All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

NATIONAL PRESCRIBING INDICATORS 2011-12

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INTRODUCTION

In October 2003, The All Wales Medicines Strategy Group (AWMSG) agreed that prescribing indicators were useful tools to promote rational prescribing. It was also noted that there was unease with indicators that had an over-emphasis on cost rather than quality.

This guidance represents the view of AWMSG, which was arrived at after careful consideration of the available evidence. Implementation of the national indicators 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.

METHOD USED TO REVIEW AND UPDATE NATIONAL PRESCRIBING INDICATORS

The North Wales Indicator Working Group reviewed the 2010-11 prescribing indicators to ensure they were still valid and reflected best practice. During 2010-11 the chiral indicator was reviewed and it was the view of the group and AWPAG that this indicator was no longer valid and should be replaced. A new prescribing indicator was prepared using the following principles previously agreed by AWMSG:

- Indicators should be evidence based.
- Indicators should be clear, easily understood and applicable at practice level.
- Targets should be challenging but achievable and based on the principle of encouraging all Health Boards to achieve the prescribing rates of the best quartile.
- Targets should be set based on prescribing data for the quarter ending March 2011.
- Targets should address efficiency as well as quality.

To reflect a desire to monitor the implementation of the National Institute for Health and Clinical Excellence (NICE) guidance, AWMSG decided to replace the chiral indicator with an indicator on the use of dosulepin, as its use is no longer recommended for use by NICE[1].

The non-steroidal anti-inflammatory drugs (NSAID) volume indicator has been updated from defined daily doses (DDD) per 1000 prescribing units (PUs) to average daily quantity (ADQ) per 1000 PUs.

This was considered necessary because one DDD for diclofenac (currently the most commonly prescribed NSAID in Wales) is 100mg; for naproxen one DDD is 500mg (or 1.5 for 750mg).

If naproxen 750mg is prescribed instead of diclofenac 100mg, this would result in an overall increase of 50% in measured DDDs, and would incorrectly suggest an increased volume of NSAID usage.

The ADQ for diclofenac is 100mg, and 750mg for naproxen, which makes it a more appropriate measure e.g. if naproxen 750mg is prescribed instead of diclofenac 100mg, there would be no net increase in measured ADQs.

Additionally, a proton pump inhibitor (PPI) indicator has been created to support the Welsh Medicines Partnership (WMP) Invest to Save project for the Welsh Assembly Government (WAG) on the appropriate use of PPIs.

References

1. National Institute for Health and Clinical Excellence. Clinical Guideline 90. Depression: the treatment and management of depression in adults; October 2010. Available at: http://guidance.nice.org.uk/CG90.

TABLE 1: NATIONAL PRESCRIBING INDICATORS 2011-12

Indicator	Unit	Target
Statins	Items of low cost statins (simvastatin and pravastatin) as a percentage of all statin prescribing (including combinations of ezetimibe with statins)	Maintain performance levels within the upper quartile or show an increase towards the quartile above
ACE inhibitors	Items of ace inhibitors as a percentage of drugs affecting the renin-angiotensin system	Maintain performance levels within the upper quartile or show an increase towards the quartile above
Dosulepin	DDD per 1000 PUs	Maintain performance levels within the lower quartile or show a reduction towards the quartile below
Hypnotics and anxiolytics	DDD per 1,000 patients (measured separately and as a combined entity)	Maintain performance levels within the lower quartile or show a reduction towards the quartile below
NSAIDs	Average Daily Quantity (ADQ) per 1000 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
Antibiotics	Antibacterial items per 1000 PUs	Maintain performance levels within the lower quartile or show a reduction towards the quartile below
	Top nine antibacterials (penicillin V, flucloxacillin, amoxicillin, oxytetracycline, doxycycline, erythromycin, clarythromycin, trimethoprim, nitrofurantoin) as a percentage of antibacterial items	Maintain performance levels within the upper quartile or show an increase towards the quartile above
	Quinolone items per 1000 PUs	Maintain performance levels within the lower quartile or show a reduction towards the quartile below
	Trimethoprim 200mg 3 day treatment courses as a percentage of trimethoprim treatment	Maintain performance levels within the upper quartile or show an increase towards the quartile above
Proton pump inhibitors (PPIs)	DDD per 1000 PUs	Maintain performance levels within the lower quartile or show an increase towards the quartile below
	PPI items of low acquisition cost (LAC PPI) as a percentage of all PPIs	Maintain performance levels within the upper quartile or show an increase towards the quartile above

NB: The prescribing indicators highlighted in Table 1 constitute guidance **only** and neither this document in isolation (nor as part of a wider policy) comprises a financial incentive scheme to any medical practices and/or practitioners to prescribe a specific named medicine. Implementation of the national indicators 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.

1.0 COST EFFECTIVE USE OF STATINS

***Purpose*:** Ensure appropriate prescribing of statins with the lowest acquisition cost.

Unit of measure: Items of simvastatin and pravastatin as a percentage of total statin items (including combinations of statins with ezetimibe).

Target for 2011/2012: Maintain performance levels within upper quartile or show an increase towards the quartile above.

Background and Evidence

NICE Technology Appraisal (TA94) "Statins for the prevention of cardiovascular events"[1] and NICE Clinical Guideline(CG67)[2] "Lipid Modification" recommend that:

- 40mg simvastatin (or drug of similar efficacy and acquisition cost) should be offered to:
    - Adults over 40 who have a ≥20% ten year risk of developing CVD.
    - All adults with clinical evidence of CVD.

