximum daily dose of simvastatin in conjunction with amlodipine or diltiazem is 20 mg, because these drugs increase blood levels of simvastatin[12,13].

NICE CG71 on the management of familial hypercholesterolaemia (FH) recommends using the maximum licensed or tolerated dose of statins, plus ezetimibe if necessary, to try to achieve at least 50% reduction in LDL cholesterol from baseline[3]. However, if a patient cannot tolerate or does not wish to take such intensive treatment, one cohort study showed that the prognosis for patients with FH improved substantially when standard doses of "less intensive" statins were introduced (and other risk factors e.g. hypertension and smoking were addressed), such that risk of coronary heart disease may be reduced to that of the general population[14].

NICE TA132 recommends ezetimibe as an option for the treatment of adults with primary (heterozygous-familial or non-familial) hypercholesterolaemia, in the following circumstances:

- where statins are contraindicated or not tolerated;
- in conjunction with a statin where serum total or LDL cholesterol is not appropriately controlled by initial statin therapy (after appropriate dose titration or because dose titration is limited by intolerance), and when consideration is being given to changing the initial statin therapy to an alternative statin[5].

There is currently no evidence that ezetimibe, alone or added to a statin, reduces the risk of cardiovascular disease or mortality compared with an active comparator[15].

An update to NICE CG67 'Lipid modification: Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease' is currently being undertaken. The intended publication date is July 2014. This NPI will be reviewed following its publication.

Useful resources

- AWMSG Statin Template Guidance: Use of statins in primary and secondary prevention of vascular disease. Available here.
- NICE CG67 (currently being updated, publication date July 2014): Lipid modification: Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. Available here.
- NICE CG71: Familial hypercholesterolaemia. Identification and management of familial hypercholesterolaemia. Available here.
- NICE CG87 (currently being updated): Type 2 diabetes – newer agents (partial update of CG66). Available here.
- NICE TA132: Hypercholesterolaemia – ezetimibe: Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia. Available here.

2.0 HYPNOTICS AND ANXIOLYTICS

***Purpose*:** Reduce inappropriate prescribing of hypnotics and anxiolytics.

Unit of measure: Average daily quantities (ADQs) per 1,000 STAR-PUs of hypnotics and anxiolytics (user-defined group [UDG]).
Target for 2014–2015: 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 anxiolytic and hypnotic prescribing within NHS Wales. Some prescribing may be inappropriate and contribute to the problem of physical and psychological dependence, and/or may be responsible for masking underlying depression. In 1988, Committee on Safety of Medicines (CSM) advice recommended that benzodiazepines should be used for no more than two to four weeks for insomnia and anxiety, only if it is severe, disabling, or subjecting the individual to extreme distress[16]. The National Service Framework (NSF) for Mental Health stated that by 2001 all health authorities should have systems in place to monitor and review prescribing rates of benzodiazepines within the local clinical audit programme[17]. Key action point 33 in the revised Adult Mental Health NSF and Action Plan for Wales states that "*healthcare organisations are to ensure that patients and service users are provided with effective treatment and care that conforms to the NICE technological appraisals and interventional procedures and the recommendations of AWMSG and is also based on nationally agreed best practice guidelines as defined in NSFs, NICE clinical guidelines, national plans and agreed national guidance on service delivery*"[18]. The performance target set was that by March 2007, local health boards/NHS trusts should have undertaken a systematic review of NICE clinical guidelines and technology appraisals, and developed a local incremental implementation plan[18].

The substance misuse strategy of the Welsh Government ("Working together to reduce harm") calls for the reduction of inappropriately prescribed benzodiazepines[19].

The prescribing volume of hypnotics and anxiolytics (UDG) in Wales has declined over recent years. In the financial year 2012–2013, the number of items dispensed was 1,515,667 compared with 1,587,295 the previous year: a reduction of 4.5% (total quantity of tablets reduced by 6.3% from 45,955,576 to 43,040,735 for the same period)[20]. There is still a large variation in prescribing rates of these drugs across health boards, and also variation between GP practices within health boards. When comparing hypnotic and anxiolytic prescribing in Wales to North East England (the area of England most similar to Wales demographically), it was observed that Wales prescribed 50% more items per 1,000 patients for the year April 2012–March 2013[21].

Useful resources
- The Welsh Medicines Partnership educational pack: Material to support appropriate prescribing of hypnotics and anxiolytics across Wales. Available here.

3.0 ANTIDEPRESSANTS

Purpose: Review and, if appropriate, revise prescribing of antidepressants in adults, identifying reasons for variation in prescribing between practices.

Unit of measure: ADQs per 1,000 STAR-PUs for a selected group of antidepressants (UDG).
Target for 2014–2015: No target set.

UDG: Revised antidepressant subset as per England QIPP Prescribing Comparator: Antidepressant Drugs (British National Formulary [BNF] code 0403) excluding amitriptyline hydrochloride, clomipramine hydrochloride, imipramine hydrochloride, nortriptyline, trimipramine, monoamine-oxidase inhibitors, flupentixol hydrochloride[22].

Background and evidence
NICE CG90 and CG113 discuss the use of antidepressants in adults with depression or generalised anxiety disorder (GAD)[23,24]. NICE recommends a stepwise approach to managing common mental health disorders, offering the least intrusive, most effective intervention first[23,24]. Therefore, non-drug interventions such as cognitive behavioural therapy (CBT) should be the mainstay of treatment for many people with depression or GAD, with drugs generally reserved for more severe illness or when symptoms have failed to respond to non-drug interventions.

NICE recommends the use of selective serotonin reuptake inhibitors (SSRIs) as first-line pharmacological treatment for depression. SSRIs are as effective as any other antidepressant, have a favourable side effect profile, and are relatively safe in overdose[23]. Paroxetine has a shorter half-life than other SSRIs and is therefore associated with a higher risk of withdrawal symptoms[25]. The December 2011 edition of Drug Safety Update reported that citalopram and escitalopram were associated with dose-dependent QT interval prolongation and should not be used in those with pre-existing QT interval prolongation; or in combination with other medicines that prolong the QT interval (e.g. amiodarone, dronedarone, phenothiazine derivatives, haloperidol, erythromycin IV, astemizole, mizolastine). New restrictions on maximum daily doses for citalopram were also recommended: 40 mg for adults and 20 mg for patients older than 65 years and those with hepatic impairment. For escitalopram, the maximum daily dose for patients older than 65 years was reduced to 10 mg/day[26].

Wales Mental Health in Primary Care aims to promote primary mental health care and improve mental health services across Wales. It has produced resources to help GPs and their teams understand how the recently launched Part 1 of the Mental Health Measure is intended to change and improve mental health services across Wales[27]. Better access to psychological therapies in the community should provide alternative treatments for addressing milder forms of mental illness, reducing reliance on medication as the pragmatic solution.

Prescribing data indicate that antidepressant prescribing is increasing, and there is considerable variation in overall antidepressant usage across health boards in Wales (range 1,485–2,475 ADQs per 1,000 STAR-PUs for quarter ending December 2012)[20]. A review of local antidepressant prescribing is therefore recommended. This should be considered alongside the local availability of non-drug treatments, such as CBT.

No target has been set for this NPI, as it is unclear what level of antidepressant use could be considered appropriate; however, reviewing the variation in use, alongside prevalence and deprivation data and alternative non-pharmacological services, is considered necessary.

The basket of antidepressant drugs has been amended for 2014–2015 to ensure that the focus is on medicines indicated primarily for GAD and depression, and those commonly initiated in primary care. This basket reflects the QIPP prescribing comparator used in England[28]. The Health and Social Care Information Centre in England is currently developing STAR-PUs for this particular subset of antidepressants.

Useful resources

- NICE CG90: Depression in adults (update). Available here.
- NICE CG113: Generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults. Available here.
- NICE. Evidence Topic: Depression (2013). Available here.
- NICE. Evidence Topic: Anxiety (2013). Available here.
- NICE Pathway: Depression (2013). Available here.
- NICE Pathway: Generalised Anxiety Disorder (2013) is available here.
- AWMSG CEPP National Audit: Towards more appropriate management of depression in a primary care setting. Available here.
- Wales Mental Health in Primary Care downloadable resource. Available here.

4.0 OPIOID ANALGESICS

***Purpose*:** Encourage the appropriate prescribing of all opioid analgesics (including combination products containing codeine and dihydrocodeine 30 mg).

1*. Unit of measure:* Total items per 1,000 PUs for all opioid analgesics (including combination products containing codeine and dihydrocodeine 30 mg).
Target for 2014–2015: No target set (measure is intended to be used as a comparator for other NPIs).

2. *Unit of measure:* Items of morphine as a percentage of strong opioid prescribing (UDG)
Target for 2014–2015: Maintain performance levels within upper quartile, or show an increase towards the quartile above.

UDG: Buprenorphine, dipipanone, fentanyl, hydromorphone, morphine, oxycodone, pentazocine, pethidine, tapentadol* (excluding injection formulations and buprenorphine preparations prescribed for the management of opioid dependence[25]).

*Note that, as of January 2014, tapentadol modified-release (Palexia SR®) is the only formulation of tapentadol that has been recommended by AWMSG and ratified by the Minister for Health and Social Services for use within NHS Wales.

3. Unit of measure: DDDs of tramadol and tramadol-containing products per 1,000 patients.
Target for 2014–2015: Maintain performance levels within lower quartile, or show a reduction towards the quartile below.

Background and evidence

Opioid analgesics

Opioids have a well-established role in the management of acute pain following trauma (including surgery), and in the management of pain associated with terminal illness. There is evidence from clinical trials that opioids can be effective, in the short and medium term, in providing symptomatic improvement in a variety of non-cancer pain conditions. Repeated administration may cause problems of tolerance, dependence and addiction. The benefits of opioid treatment for the patient must be balanced

against the burdens of long-term use, as therapy for persistent pain may need to be continued for months or years[29].

The World Health Organisation has developed a three-step "ladder" for cancer pain:

Step 1. Non-opioid analgesic (e.g. paracetamol, NSAID)
Step 2. Opioid for mild to moderate pain (e.g. codeine) with or without a non-opioid analgesic
Step 3. Strong opioid (e.g. morphine) with or without a non-opioid analgesic[30]

NICE CG140 recommends oral modified-release morphine as the first-line maintenance treatment for patients with advanced and progressive disease who require strong opioids[31]. Morphine remains the most valuable opioid analgesic for severe pain. It is the standard against which other opioid analgesics are compared[25]. The majority of patients tolerate oral morphine well[32]. Where possible, modified-release opioids administered at regular intervals should be used in the management of patients with persistent pain. Use of more flexible dosing regimens using immediate-release preparations (alone or in combination with modified-release preparations) may be justified in some circumstances[29].

The efficacy and safety of morphine is established in clinical practice. There is a lack of evidence from high-quality comparative trials that other opioids have advantages in terms of either efficacy or side effects that would make them preferable to morphine for first-line use in cancer pain. Familiarity with the use of morphine by most practitioners is an additional consideration for patient safety[32].

Eighty percent of patients taking opioids will experience at least one adverse effect[29]. These should be discussed with the patient before treatment begins. The most common adverse effects are constipation, nausea, somnolence, itching, dizziness and vomiting. Tolerance to some side effects usually occurs within the first few days of treatment; pruritus and constipation tend to persist. Adverse effects should be managed actively with anti-emetics, antihistamines and laxatives as appropriate[29].