- If there are potential drug interactions, or simvastatin 40mg is contraindicated, a lower dose or alternative preparation such as pravastatin may be chosen. Higher intensity statins should not routinely be offered to people for the primary prevention of CVD.

- For primary prevention, the level of CVD risk should be estimated using an appropriate risk calculator, or by clinical assessment for people for whom an appropriate risk calculator is not available (for example, older people, people with diabetes or people in high-risk ethnic groups).

- For primary prevention, there is no target for total or low density lipoprotein (LDL) cholesterol.

- For secondary prevention, where 40mg daily of simvastatin does not reduce the total cholesterol (TC) to below 4mmol/l or the LDL cholesterol does not fall below 2mmol/l consider increasing the dose of simvastatin to 80mg daily or a drug of similar efficacy and acquisition cost. Any decision to offer a higher intensity statin should take into account informed preference, co-morbidities, multiple drug therapy and the benefit and risks of treatment.

- These levels are intended to "guide treatment rather than be a figure patients are expected to achieve". This is because "more than a half of patients will not achieve a total cholesterol of less than 4mmol/litre or an LDL cholesterol of less than 2mmol/litre"**.** An 'audit' level of TC of 5mmol/l should be used to assess progress in patient groups with CVD.

- People with acute coronary syndrome (ACS) should be treated with a higher intensity statin for secondary prevention. Any decision to offer a higher intensity statin should take into account the patients informed preference, co-morbidities, multiple drug therapy and the benefits and risks of treatment.

- NICE Clinical Guidelines on lipid management in people with type 2 diabetes (CG87) recommends simvastatin 40mg/day as the usual choice and dose of statin, with an increase to 80mg/day if total cholesterol is more than 4mmol/L and also LDL-cholesterol is more than 2mmol/L on treatment. In people with type 2 diabetes and existing or new

CVD, or increased albumin excretion, NICE advises considering intensifying lipid lowering treatment to achieve a total cholesterol of less than 4mmol/L or an LDL-cholesterol of less than 2mmol/L[3].

- Following the SEARCH[4] study, the Medicines and Healthcare products Regulatory Agency (MHRA) issued guidance on the use of high dose simvastatin (80mg) and the dose related risk, in common with other statins, of myopathy[5]. The MHRA guidance is consistent with NICE and recommends that the 80mg daily dose should be considered only in patients with severe hypercholesterolaemia and 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.

The NICE meta-analysis of all placebo-controlled trials (primary and secondary prevention studies) that published data in a usable form indicated that therapy with a statin was associated with a statistically significant reduction in risk of all-cause mortality, cardiovascular mortality, coronary heart disease (CHD) mortality and fatal myocardial infarction (MI)[1].

Similarly a recent meta-analysis by Zhou and colleagues looking at the evidence for pravastatin, simvastatin and atorvastatin showed there was no difference among the statins in reducing fatal CHD, non-fatal MI, fatal and non-fatal strokes, all CVD, or mortality due to any cause[6]. All of the studies showed a similar reduction in lipid levels.

Simvastatin 20–40mg daily has been shown in large, well conducted clinical trials (4S and HPS) to reduce clinically relevant events such as heart attacks and strokes[7,8].

Pravastatin is also available as a generic product. Pravastatin has clinical outcome data from the PROSPER[9], WOSCOPS[10], CARE[11] and LIPID[12] studies that show reduced rates of MI and death due to cardiovascular causes. The PROSPER study provides good evidence for the use of pravastatin in elderly patients. It is pragmatic to use pravastatin 40mg daily in simvastatin or atorvastatin intolerant patients where benefits and risks have been assessed[13].

Atorvastatin 10mg daily also has clinical outcome data showing evidence of benefit (ASCOT-LLA and CARDS)[14,15]. It is, however, over nine times the cost of generic simvastatin 40mg daily.

For secondary prevention in stable coronary artery disease patients, economic modelling suggests it is not cost effective to try and take patients to target using higher cost statins such as atorvastatin. However in ACS patients, NICE guidelines recommend high intensity statins as outlined above.

The following table (Table 2) shows the absolute and percentage reductions in LDL-cholesterol concentration according to the statin and the daily dose used[16].

Table 2: The absolute and percentage reductions in LDL-cholesterol concentration according to the statin and the daily dose used

	Dose				
Drug	**5mg**	**10mg**	**20mg**	**40mg**	**80mg**
Atorvastatin	1.51 (1.28-1.74) 31%	1.79 (1.62 to 1.97) 37%	2.07 (1.90 to 2.25) 43%	2.36 (2.12 to 2.59) 49%	2.64 (2.31 to 2.96) 55%
Fluvastatin	0.46 (0.18-0.75) 10%	0.74 (0.55-0.93) 15%	1.02 (0.90 to 1.13) 21%	1.30 (1.19 to 1.41) 27%	1.58 (1.40 to 1.76) 33%
Pravastatin	0.73 (0.54-0.92) 15%	0.95 (0.83 to 1.07) 20%	1.17 (1.10 to 1.23) 24%	1.38 (1.31 to 1.46) 29%	1.6 (1.46-1.74) 33%
Rosuvastatin	1.84 (1.74 to 1.94) 38%	2.08 (1.98 to 2.18) 43%	2.32 (2.20 to 2.44) 48%	2.56 (2.42 to 2.70) 53%	2.8 (2.63-2.97) 58%
Simvastatin	1.08 (0.93-1.22) 23%	1.31 (1.22 to 1.40) 27%	1.54 (1.46 to 1.63) 32%	1.78 (1.66 to 1.90) 37%	2.01 (1.83 to 2.19) 42%

From the table below (Table 3) it can be seen that simvastatin 40mg daily reduces LDL-cholesterol to the same extent as atorvastatin 10mg daily.