The clinical response to morphine is highly variable as the systemic bioavailability of morphine by the oral route is poor, with wide variation between individuals. However, with individual dose titration, a satisfactory level of analgesia can usually be achieved. A significant minority of patients are unable to tolerate morphine, mainly due to adverse side effects.

NICE CG140 states that transdermal patch formulations should not routinely be used as first-line maintenance treatment in palliative care. It does, however, state that they can be considered in patients for whom oral opioids are not suitable and analgesic requirements are stable[31]. The MHRA reports several instances of unintentional overdose of fentanyl due to dosing errors, accidental exposure and exposure of the patch to a heat source. Fentanyl is a potent opioid analgesic and should be used only in patients who have previously tolerated opioids[33].

The Welsh average for morphine prescribing as a percentage of strong opioids for the quarter to March 2013 is 46.3%[20].

Tramadol

Tramadol accounts for an increasing number of deaths and reports to the National Poisons Information Service[34]. 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 175 in 2012[35].

Tramadol is licensed for treatment of moderate to severe pain. However, it is neither more effective nor better tolerated than other weak opioid analgesics such as codeine. For severe pain, strong opioids are more effective.

Dizziness and nausea are the most commonly reported adverse effects of tramadol. Headache, somnolence, vomiting, constipation, dry mouth, fatigue and sweating are other common side-effects[36]. Hallucinations, confusion and convulsions, as well as rare cases of drug dependence and withdrawal, have been reported with tramadol at therapeutic doses[37].

To minimise the risk of convulsions, the Committee on Safety of Medicines (CSM) recommended that patients with a history of epilepsy take tramadol only if there are compelling reasons to do so[37]. In addition, tramadol should be used with caution in patients taking concomitant drugs that can lower the seizure threshold, such as tricyclic antidepressants or selective serotonin reuptake inhibitors[37]. 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.

This NPI seeks to ensure the appropriate use and review of tramadol, minimising the potential for misuse.

Useful resources

- The National Patient Safety Agency report on reducing dosing errors with opioid medicines. Available here.
- An MHRA Opioids Learning Module aimed at helping healthcare professionals to reduce the risks associated with opioid prescribing. Available here.
- World Health Organisation pain ladder. Available here.
- NICE CG140: Opioids in palliative care: safe and effective prescribing of strong opioids for pain in palliative care of adults. Available here.
- AWTTC Tramadol Resource Pack. Available here.

5.0 ANTIBIOTICS

***Purpose*:** The development of NPIs for antibiotic prescribing supports the core aims of the Antimicrobial Resistance Programme in Wales to inform, support and promote the prudent use of antimicrobials[38].

1. Unit of measure: Total antibacterial items per 1,000 STAR-PUs.
Target for 2014–2015: No target set.

2. Unit of measure: Quinolone items as a percentage of total antibacterial items.
Target for 2014–2015: Maintain performance levels within the lower quartile, or show a reduction towards the quartile below.

3. Unit of measure: Cephalosporin items as a percentage of total antibacterial items.
Target for 2014–2015: Maintain performance levels within the lower quartile, or show a reduction towards the quartile below.

4. Unit of measure: Co-amoxiclav items as a percentage of total antibacterial items.
Target for 2014–2015: Maintain performance levels within the lower quartile, or show a reduction towards the quartile below.

The above NPIs only cover antibacterials that appear in BNF Chapter 5 (Infections)[25].

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

cephalosporins and co-amoxiclav should be viewed alongside total antibacterial usage, as high total antibacterial usage may mask high usage of a particular group of antibacterials.

Background and evidence

Total antibacterial items per 1,000 STAR-PUs

The Public Health Wales report "Antimicrobial resistance and usage in Wales (2005–2011)" presents the different prescribing and antimicrobial resistance (AMR) patterns across Wales[39]. The report shows that AMR in Wales has increased over the seven years reported for some of the major pathogens. In some cases there is considerable variability in resistance rates between different hospitals and health boards in Wales, suggesting an opportunity to reduce antibiotic use in some areas[39]. For the year April 2012–March 2013, primary care prescribing rates varied from 511 to 647 items per 1,000 PUs across Welsh health boards[20].

The UK Five Year Antimicrobial Resistance Strategy was published in September 2013[40]. 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.

The Health Protection Agency (HPA) states "Prescribers are advised to use simple generic antibiotics where possible and to avoid broad-spectrum antibiotics (e.g. co-amoxiclav, quinolones and cephalosporins) where narrow antibiotics remain effective" as they increase the risk of methicillin-resistant *Staphylococcus aureus* (MRSA), *Clostridium difficile* and resistant urinary tract infections[41]. 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[41].

Quinolone items as a percentage of total antibacterial items

The prescribing of quinolones in general practice remains a concern due to increasing resistance (for example, quinolone-resistant *Neisseria gonorrhoeae*, *Escherichia coli* and other Enterobacteriaceae), They are recommended first-line by the HPA only in limited situations (e.g. acute pyelonephritis or acute prostatitis)[41]. There is also an association between quinolone use and the incidence of *C. difficile*-associated diarrhoea (CDAD)[42].

Cephalosporin items as a percentage of total antibacterial items

The cephalosporins are broad-spectrum antibiotics, which are used for the treatment of septicaemia, pneumonia, meningitis, biliary-tract infections, peritonitis and urinary tract infections[25] mainly in secondary care settings. Cephalosporins are not listed as first- or second-line treatments in the HPA report "Management of infection guidance for primary care" because of the association between cephalosporin use and the incidence of CDAD[41].

Co-amoxiclav items as a percentage of total antibacterial items

Co-amoxiclav is a broad-spectrum penicillin with activity against beta-lactamase-producing organisms such as *S. aureus* and *E. coli*. In 1997, the CSM (now the MHRA) issued guidance which limited the indications for co-amoxiclav due to an increased risk of cholestatic jaundice compared with other antibacterial agents[43]. The use of co-amoxiclav is also associated with a moderate risk of *C. difficile* infection[44], which is increased with the duration of treatment and use in at-risk patient groups, such as those aged over 65.

Useful resources
CEPP National Audit: Focus on Antibiotic Prescribing. Available here
WeMeReC bulletin: Appropriate antibiotic use – whose responsibility? Available here.
TARGET Antibiotics toolkit. Available here.

6.0. INSULIN

Purpose: Ensure prescribing of long-acting insulin analogues in type 2 diabetes mellitus is in line with NICE guidance[4]. It is intended that this indicator should be a collaborative indicator for hospital and primary care prescribing.

Unit of measure: Items of long-acting insulin analogues as a percentage of total long- and intermediate-acting insulin (excluding biphasics).
Target for 2014–2015: Maintain performance levels within the lower quartile, or show a decrease towards the quartile below.

Background and evidence
NICE CG87 on the management of type 2 diabetes recommends that when insulin therapy is necessary, human isophane (NPH) insulin is the preferred option[4]. Long-acting insulin analogues have a role in some patients, and can be considered for those who fall into specific categories, e.g. those who require assistance from a carer or healthcare professional to administer their insulin injections, or those with problematic hypoglycaemia. The All Wales Diabetes Forum and the Welsh Endocrine and Diabetes Society support the current NICE guidelines.

However, for most people with type 2 diabetes, long-acting insulin analogues offer no significant advantage over human NPH insulin, and are more expensive. A health economic analysis by NICE found that the cost-effectiveness of long-acting insulin analogues was not favourable[45]. The incremental cost per quality-adjusted life-year (compared with conventional insulin) was greater than £100,000 in all scenarios, and in some scenarios in excess of £400,000. Importantly, this analysis incorporated the anticipated health-related quality of life gain associated with the reduced fear of severe hypoglycaemic episodes[46].

A Canadian health technology assessment concluded that the newer insulin analogues offer little clinical advantage over older, conventional insulins in terms of glycaemic control or reduced hypoglycaemia for the management of patients with type 1, type 2 or gestational diabetes. These results are consistent with NICE findings for long-acting insulin analogues in type 2 diabetes[45].

Nevertheless, the prescribing of these agents has increased substantially over the past few years. England has also developed a prescribing comparator to support this QIPP topic, entitled "Long/intermediate acting insulin analogues"[47]. For the financial year 2012–2013, total spending in Wales in primary care on long/intermediate-acting insulin analogues was £8.1 million. For the period April–June 2013, long-acting insulin analogues as a percentage of total long- and intermediate-acting insulin (excluding biphasics) for Wales was 91.7% (localities range 69.6–97.8%)[20]. English comparative data for the same period show clinical commissioning groups prescribing 38–97%[21].

People with glycaemic control problems should be properly assessed for underlying causes before these newer, more expensive insulins are considered. This includes education and checking the patient's understanding of how to manage their disease and treatment. Any decision to start a long-acting insulin analogue needs to be balanced carefully against the lack of long-term safety data available for these agents and their high prescribing costs.

A large randomised controlled trial, named ORIGIN, found that, compared with standard care, the early use of basal insulin glargine for a median of six years had no effect on cardiovascular outcomes in people with impaired fasting glucose, impaired glucose tolerance or early type 2 diabetes who also had cardiovascular risk factors. As perhaps expected, episodes of severe hypoglycaemia were more common in those receiving insulin glargine. This is consistent with current NICE guidance on type 2 diabetes which recommends using appropriate stepped care with patients to manage their diabetes, using NPH insulin as first choice in those who require insulin[48].

Useful resources

- NICE CG87 (currently being updated, publication date not confirmed): Type 2 diabetes – newer agents (partial update of CG66). Available here.

7.0 NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

Purpose: Ensure that the risks associated with non-steroidal anti-inflammatory drugs (NSAIDs) are minimised by appropriate choice and use.

1. Unit of measure: NSAID ADQs per 1,000 STAR-PUs.
Target for 2014–2015: Maintain performance levels within the lower quartile, or reduce towards the quartile below.

2. Unit of measure: Ibuprofen and naproxen as a percentage of total NSAID items.
Target for 2014–2015: Maintain performance levels within the upper quartile, or show an increase towards the quartile above.

Background and evidence

There is overwhelming evidence to reduce prescribing of NSAIDs, especially in the elderly, due to the risk of gastro-intestinal (GI), cardiovascular and renal complications[49–52].

Aspirin should only be used with another NSAID when absolutely necessary; the combination substantially increases risk of GI complications. Patients taking long-term aspirin should be reminded to avoid other NSAIDs, including those bought without prescription[53,54]. Ibuprofen and selective COX-2 inhibitors are associated with the lowest GI risk, but serious and fatal GI reactions have nevertheless been reported[49]. It should be noted that co-prescription of serotonin selective reuptake inhibitors may be associated with a similar increase in the risk of GI complications as low-dose aspirin[55].

The MHRA has issued warnings on the increased risk of renal failure and thrombotic events associated with the use of NSAIDs[50–52]. COX-2 inhibitors, diclofenac and ibuprofen 2.4 g daily are associated with an increased risk of thrombotic events[25]. NSAIDs are contraindicated in severe heart failure and should only be prescribed for patients with signs of heart failure when considered essential[56]. A 2011 systematic review concluded that naproxen and low-dose ibuprofen (≤ 1,200 mg daily) appear least harmful in respect of cardiovascular toxicity[57] and naproxen (250 mg twice-daily as required) should be considered first-line.