Table 3: The percentage reductions in LDL-cholesterol concentration and the cost for 28 days according to the statin and daily dose used

Drug	Strength (daily dose)	Reductions in serum LDL-cholesterol	Cost for 28 days*
Simvastatin	40mg	37%	£1.32
Pravastatin	40mg	29%	£2.78
Fluvastatin	80mg	33%	£19.20
Atorvastatin	10mg	37%	£13.00
Rosuvastatin	5mg	38%	£18.03

*November 2010 drug tariff prices (based on BNF dose range for hypercholesterolaemia)[17].

The Joint British Societies' guidelines acknowledge that there are no clinical trials which have evaluated the relative and absolute benefits of cholesterol lowering to different total and LDL cholesterol targets in relation to clinical events[18]. The NICE Clinical Guideline (CG67) suggests that after simvastatin 80mg, there is no value in chasing these targets with other, less cost effective, treatments[2].

In June 2010, simvastatin and pravastatin accounted for 72% of statin prescribing in primary care, a slight rise on the 71% achieved in March 2009[19]. The performance of the localities ranged between 59% and 77%. Benchmarking with England, however, demonstrates that no LHB locality is achieving the highest level of performance with the upper quartile of Primary Care Trusts (PCTs; 79%)[20]. This demonstrates that greater efficiencies could be made in Wales.

References

1. National Institute for Health and Clinical Excellence. Technology Appraisal 94. Statins for the prevention of cardiovascular events; January 2006. Available at: http://guidance.nice.org.uk/TA94.
2. National Institute for Health and Clinical Excellence. Clinical Guideline 67. Lipid modification; May 2008. Available at: http://guidance.nice.org.uk/CG67.
3. National Institute for Health and Clinical Excellence. Clinical Guideline 87. Lipid modification. (Partial update of NICE Clinical Guideline 66). Available at: http://guidance.nice.org.uk/CG87.
4. SEARCH Study Collaborative Group. Study of the effectiveness of additional reductions in cholesterol and homocysteine (SEARCH): Characteristics of a randomized trial among 12 064 myocardial infarction survivors. Am Heart J 2007; 154: 815–823.
5. MHRA. Drug Safety Update: Increased risk of myopathy with high dose simvastatin (80mg); May 2010; 3(10): 7–8.
6. Zhou Z, Rahme E, Pilote L. Are statins created equal? Evidence from randomised trials of pravastatin, simvastatin and atorvastatin for cardiovascular disease prevention. Am Heart J 2006; 151: 273–281.
7. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994; 344: 1383–1389.
8. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high risk individuals: a randomised placebo-controlled trial. Lancet 2002; 360: 7–22.
9. Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomized controlled trial. Lancet 2002; 360: 1623–1630.
10. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group (WOSCOPS). N Engl J Med 1995; 333(20): 1301–1307.
11. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels (CARE). N Engl J Med 1996; 335: 1001–1009.
12. Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med 1998; 339: 1349–1357.
13. NHS Clinical Knowledge Summaries. Lipid modification - primary and secondary CVD prevention - Management. Available at: http://www.cks.nhs.uk/lipid_modification_cvd_prevention/management/detailed_answers#-337005. Accessed 22 November 2010.
14. Sever PS, Dahlöf B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial — Lipid Lowering Arm (ASCOT-LLA): a multicentre randomized controlled trial. Lancet 2003; 361: 1149–1158.
15. Colhoun HM, Betteridge DJ, Durrington PN et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet 2004; 364(9435): 685–696.
16. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. BMJ 2003; 326: 1423–1429.
17. TSO Drug Tariff; October 2010. Available at: http://www.ppa.org.uk/ppa/edt_intro.htm. Accessed 22 November 2010.

18. Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. Heart 2005; 91 (Suppl V): v1-v52.
19. Prescribing Services Unit, Health Solutions Wales. Comparative Analysis System for Prescribing Audit (CASPA). Accessed September 2010.
20. NHS Better Care Better Value Indicators. Available at: http://www.productivity.nhs.uk/Def_Increasinhttp://www.productivity.nhs.uk/Def_IncreasingLowCostStatinPrescribing.aspxgLowCostStatinPrescribing.aspx Accessed 15 September 2010.

2.0 THE USE OF DRUGS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM

Purpose: To promote appropriate use of drugs affecting the renin-angiotensin system in line with NICE clinical guidelines (CG34, CG66).

Unit of measure: Items of angiotensin-converting enzyme inhibitors (ACE) inhibitors as a percentage of all drugs affecting the renin-angiotensin system.

Target for 2011/12: Maintain performance levels within the upper quartile or increase towards the quartile above.

Background and Evidence

NICE Clinical Guidelines (CG34) for hypertension stated that the benefit from ACE inhibitors and angiotensin-II receptor antagonists were closely correlated and that they should be treated as equal in terms of efficacy (although due to cost differences, ACE inhibitors should be initiated first)[1].

The updated NICE clinical guideline (CG66) for type 2 diabetes recommends ACE inhibitors first-line for all patients with raised blood pressure, reserving angiotensin-II receptor antagonists for continuing intolerance to ACE inhibitor[2].

In a systematic review of 43 randomised controlled trials (RCTs) of ACE inhibitors and angiotensin-II receptor antagonists versus placebo and ACE inhibitors versus angiotensin-II receptor antagonists, ACE inhibitors reduced all cause mortality in patients with diabetic nephropathy whereas angiotensin-II receptor antagonists did not. Both had similar effects on renal outcomes although reliable results were not obtained due to small sample sizes[3].

Angiotensin-II receptor antagonists have not been shown to increase life expectancy compared to ACE inhibitor therapy for patients with heart failure due to left ventricular systolic dysfunction in several RCTs[3,4]. Three Angiotensin-II receptor antagonists marketed in the UK currently have a licence for the treatment of heart failure[5].

The incidence of cough as a side effect with ACE inhibitors is estimated to be 3-25%[6]. The NICE Clinical Guideline (CG34) for hypertension states that “80% of patients starting on ACE inhibitors would continue with these, but that 20% would switch to angiotensin-II receptor antagonists due to an inability to tolerate ACE inhibitors (expert opinion)”[1].

In June 2010, ACE inhibitors accounted for 75% of the drugs acting on the renin angiotensin system prescribed in primary care unchanged from March 2009. The performance of localities ranged between 67% and 78%[7]. The upper quartile of English Primary Care Trusts (PCTs) is 74%[8]. This demonstrates that greater efficiencies could be made in Wales.

A recent meta-analysis of RCTs has found a possible increased risk of new cancer diagnoses in patients randomised to receive angiotensin-II receptor antagonists compared with controls who were not taking them[9]. The regulatory authorities are examining this data as, if true, even this relatively small (1.2% over an average of 4 years) absolute increase in risk could produce a large number of additional cancers given the large number of patients taking angiotensin-II receptor antagonists[10]. In the meantime, this safety concern adds weight to the NICE recommendations (CG34 and CG66) that ACE inhibitors, not angiotensin-II receptor antagonists, continue to be the first-line choice when a renin-angiotensin system drug is indicated**.**

References

1. National Institute for Health and Clinical Excellence. Clinical Guideline 34. Hypertension: Management of hypertension in adults in primary care; June 2006. Available at: http://guidance.nice.org.uk/CG34.
2. National Institute for Health and Clinical Excellence. Clinical Guideline 66 (update of NICE Clinical Guidelines E, F G and H). Type 2 diabetes; May 2008. Available at: http://guidance.nice.org.uk/CG66.
3. Strippoli GF, Craig M, Deeks JJ, et al. Effects of angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists on mortality and renal outcomes in diabetic nephropathy: systematic review. BMJ 2004; 329: 828.
4. National Institute for Health and Clinical Excellence. Clinical Guideline 108. Chronic heart failure: management of chronic heart failure in adults in primary and secondary care; August 2010. Available at: http://guidance.nice.org.uk/CG108.
5. British Medical Association, Royal Pharmaceutical Society of Great Britain. British National Formulary № 60, 2010.
6. Office of Fair Trading report. Annexe M: Current price inefficiencies and potential benefits of value-based pricing; February 2007. Available at: http://www.oft.gov.uk/shared_oft/reports/comp_policy/oft885m.pdf. Accessed 17 March 2007.
7. Prescribing Services Unit Health Solutions Wales. Comparative Analysis System for Prescribing Audit (CASPA). Accessed September 2010
8. NHS Better Care Better Value Indicators. http://www.productivity.nhs.uk/Def_IncreasingLowCostStatinPrescribing.aspx. Accessed 15 September 2010.
9. Sipahi I, Debanne SM, Rowland DY, et al. Angiotensin-receptor blockade and risk of cancer: meta-analysis of randomised controlled trials. Lancet Oncology 2010; 11: 627–36.
10. European Medicines Agency. Committee for Medicinal Products for Human Use Monthly Report. Review of angiotensin II receptor inhibitors started; June 2010. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Committee_meeting_report/2010/07/WC500094208.pdf. Accessed 1 December 2010.

3.0 IMPLEMENTATION OF NICE GUIDANCE: THE USE OF DOSULEPIN

Purpose: Reduce inappropriate prescribing of dosulepin in line with NICE clinical guidelines (CG90).

Unit of measure: Defined Daily Dosage (DDD) of dosulepin per 1000 PUs.

Target for 2011/12: Maintain performance levels within the upper quartile or increase towards the quartile above.

Background and Evidence

Dosulepin is a tricyclic antidepressant, historically used where an anti-anxiety or sedative effect is required. Dosulepin has a small margin of safety between the maximum therapeutic dose and potentially fatal doses[1].

The MHRA drug safety bulletin in December 2007 reported that dosulepin continued to be prescribed widely and accounted for about 10% of the antidepressant market in England[1]. At this time, up to 200 people in England and Wales committed suicide or took a potentially fatal overdose with dosulepin each year. About 20% of fatal dosulepin overdoses are associated with accidental death[1].

The updated NICE Clinical Guideline (CG90) "Depression: the treatment and management of depression in adults" strengthens the previous advice, stating that "Dosulepin should not be prescribed" [1].

Since quarter ending June 2008 usage of dosulepin in Wales has fallen slowly from 6.1% of all antidepressant items to 4.6%. Absolute usage of dosulepin has fallen from 43,068 to 37,965 items in the same period, equivalent to an 11.8% reduction[3].