In June 2013, the MHRA issued advice confirming that diclofenac should not be used in patients with serious underlying heart conditions such as heart failure, heart disease, circulatory problems or previous heart attack or stroke[58]. This followed a review of the safety of NSAIDs conducted by the EMA, which concluded that the cardiovascular risk associated with diclofenac was similar to that of selective COX-2 inhibitors[59].

The National Prescribing Centre (NPC) advised that GI and cardiovascular adverse effects of NSAIDs may be minimised by selecting the lowest effective dose for the shortest duration necessary[60]. 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).

Useful resources

- AWMSG CEPP Audit 2010–2012: Towards appropriate NSAID prescribing. Available here.
- NPC advice on cardiovascular and GI safety of NSAIDs (2007). Available here.

8.0 YELLOW CARDS

***Purpose*:** Increase the number of yellow cards submitted by GPs in Wales.

***Unit of measure*:** Number of yellow cards submitted per practice and per health board.
***Target for 2014–2015*:** Target for GP practice – GPs 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[61,62]. In addition, 6.7% of inpatients will suffer a serious ADR[63] and 0.15% of hospital inpatients suffer fatal ADRs[61,63].

The Yellow Card Scheme is vital in helping the MHRA monitor the safety of medicines and vaccines that are on the market. The Yellow Card Centre (YCC) Wales is one of five regional ADR monitoring centres, acting on behalf of the MHRA.

Data obtained from YCC Wales show that the number of ADRs reported to the MHRA from Wales fell by 9% in 2012–2013. The total annual number of reports is the lowest for the past ten years. This is despite the total number of UK reports to the MHRA increasing by 9% for the same period.

The number of reports from GPs across Wales has been in decline for the past eleven years. In 2012–2013, the number of yellow card reports from GPs reached a plateau, despite its inclusion as a Clinical Effectiveness Prescribing Programme (CEPP) local comparator since 2012. There is clear disparity between the yellow card reporting rates for individual health boards, even when population is taken into account.

Current initiatives include the distribution of a training package, including a poster and presentation, to all prescribing advisors; the launch of a WeMeReC Pharmacovigilance module; and the availability of local Yellow Card Champions to provide local GP training throughout Wales.

Useful resources

- MHRA website
- Yellow Card reporting website
- WeMeReC Pharmacovigilance bulletin. Available here
- YCC Wales website
- Local comparator training package. Available here
- BMJ Learning Pharmacovigilance module. Available here

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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.

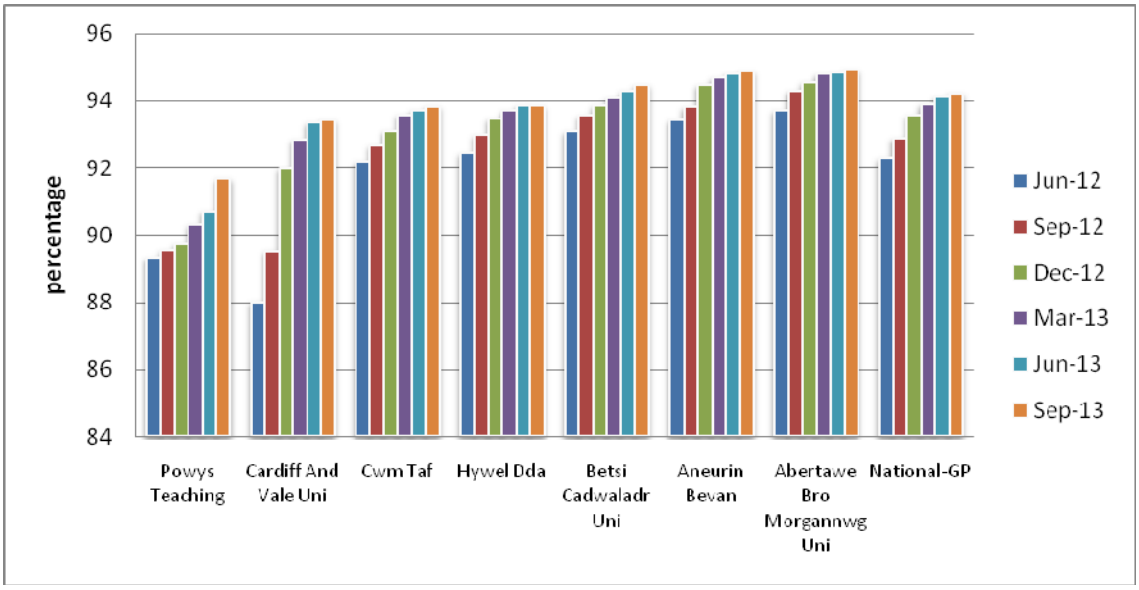
STAR-PU: Specific therapeutic group age–sex related prescribing units (STAR-PUs) are designed to measure prescribing weighted for age and sex of patients. There are differences in the age and sex of patients for whom medicines in specific therapeutic groups are usually prescribed. To make such comparisons,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

APPENDIX 1. Performance of NHS Wales against the 2014–2015 NPIs using data to September 2013

The following bar charts and line graphs show the trend in prescribing for each health board against the 2014–2015 NPIs.

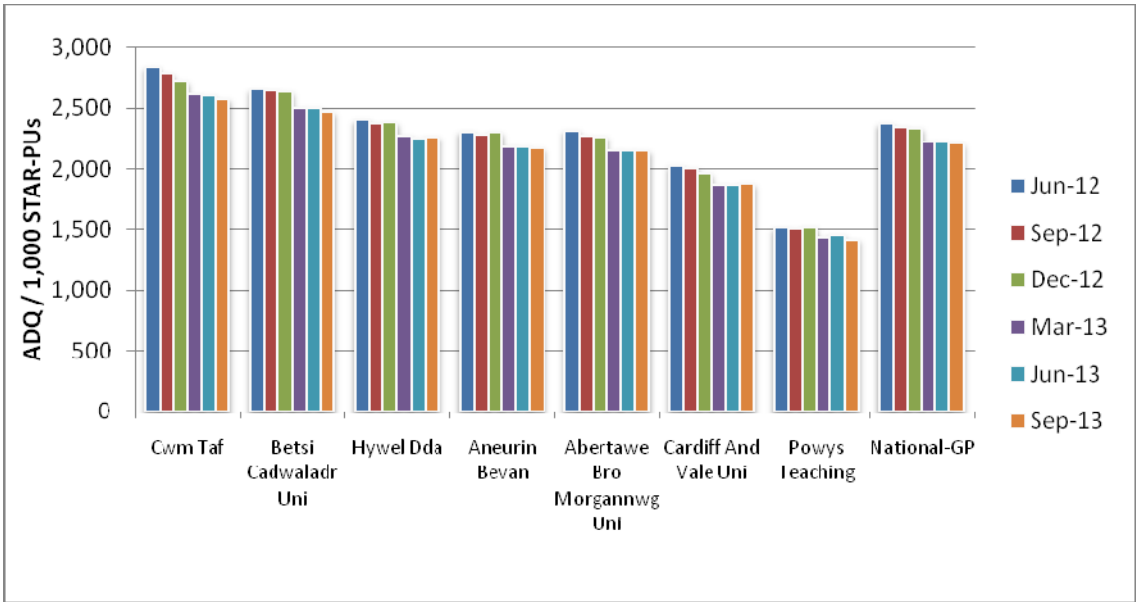
1.0 LIPID-MODIFYING DRUGS

Items of LAC statins as a percentage of all statin, ezetimibe and simvastatin/ezetimibe combination prescribing – Quarter ending June 2012 to quarter ending September 2013



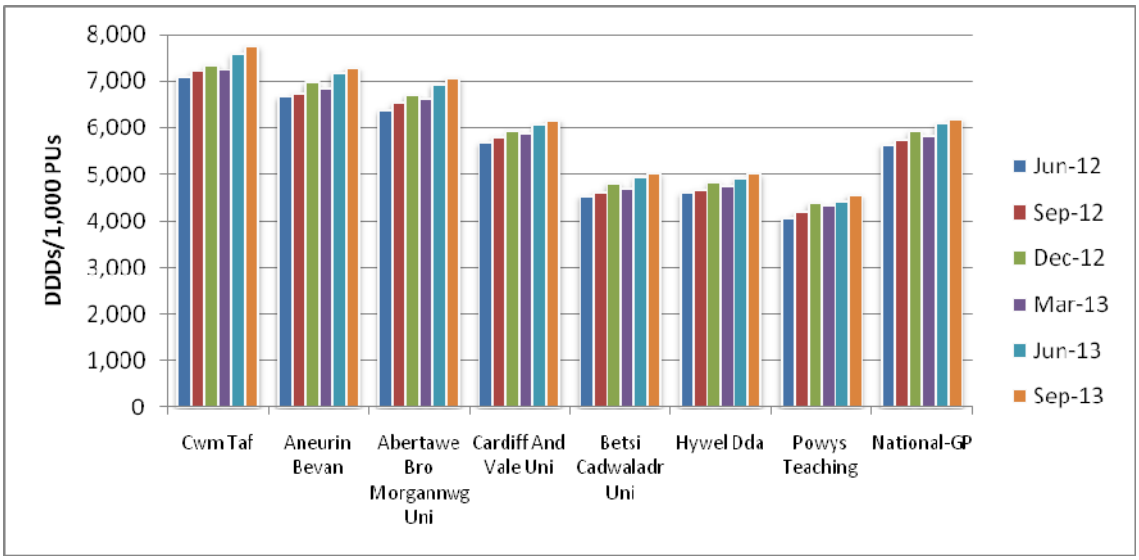
2.0 HYPNOTICS AND ANXIOLYTICS

Hypnotics and anxiolytics (ADQs per 1,000 STAR-PUs) (2012–2013 UDG) – Quarter ending June 2012 to quarter ending September 2013



3.0 ANTIDEPRESSANTS

Antidepressants (DDDs per 1,000 PUs) (2014–2015 UDG) – Quarter ending June 2012 to quarter ending September 2013

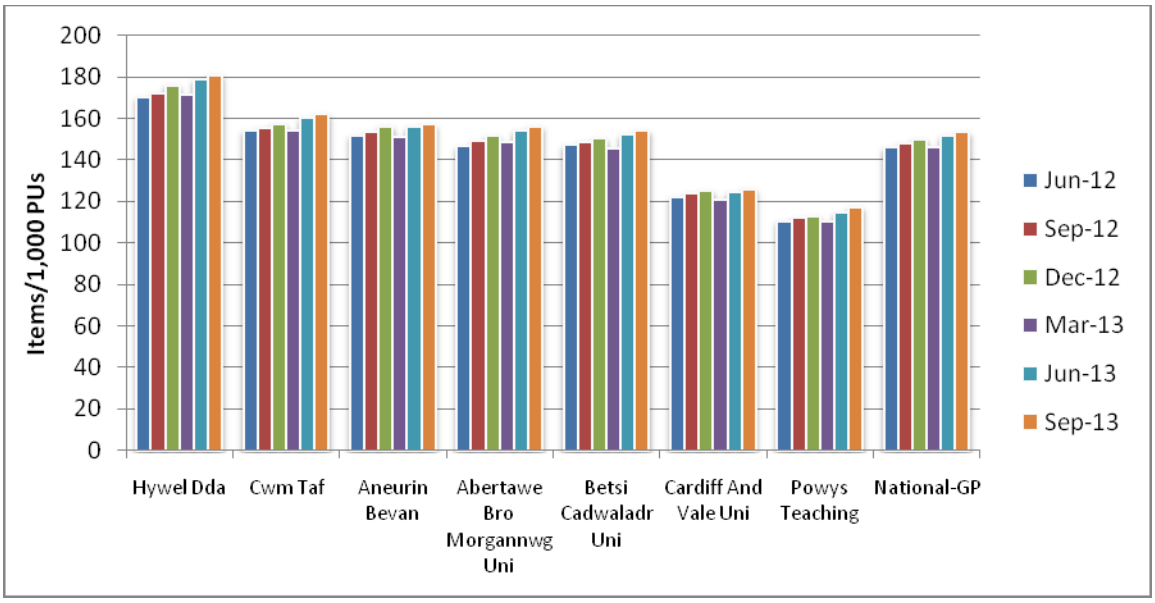


The figure above shows prescribing measured as DDDs per 1,000 PUs rather than ADQs per 1,000 STAR-PUs as the drug basket has been revised for 2014–2015; therefore, there are no historical prescribing data.