In the three months up to May 2010, 46% of the dosulepin was prescribed as 25mg capsules and 54% as 75mg tablets[3].

References

1. Drug Safety Update: Volume 1, Issue 5, December 2007. Available at: http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/CON2033216. Accessed 11 August 2010.
2. National Institute for Health and Clinical Excellence. Clinical Guideline 90. Depression: the treatment and management of depression in adults; October 2009. Available at: http://guidance.nice.org.uk/CG90.
3. Prescribing Services Unit, Health Solutions Wales. Comparative Analysis System for Prescribing Audit (CASPA). Accessed August 2010.

4.0 HYPNOTICS AND ANXIOLYTICS

***Purpose*:** To reduce inappropriate prescribing of hypnotics and anxiolytics.

Unit of measure: Defined daily dosage (DDD) of hypnotics (4.1.1) and anxiolytics (4.1.2) prescribed per 1000 patients. These will be measured separately and as a combined entity.

Target for 2011/12: Maintain performance levels within the lower quartile or reduction towards the quartile below.

Background and Evidence

There has been concern with regard to the high volume 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 1999 the Mental Health National Service Framework (NSF)[1] reinforced the Committee on Safety of Medicines (CSM) advice[2] and recommended that benzodiazepines should be used for no more than two to four weeks for severe and disabling anxiety. It 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. Key action point 33 in the revised Adult Mental Health NSF 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 National Institute of Clinical Excellence (NICE) technology appraisals and interventional procedures and the recommendations of the All Wales Medicines Strategy Group (AWMSG) also based on nationally agreed best practice guidelines as defined in NSFs, NICE clinical guidelines, national plans and agreed national guidance on service delivery" [3]. The performance target set was that by March 2007, Local health boards (LHBs)/NHS Trusts should have undertaken a systematic review of NICE guidelines and technology appraisals and developed a local incremental implementation plan.

The new substance misuse strategy of the Welsh Assembly Government (2008) "Working Together to Reduce Harm" calls for the reduction of inappropriately prescribed benzodiazepines[4].

The prescribing volumes of hypnotics and anxiolytics in Wales have declined over recent years. In the financial year 07/08, 395,589 hypnotic and anxiolytic prescription items were dispensed (total quantity 11,895,770) with basic price costs of £860,448 as a result of GP prescribing in Wales. In 08/09 this had fallen to 388,351 items (total quantity 11,395,932), at a total increased cost of £1,208,439.
There is still a large variation in prescribing rates of these drugs across the former 22 LHBs and also variation between GP practices within certain LHBs[5].

Ensuring appropriate prescribing of hypnotics and anxiolytics is also one of WMP's "Invest to Save" projects commissioned by the Welsh Assembly Government (WAG).

References

1. Department of Health HSC 1999/223NSF National Service Framework for Mental Health. Modern standards and service models for mental health. London; 1999.
2. Committee on Safety of Medicines. Benzodiazepines, dependence and withdrawal symptoms. Current Problems 1988; 21: 1-2.
3. Adult Mental Health Services: Raising the Standard. The revised adult mental health national service framework and an action plan for Wales; October 2005.
4. Welsh Assembly Government. The substance misuse strategy for Wales 2008-2018: "Working together to reduce harm"; 2008. Available at: http://wales.gov.uk/topics/housingandcommunity/safety/publications/strategy0818/?lang=en. Accessed 1 December 2010.
5. Prescribing Services Unit, Health Solutions Wales. Comparative Analysis System for Prescribing Audit (CASPA).Accessed July 2009

5.0 NON-STEROIDAL ANTI-INFLAMMATORY DRUG (NSAID) PRESCRIBING

Purpose: To ensure that the cardiovascular and gastrointestinal (GI) risks from non-steroidal inflammatory drugs (NSAIDs) are minimised by appropriate choice and use of NSAIDs. Ensuring appropriate prescribing of NSAIDs is also one of the "Invest to Save" projects commissioned by the Welsh Assembly Government (WAG).

Unit of measure: NSAID *a*verage daily quantity (ADQ) per 1000 PUs.

Target for 2011/12: Maintain performance levels within the lower quartile or reduction towards the quartile below.

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

Target for 2011/12: 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. The Committee on Safety of Medicines (CSM), now the Medicines and Healthcare products Regulatory Agency (MHRA), have issued five warnings to prescribers regarding the gastrointestinal dangers of NSAIDs, culminating in the following warning issued in 2003[1]:

- All NSAIDs, including ibuprofen and cyclo-oxygenase-2 selective (COX-2) inhibitors are associated with reports of serious gastrointestinal (GI) toxicity. The elderly and those taking concomitant aspirin are high-risk groups.

- Detailed advice on the GI safety of NSAIDs (including aspirin and selective COX-2 inhibitors) has previously been provided. The CSM continues to receive reports of serious and fatal GI reactions associated with NSAIDs.

In October 2006 and December 2007, the MHRA issued further warnings on the increase risk of thrombotic events associated with the long term use of NSAIDs[2,3].

In May 2009 the NPC reminded Prescribers that:

- GI and cardiovascular risks of NSAIDs may be minimised by selecting the lowest dose for the shortest duration.
- Risks of GI toxicity are higher in the elderly.
- Diclofenac 150mg daily has the same thrombotic risk profile similar to that of at least one coxib (etoricoxib) and possibly others.
- Epidemiological data do not suggest an increased risk of myocardial infarction when naproxen 1000mg daily or ibuprofen at lower doses (less than 1,200mg daily) are used.
- Aspirin and another NSAID should only be used together when absolutely necessary - the combination substantially increases GI risk. Patients taking long-term aspirin should be reminded to avoid NSAIDs, including those bought without prescription.
- Ibuprofen is associated with the lowest GI risk of the traditional NSAIDs, but serious and fatal GI reactions have been reported in association with its use.
- Clinical trial data suggest that selective COX-2 inhibitors have GI safety advantages over standard NSAIDs, but serious and fatal GI reactions have nonetheless been associated with these drugs.

- Prescribing should be based on the safety profiles of individual NSAIDs or coxibs and on individual patient risk profiles (e.g. GI and cardiovascular).
- Prescribers should not switch between NSAIDs without careful consideration of the overall safety profile of the products, a patient's individual risk factors, and patient preference.
- Ensure NSAID treatment is not contraindicated before prescribing[4].

NICE Clinical Guideline(CG59) "The care and management of osteoarthritis" and NICE Clinical Guideline (CG79) "Rheumatoid arthritis national clinical guideline for management and treatment in adults" both recommend:-

- Oral NSAIDs/cyclo-oxygenase-2 selective inhibitors (COX-2) should be used at the lowest effective dose for the shortest possible period of time.
- When offering treatment with an oral NSAID/Cox-2 inhibitor, the first choice should be either a standard NSAID or a COX-2 inhibitor. In either case, these should be co-prescribed with a proton pump inhibitor (PPI).
- All oral NSAIDs/COX-2 inhibitors have analgesic effects of a similar magnitude but vary in their potential GI, liver and cardio-renal toxicity and therefore when choosing the agent and dose, healthcare professionals should take into account individual patient risk factors, including age. When prescribing these drugs, consideration should be given to appropriate assessment and/or ongoing monitoring of these risk factors.
- If a person with osteoarthritis/rheumatoid arthritis (respectively) needs to take low dose aspirin, healthcare professionals should consider other analgesics before substituting or adding an NSAID or COX-2 inhibitor (with a PPI) if pain relief is ineffective or insufficient[6,7].

References

1. MHRA/CSM. Gastrointestinal toxicity of NSAIDs. Current problems in pharmacogivilance. 2003 29: 8–9.
2. MHRA safety warning; October 2006. Available at: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON2025040. Accessed 24 February 2010.
3. MHRA Drug Safety Update: Volume 1, Issue 5, December 2007. Available at: http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/CON2033216. Accessed 24 June 2008.
4. MeReC Monthly № 2. Update on the prescribing of NSAIDs, May 2008. Available at: http://www.npci.org.uk/therapeutics/pain/musculo/resources/library_merec_monthly_no02.pdf. Accessed 1 December 2010.
5. MeReC Monthly № 14. NSAID risks in heart failure, May 2009. Available at http://www.npc.co.uk/ebt/merec/cardio/heart/resources/merec_monthly_no14.pdf. Accessed 1 December 2010.
6. National Institute of Health and Clinical Excellence. Clinical Guideline 59. Osteoarthritis. The care and management of osteoarthritis in adults. 2008 Available at http://www.nice.org.uk/CG59. Accessed Jan 2011
7. National Institute of Health and Clinical Excellence.Clinical Guideline 79. Rheumatoid arthritis national clinical guideline for management and treatment in adults. 2009 Available at http://www.nice.org.uk/CG79. Accessed Jan 2011

6.0 USE OF ANTIBIOTICS

***Purpose*:** The development of antibiotic prescribing indicators would support the core aims of the Antimicrobial Resistance Programme in Wales to inform, support and promote the prudent use of antimicrobials[1].

1) Unit of measure: Antibacterial items per 1000 PUs.

Target for 2011/2012: Maintain performance levels within the lower quartile or show a reduction towards the quartile below.

2) Unit of measure: Top nine antibacterials (penicillin V, flucloxacillin, amoxicillin, oxytetracycline, doxycycline, erythromycin, clarithromycin, trimethoprim nitrofurantoin) usage as a percentage of total antibacterial items.

Target for 2011/2012: Maintain performance levels within the upper quartile or show an increase towards the quartile above.

3) Unit of measure: Quinolone items per 1000 PUs.

Target for 2011/2012: Maintain performance levels within the lower quartile or show a reduction towards the quartile below.

4) Unit of measure: Trimethoprim 200mg 3 day treatment courses as a percentage of trimethoprim treatment.

Target for 2011/2012: Maintain performance levels within the upper quartile or show an increase towards the quartile above.

The above indicators only cover antibacterials appearing in Chapter 5 (Infections) of the BNF.

Background and Evidence

Members of AWMSG have previously supported the suggestion that the Antimicrobial Resistance Group (ARG) should advise on the development of any antimicrobial national prescribing indicators. The National Public Health Service report "Antimicrobial Dispensing In Primary Care in Wales (2006 – 2008)" and the Health Protection Agency report "Antimicrobial Resistance and Prescribing in England, Wales and Northern Ireland, 2008" present the different prescribing and antimicrobial resistance patterns across Wales and the UK[2,3]. Data published by the Public Health Wales Antimicrobial Resistance Programme shows that antimicrobial use across primary and secondary care is common and variable across Wales. In primary care in 2008, there were 2,417,104 antimicrobial prescription items dispensed across Wales (i.e. almost 1 antibiotic for every member of the population). Dispensing varied between "old" local health boards from 487.9 prescriptions/1000 PUs per annum to 659.5 prescriptions/1000 PUs per annum[2].