4.0 OPIOID ANALGESICS

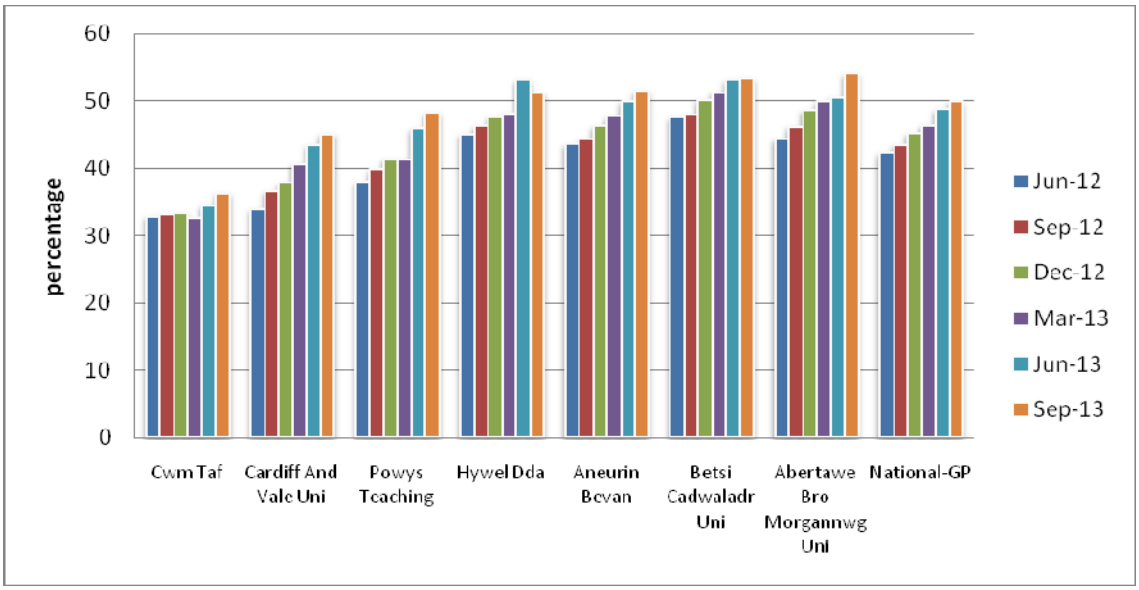
4.1 Total opioid items prescribed

All opioid analgesics (including combination products containing codeine and dihydrocodeine 30 mg) (items per 1,000 PUs) – Quarter ending June 2012 to quarter ending September 2013



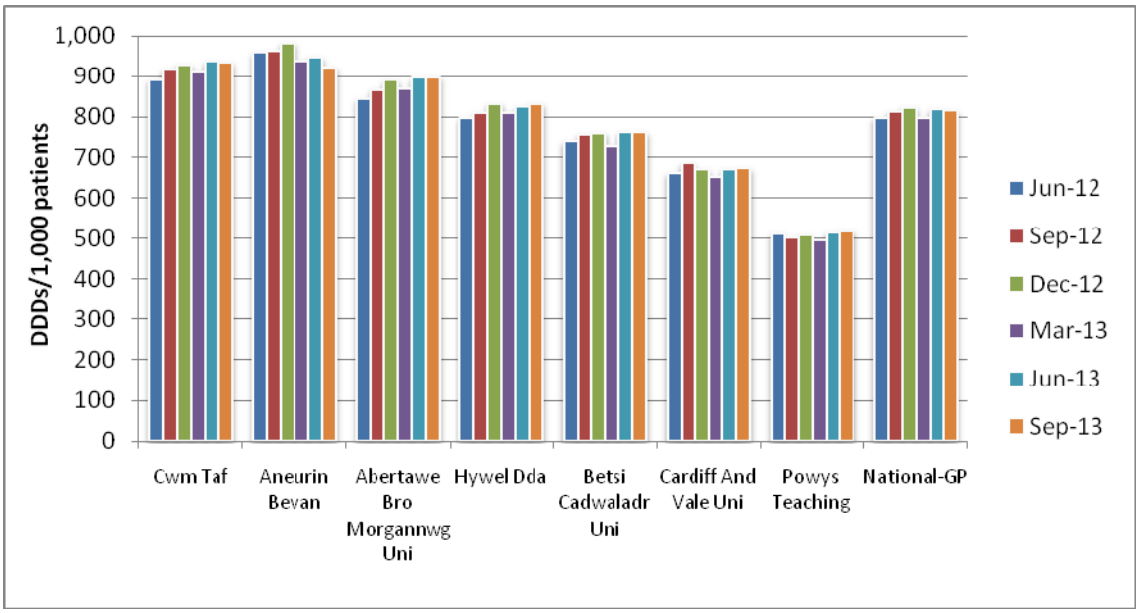
4.2 Morphine

Items of morphine as a percentage of strong opioid prescribing (2013–2014 UDG) – Quarter ending June 2012 to quarter ending September 2013



4.3 Tramadol

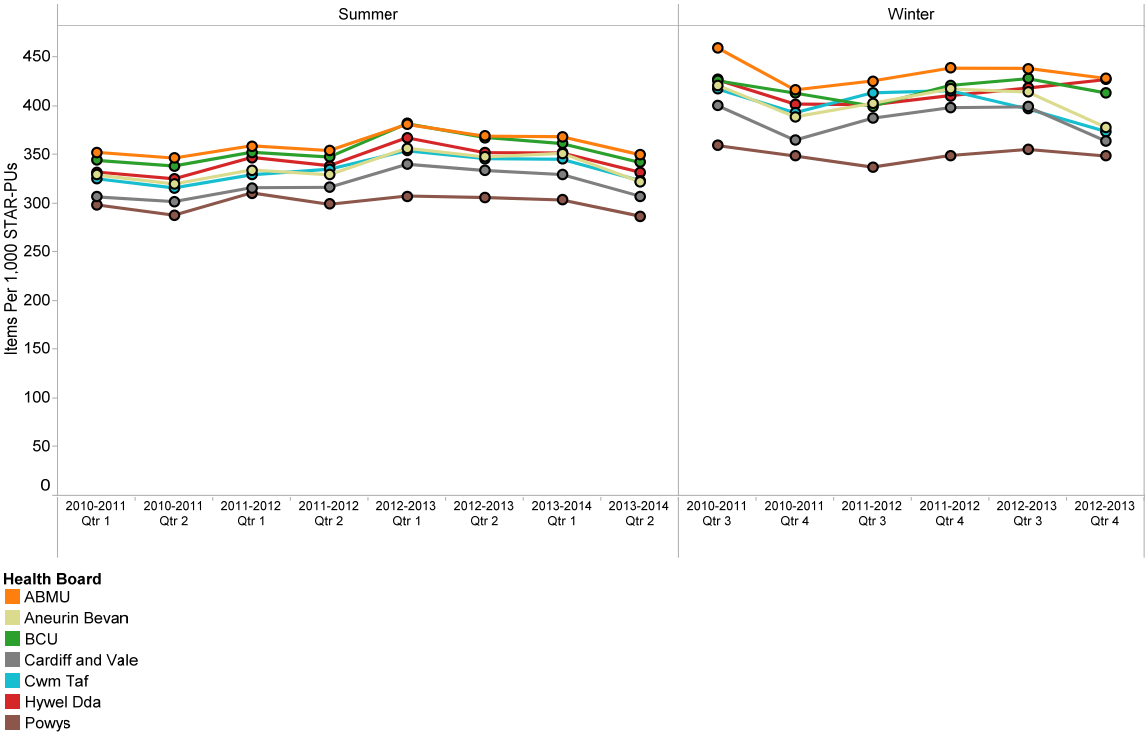
Tramadol (DDDs per 1,000 patients) – Quarter ending June 2012 to quarter ending September 2013



5.0 ANTIBIOTICS

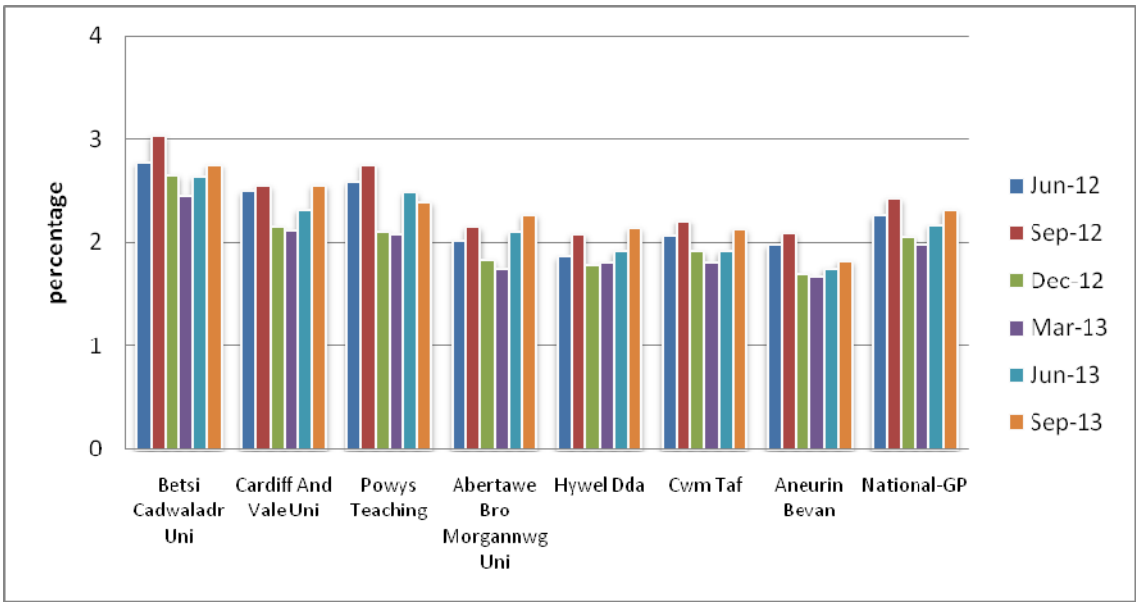
5.1 Total antibiotics

Trend in antibacterial items per 1,000 STAR-PUs for summer (April–September) and winter (October–March) quarters, April 2010 to September 2013