Concern has been expressed from ARG regarding the establishment of targets for antibiotic prescribing indicators, as there is no clear evidence base for setting the targets. ARG has recommended that data on indicators should be presented in a comparative form without targets. It is, however, recognised that for the purposes of establishing a set of national indicators there needs to be an associated target despite this limitation. It is therefore proposed that for indicators 1 and 3 this should be "Maintain performance levels within the lower quartile or reduction towards the quartile below" and for indicator 2 and 4 this should

be “Maintain performance levels within the upper quartile or increase towards the quartile above”.

1) Antibacterial items per 1000 PUs

The Standing Medical Advisory Committee (which has since been superseded) Sub-Group on Antimicrobial Resistance, report “The path of least resistance” stated that the evidence that use of antimicrobial causes resistance was overwhelming, although mostly circumstantial. The evidence was that resistance is greatest where use of antibacterial agents is heaviest. This applies at both national and clinical unit level[4,5]. This has further been corroborated in a European cross-national database study[6]. In contrast, a 12-year resistance surveillance study demonstrated that resistance was stable despite an increase in cephalosporin dosage, and in another case, resistance increased with reduced trimethoprim-sulfamethoxazole treatment[7].

2) Top nine antibacterials (penicillin V, flucloxacillin, amoxicillin, oxytetracycline, doxycycline, erythromycin, clarithromycin trimethoprim nitrofurantoin) as a percentage of antibacterial items

The Health Protection Agency guidance for primary care identifies the most appropriate treatment protocol and antibiotics for common infections experienced in primary care. The top nine antibacterials provide sufficient cover to treat: upper and lower respiratory tract infections, urinary tract infections (UTIs) except acute pyelonephritis, and common skin infections. The use of simple generic antibiotics and the avoidance of broad spectrum antibiotics (e.g. co-amoxiclav, quinolones and cephalosporins) preserves these antibiotics from resistance and reduces the risk of *Clostridium difficile* (*C. difficile*), MRSA and resistant UTIs[8].

3). Quinolone items per 1000 PUs

There is an association between quinolone use and the incidence of *C. difficile* associated diarrhoea (CDAD)[9,10]; therefore, use should be restricted to specific indications to reduce risk of potential antimicrobial resistance. The average cost of a *C. difficile* infection has been estimated to be £4,007[11].

4) Trimethoprim 200mg 3 day treatment courses as a percentage of trimethoprim treatment

The Cochrane review regarding course duration of antibacterial treatment for uncomplicated UTI in women found that three days of treatment were adequate to achieve symptomatic relief for most patients, but long-term therapy may be better in terms of bacteria elimination from the urine, irrespective of the antibiotic used. Long-term UTI therapy was related to a higher rate of adverse reactions to the antibiotics used[12]. This however cannot be concluded in elderly (≥ 60 years of age) women[13] or children[14] due to limited reliable research.

References

1. Welsh Antimicrobial Resistance Programme. Available at: http://www.wales.nhs.uk/sites3/page.cfm?orgid=457&pid=28418. Accessed 14 September 2010.
2. Antimicrobial Dispensing In Primary Care in Wales (2006–2008) National Public Health Service for Wales, 2009. Available at: www.wales.nhs.uk/sites3/Documents/719/Antimicrobial_Prescribing_in_Primary_Care_in_Wales.pdf Accessed 1 December 2010.
3. Antimicrobial Resistance and Prescribing in England, Wales and Northern Ireland, 2008. Available at: www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1216798080469. Accessed 1 December 2010.
4. Department of Health: Standing Medical Advisory Committee Sub-Group on Antimicrobial Resistance report: The path of least resistance; September 1998. Available at: www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4120729.pdf. Accessed 1 December 2010.
5. Costelloe C, Metcalfe C, Lovering A, et al. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. BMJ 2010; 340: c2096.
6. Goosens H, Ferech M, Vonder Stichek R, et al. ESAC Project Group. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. Lancet 2005; 365 (9459): 579–587.
7. Sörberg M, Farra A, Ransjö U, et al. Long-term antibiotic resistance surveillance of gram-negative pathogens suggests that temporal trends can be used as a resistance warning system. Scand J Infect Dis 2002; 34(5): 372–378.
8. Health Protection Agency. Management of infection guidance for primary care for consultation and local adaptation; July 2010. Available at: www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1279888711402. Accessed 1 December 2010.
9. Dial S, Kezouh A, Dascal A, et al. Patterns of antibiotic use and risk of hospital admission because of *Clostridium difficile* infection. CMAJ 2008; 179 (8).
10. Mera RM, Beach KJ, Powell GE, et al. Semi-automated risk estimation using large databases: quinolones and *clostridium difficile* associated diarrhea., Pharmacoepidemiology and Drug Safety 2010; 19(6): 610–617.
11. Wilcox MH, Cunniffe JG, Trundle C, et al. Financial Burden of hospital acquired *C. difficile* infection. Journal of Hospital Infection 1996; 34:23–30.
12. Milo G, Katchman E, Paul M, et al. Duration of antibacterial treatment for uncomplicated urinary tract infection in women. Cochrane Database of Systematic Reviews; 2005, issue 2, article №: CD004682.
13. Lutters M, Vogt-Ferrier NB. Antibiotic duration for treating uncomplicated, symptomatic lower urinary tract infections in elderly women. Cochrane Database of Systematic Reviews; 2008, issue 3, article №: CD001535.
14. Keren R, Chan E. A meta-analysis of randomised, controlled trials comparing short- and long-course antibiotic therapy for urinary tract infections in children. Pediatrics 2002; 109 (5): E70–0.