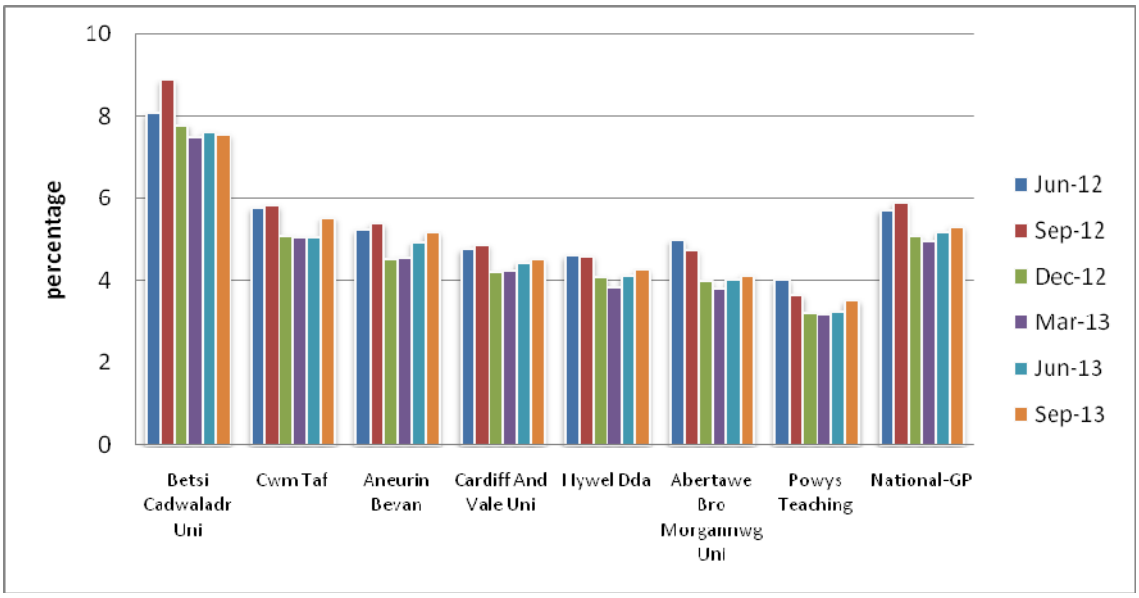
5.2 Quinolones

Quinolone items as a percentage of total antibacterial items – Quarter ending June 2012 to quarter ending September 2013



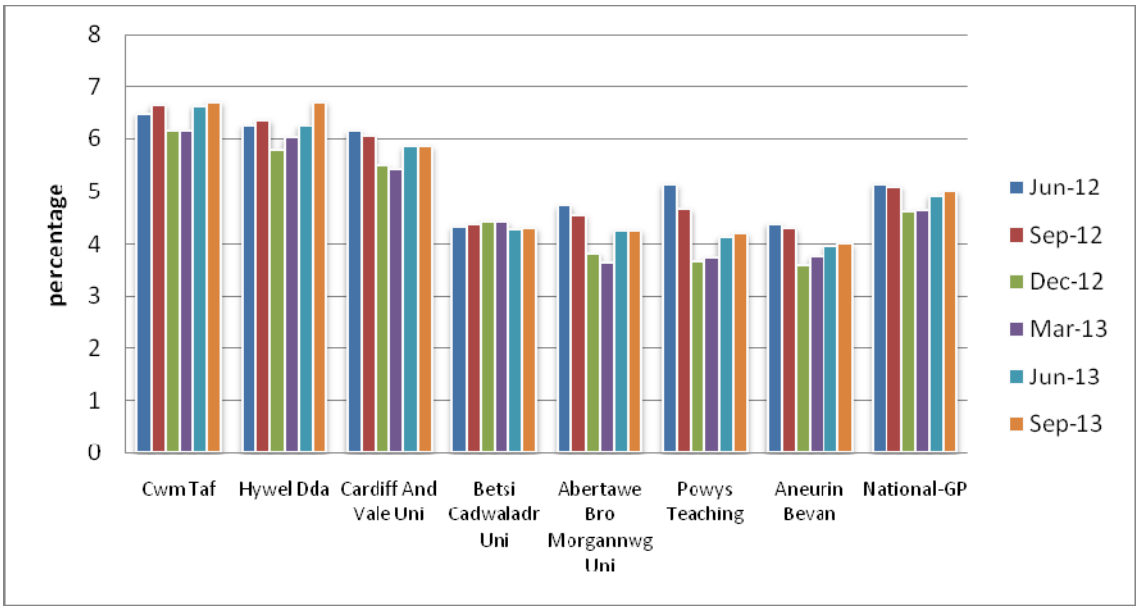
5.3 Cephalosporins

Cephalosporin items as a percentage of total antibacterial items – Quarter ending June 2012 to quarter ending September 2013



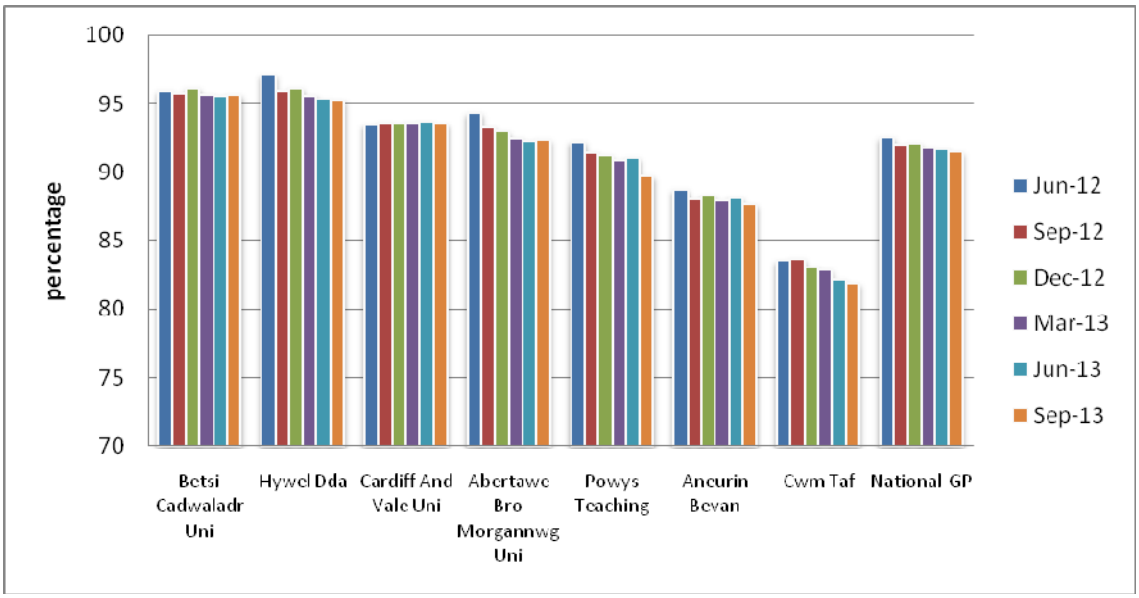
5.4 Co-amoxiclav

Co-amoxiclav items as a percentage of total antibacterial items – Quarter ending June 2012 to quarter ending September 2013



6.0 INSULIN

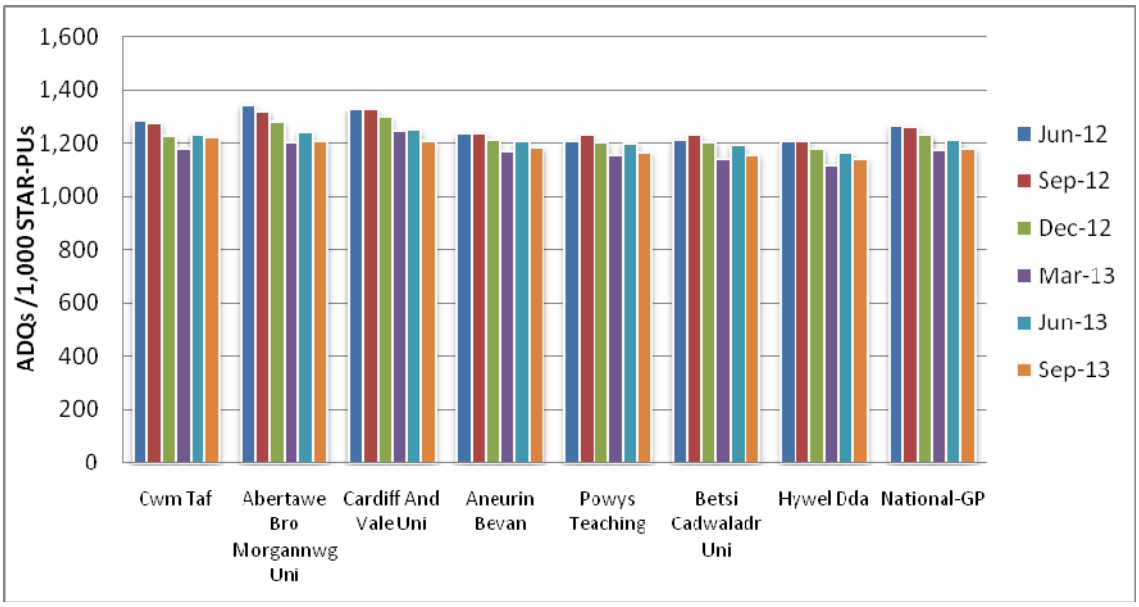
Items of long-acting insulin analogues as a percentage of total long- and intermediate-acting insulin items (excluding biphasics) – Quarter ending June 2012 to quarter ending September 2013



7.0 NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

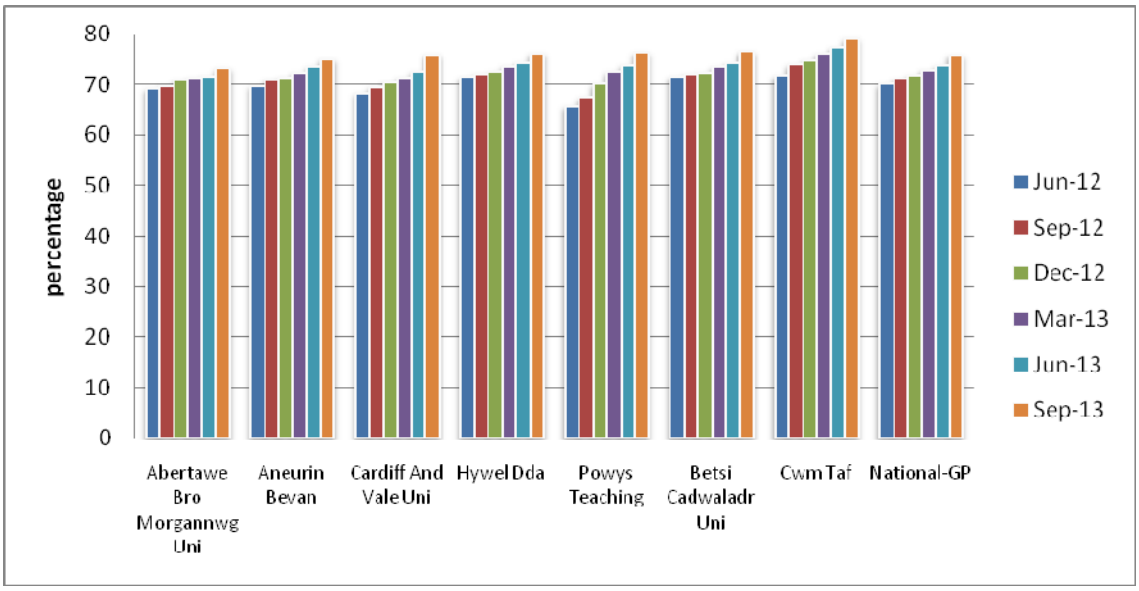
7.1 Total NSAIDS

NSAIDs (ADQs per 1,000 STAR-PUs) – Quarter ending June 2012 to quarter ending September 2013



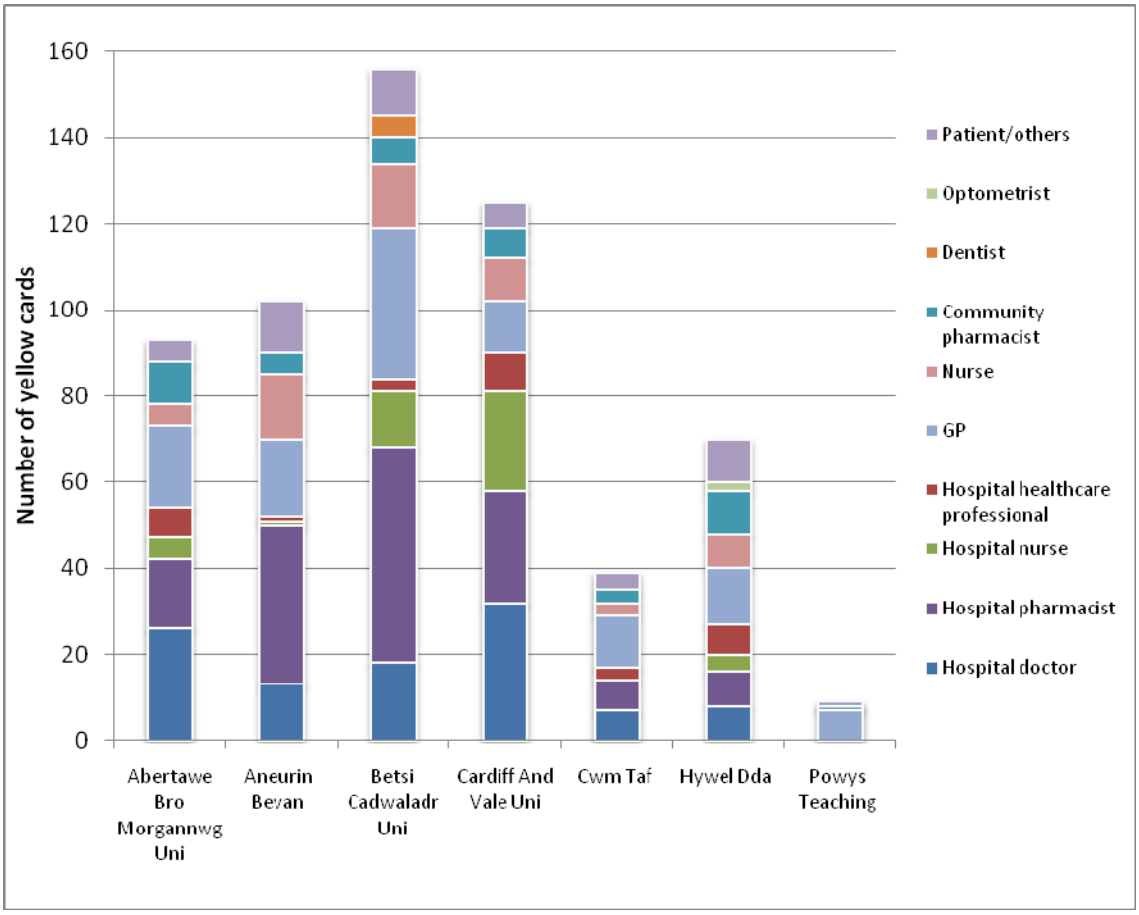
7.2 Ibuprofen and naproxen

Ibuprofen and naproxen as a percentage of NSAID items – Quarter ending June 2012 to quarter ending September 2013



8.0 YELLOW CARDS

Yellow cards by reporter type – April 2012 to March 2013

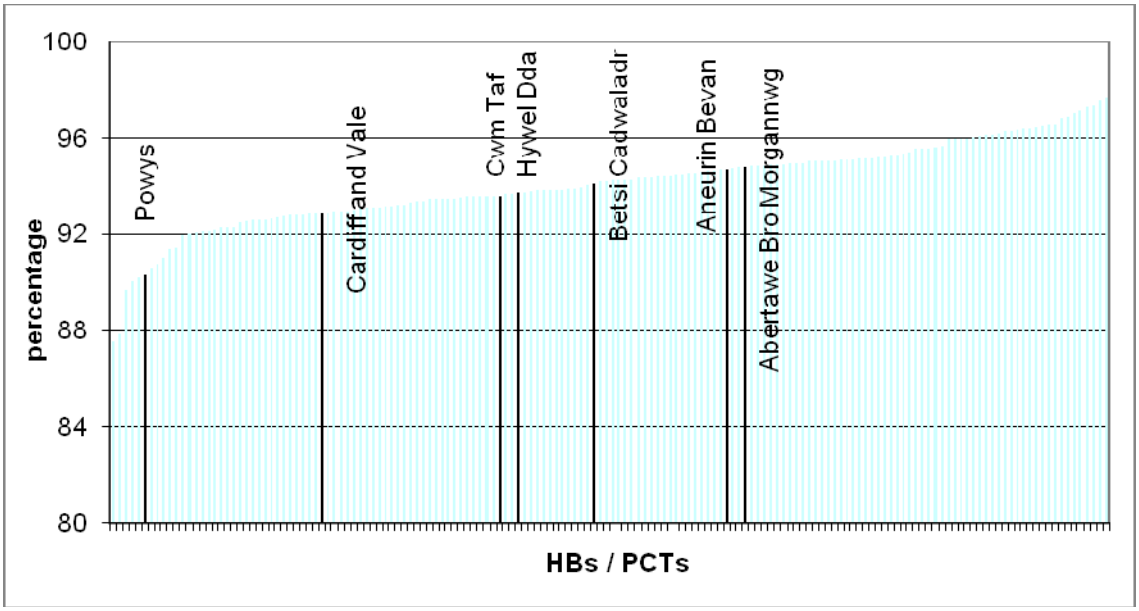


APPENDIX 2. Comparison of NHS Wales health boards against English PCTs for the 2014–2015 NPIs using data for the quarter ending March 2013

The bar charts compare prescribing of health boards in Wales with that of primary care trusts (PCTs) in England. The black bars represent the seven health boards in Wales; the blue bars represent the 151 PCTs in England.

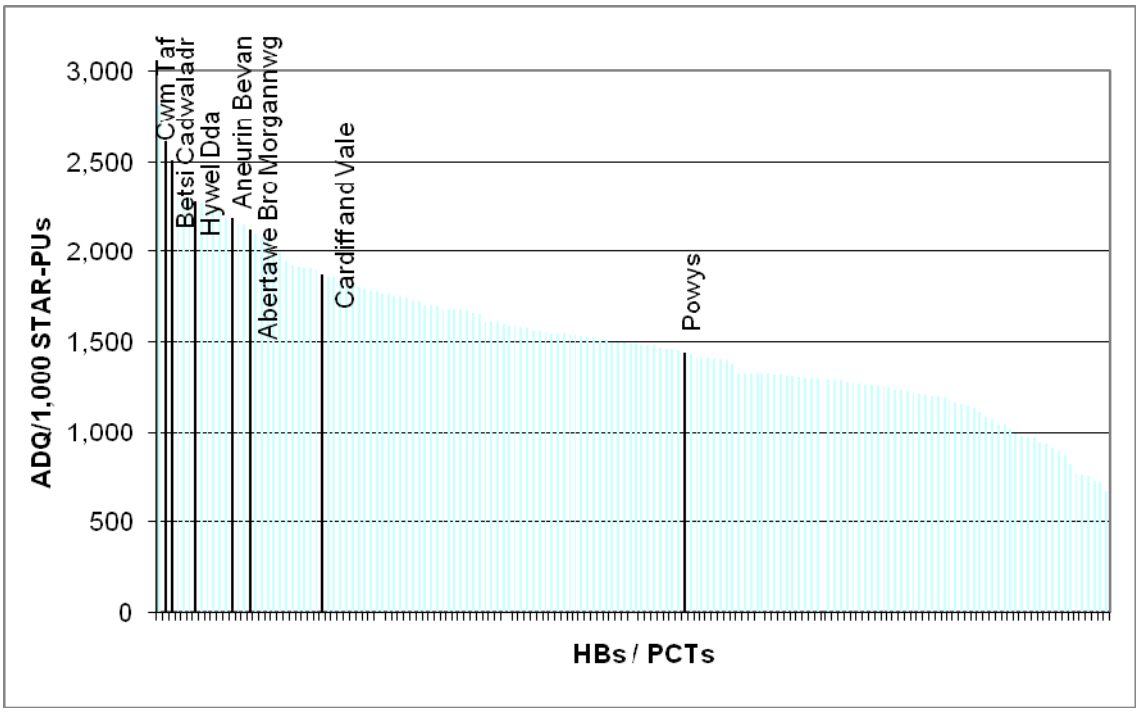
1.0 LIPID-MODIFYING DRUGS

Items of LAC statins as a percentage of all statin, ezetimibe and simvastatin/ezetimibe combination prescribing – Quarter ending March 2013



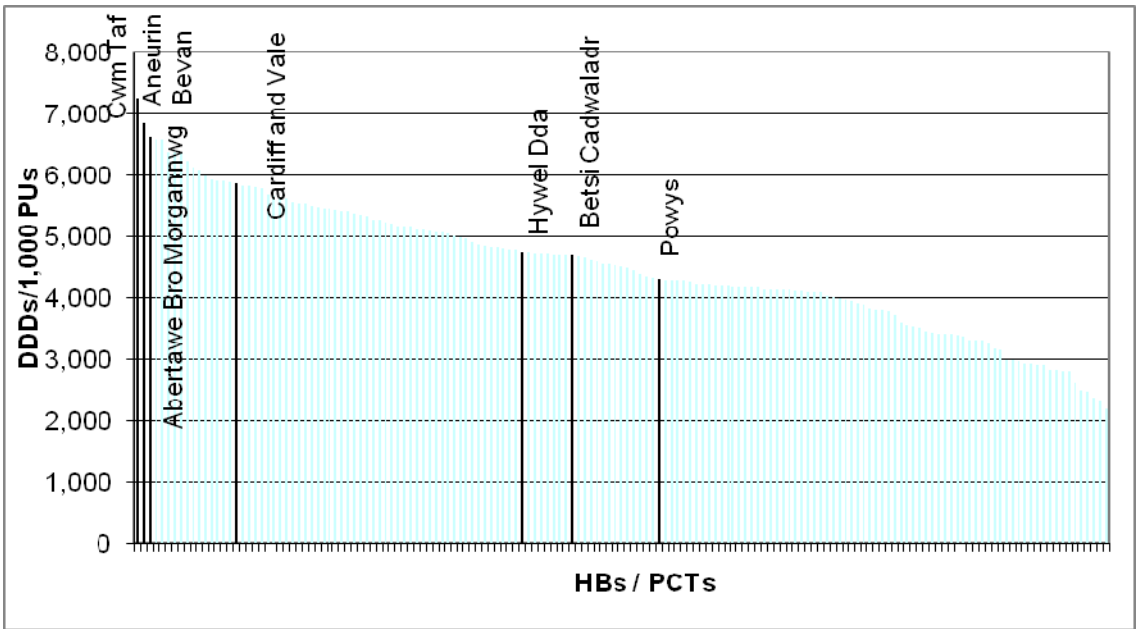
2.0 HYPNOTICS AND ANXIOLYTICS

Hypnotics and anxiolytics (ADQs per 1,000 STAR-PUs) (2012–2013 UDG) – Quarter ending March 2013



3.0 ANTIDEPRESSANTS

Antidepressants (DDDs per 1,000 PUs) (2014–2015 UDG) – Quarter ending March 2013

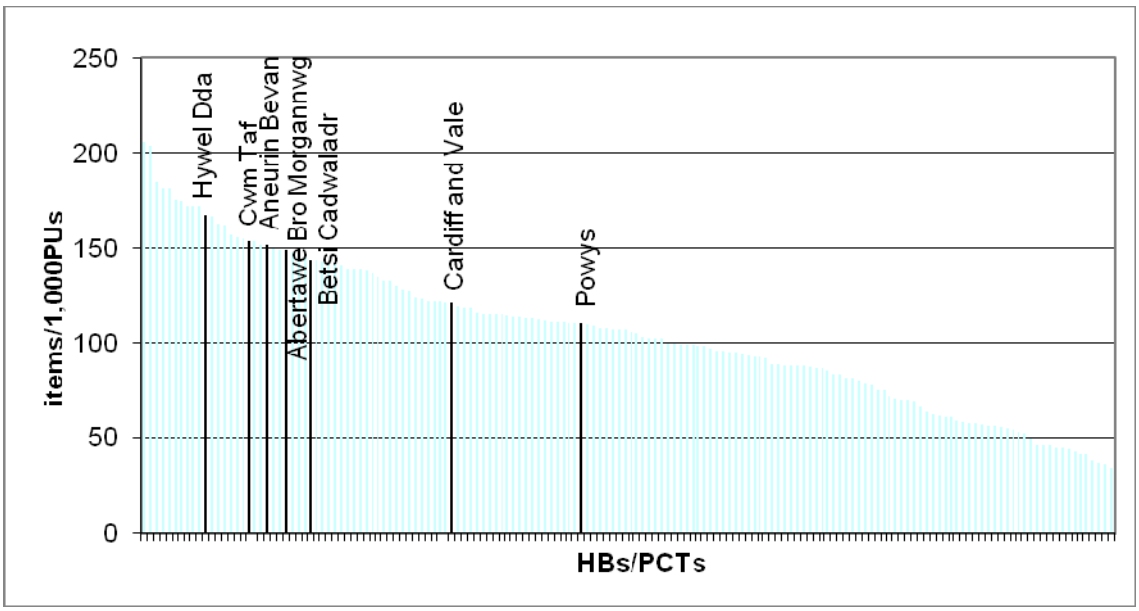


The figure above shows prescribing measured as DDDs per 1,000 PUs rather than ADQs per 1,000 STAR-PUs as the drug basket has been revised for 2014–2015; therefore, there are no historical prescribing data.

4.0 OPIOID ANALGESICS

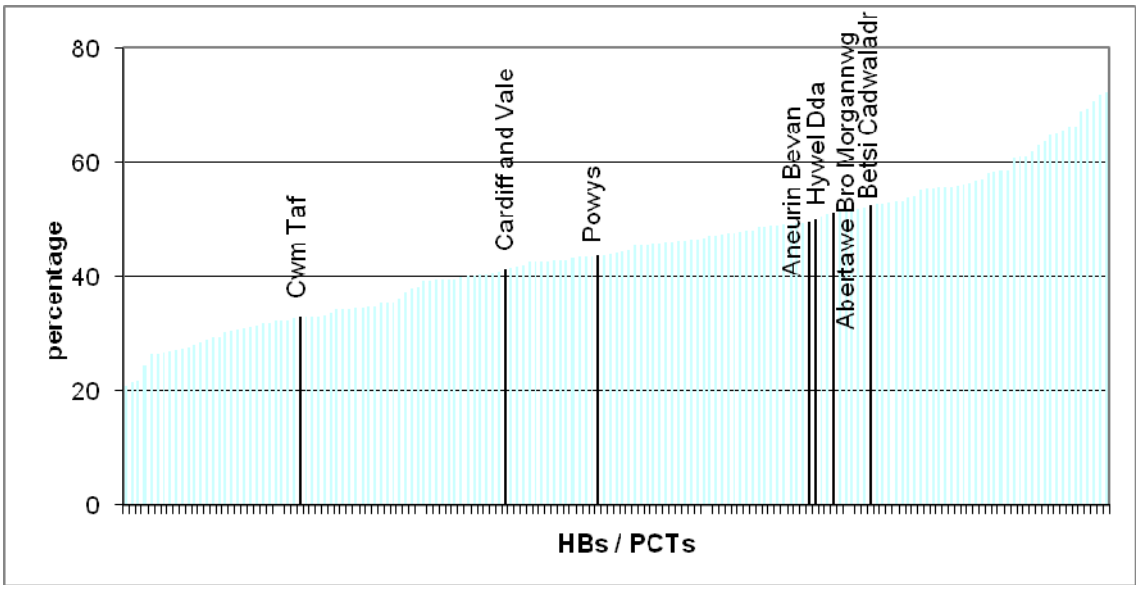
4.1 Total opioid items prescribed

Total items per 1,000 PUs for all opioid analgesics (including combination products containing codeine and dihydrocodeine 30mg) – Quarter ending March 2013



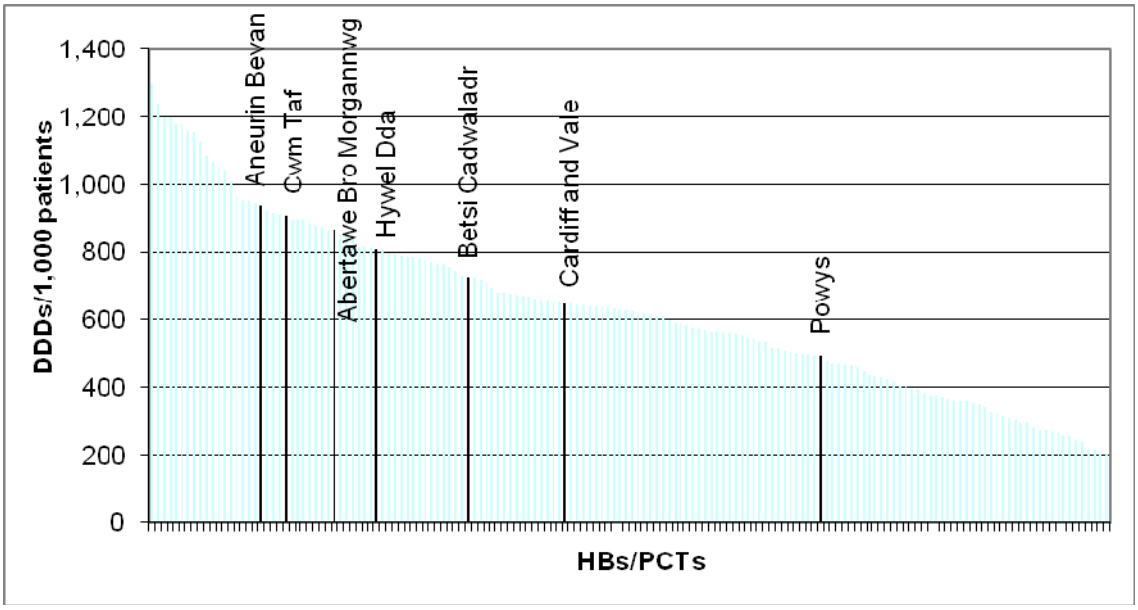
4.2 Morphine

Items of morphine as a percentage of strong opioid prescribing (2013–2014 UDG) – Quarter ending March 2013



4.3 Tramadol

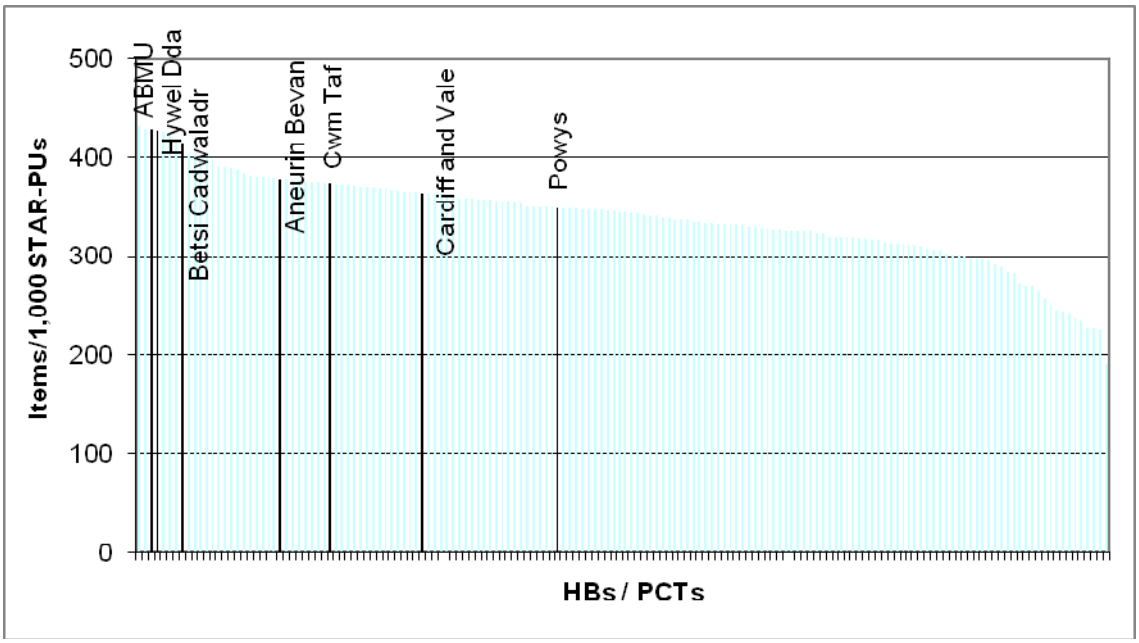
Tramadol (DDDs per 1,000 patients) – Quarter ending March 2013



5.0 ANTIBIOTICS

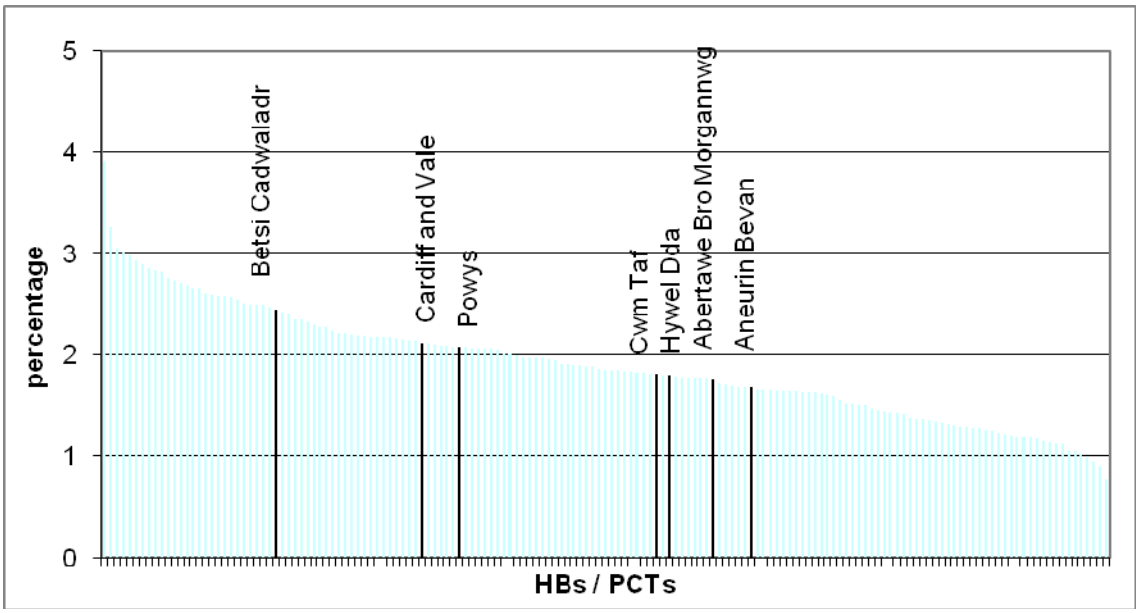
5.1 All antibiotics

Total antibacterial items per 1,000 STAR-PUs – Quarter ending March 2013



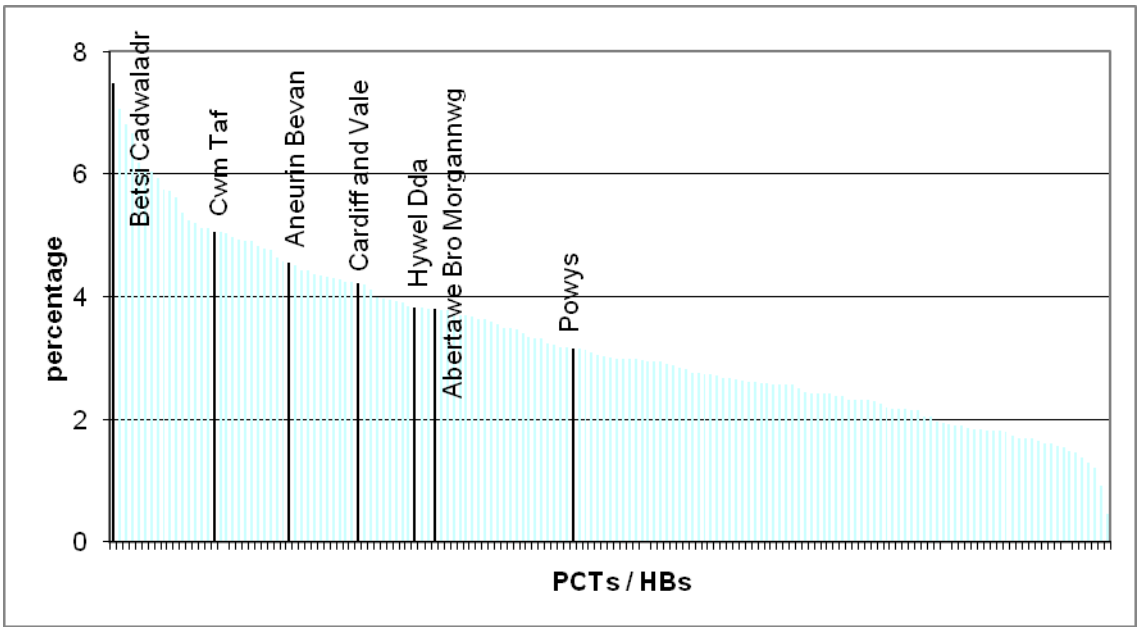
5.2 Quinolones

Quinolone items as a percentage of total antibacterial items – Quarter ending March 2013



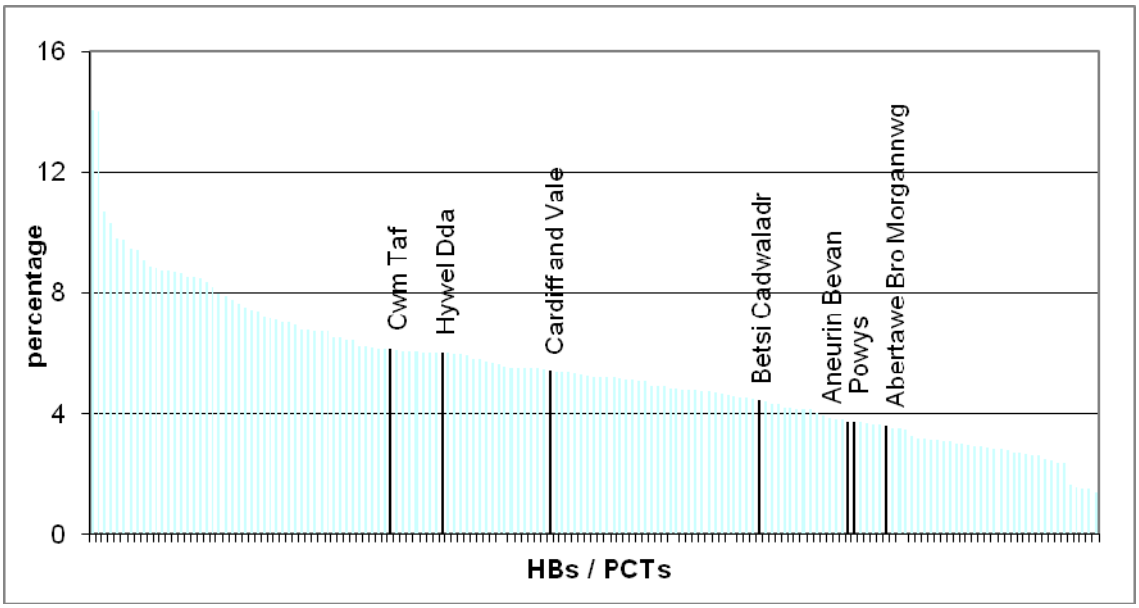
5.3 Cephalosporins

Cephalosporin items as a percentage of total antibacterial items – Quarter ending March 2013



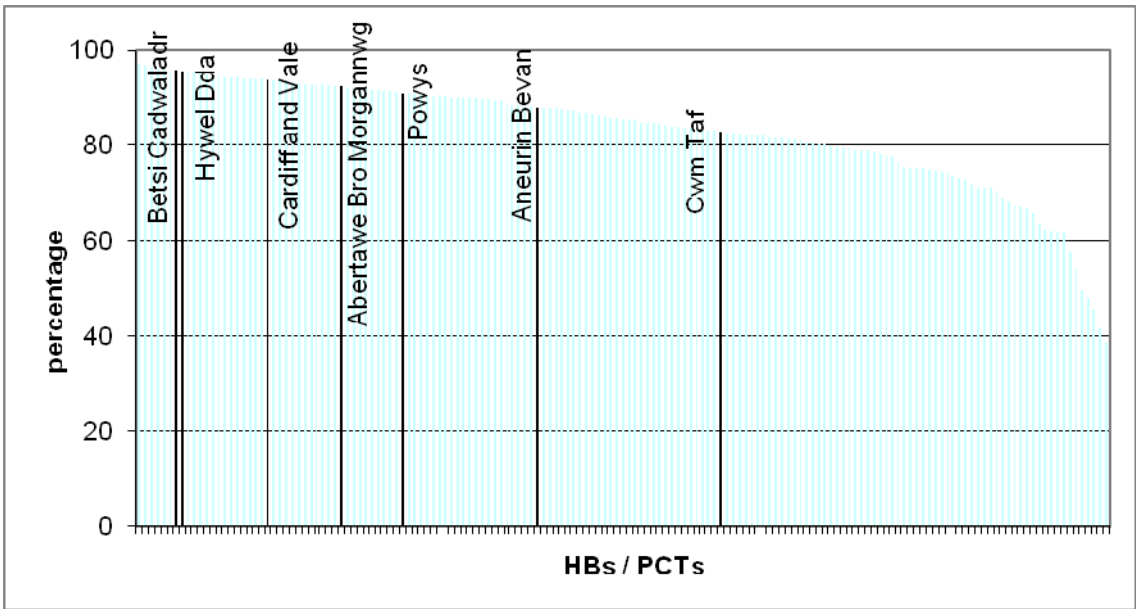
5.4 Co-amoxiclav

Co-amoxiclav items as a percentage of total antibacterial items – Quarter ending March 2013 – Comparison of Welsh health boards and English PCTs



6.0 INSULIN

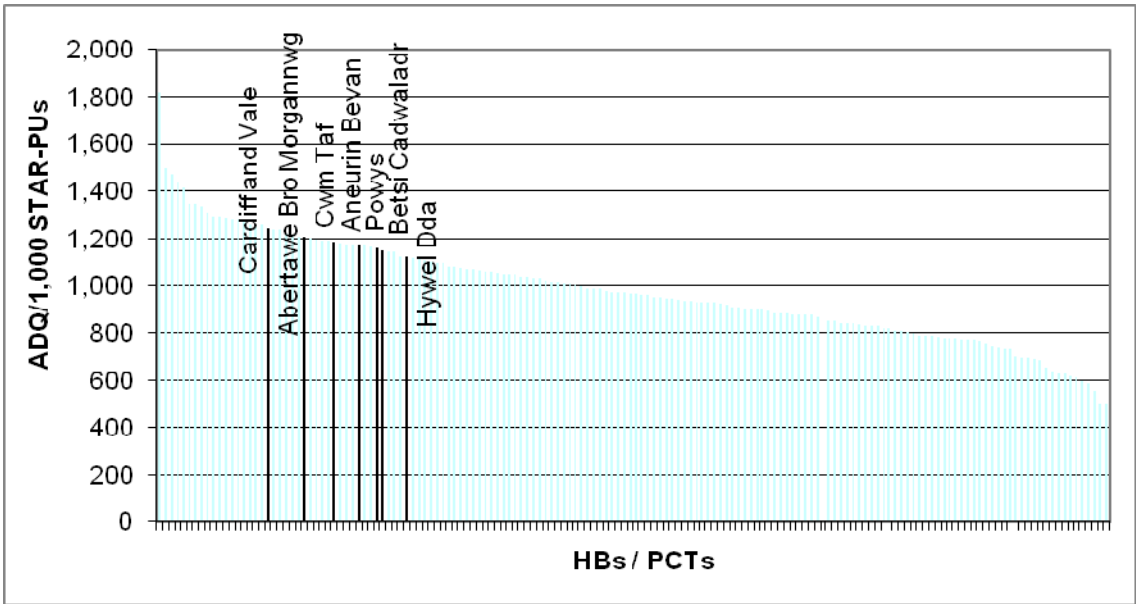
Items of long-acting insulin analogues as a percentage of total long- and intermediate-acting insulin items (excluding biphasics) – Quarter ending March 2013



7.0 NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

7.1 Total NSAIDS

Total NSAID ADQs per 1,000 STAR-PUs – Quarter ending March 2013



7.2 Ibuprofen and naproxen

Ibuprofen and naproxen as a percentage of NSAID items – Quarter ending March 2013