7.0 APPROPRIATE USE OF PROTON PUMP INHIBITORS (PPIs)

***Purpose*:** To ensure appropriate use of PPIs and that, where appropriate, a PPI with the lowest cost acquisition is chosen in line with NICE recommendations (TA7, CG17).

Ensuring appropriate prescribing of PPIs is also one of the "Invest to Save" projects commissioned by the Welsh Assembly Government (WAG).

Units of measure: 1) DDD per 1000 PUs
2) items of low acquisition cost PPIs (LAC PPI) as a percentage of all PPIs.

Target for 2010/2011: Maintain performance levels within upper quartile or show an increase towards the quartile above.

Background and Evidence

PPIs are licensed and prescribed for a range of indications including, uninvestigated dyspepsia, gastro-oesophageal reflux disease (GORD), 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 NSAID-associated ulcers[1,2]. In addition they are also used for a number of unlicensed indications (more common in hospital settings) and include the reduction of re-bleeding episodes after treatment of severe peptic ulcer bleeding, prophylaxis of acid aspiration during general anaesthesia and stress ulcer prophylaxis[2].

PPI use is continuing to increase across Wales[3]. One possible reason suggested for this is that they are often continued in patients in whom they are no longer indicated[2], as in many of these indications treatment courses are intended for short term use e.g. in peptic ulcer disease[1]. It has also been suggested that the reduction in cost has led to a more liberal usage of these drugs for a wide variety of upper gastrointestinal symptoms and that a substantial proportion, if not majority, of patients now prescribed PPIs, have no true indication for treatment[4].

The June 2010 average All Wales figure for the PPI Prescribing Indicator was 5208.51 DDD per 1000 PUs ranging from 4123.50 to 6915.33 across the 22 previous Local Health Boards localities[3].

There has been a decrease in the overall costs of PPIs over the previous few years due to the availability and reduction in costs of generic omeprazole 10mg and 20mg capsules and lansoprazole 15mg and 30mg capsules[3]. The price of generic pantoprazole has been falling since April 2010 and is now comparable with generic omeprazole and lansoprazole capsules[10]. However the costs of other PPIs such as esomeprazole and rabeprazole and other formulations of lansoprazole and omeprazole are considerably more expensive[5]. Although only 15% of the items prescribed in Wales are for the more costly preparations they account for 48% of the cost (quarter ending Jun 10) [3].

The percentage of the LAC (generic omeprazole and lansoprazole) PPIs to the high acquisition cost (HAC) PPIs in the previous 22 LHB localities range from 79% to 91% (quarter ending June 10)[3]. Increasing the All Wales percentage to 91%, assuming the number of prescription items remain the same, would potentially save £1.8 million per annum based on annual costs 2009/10[3]. For a similar indicator in England, the upper quartile of Trusts are currently achieving 91%[6].

There is no evidence for oesophagitis that at equivalent doses, any one PPI is more effective than another[1]. Newer PPIs offer no advantages in terms of clinical efficacy, and there is less evidence for long term safety[7]. They are also considerably more expensive, and NICE guidelines recommend that the least expensive PPI should be used[8]. Therefore, generic lansoprazole, omeprazole* capsules or pantoprazole tablets should be used first line.

** it is more cost effective to use 2x20mg capsules than 40mg capsules*[5]

Although PPIs are generally well tolerated, there is emerging evidence with regards to potential consequences of potent acid suppression[9]. The incidence of short-term adverse events is low. However, there is now some evidence to suggest that some serious adverse effects may be linked with long-term PPI use, and although some of the evidence is conflicting, safety concerns have been raised[2]. These include osteoporotic fractures of the hip, wrist and spine, *Clostridium difficile*, both hospital and community-acquired pneumonia, and a possible association with colorectal cancer has been investigated[2,9].

An educational and audit tool has been developed for NHS Wales to aid in stepping patients down/off PPI treatment or change patients to the least expensive PPIs, in line with NICE guidance[8].

R*eferences*

1. North of England Dyspepsia Guideline Development Group. Full Clinical Guideline № 17. Dyspepsia: managing dyspepsia in adults in primary care; August 2004.
2. WeMeReC Bulletin. Stopping medicines – proton pump inhibitor; October 2010. Available at: http://www.wemerec.org/Documents/enotes/StoppingPPIsenotes.pdf. Accessed 18 November 2010.
3. Prescribing Services Unit, Health Solutions Wales. Comparative Analysis System for Prescribing Audit (CASPA). Accessed June 2010.
4. McColl KEL, Gillen D. Evidence that proton-pump inhibitor therapy induces the symptoms it is used to treat. Gastroenterology 2009; 137: 20–39.
5. TSO Drug Tariff; November 2010. Available at: http://www.ppa.org.uk/ppa/edt_intro.htm. Accessed 24 November 2010.
6. NHS Institute for Innovation and Improvement. NHS Better Care, Better Value Indicators. Available at: http://www.productivity.nhs.uk/Def_IncreasingLowCostPPIPrescribing.aspx Accessed 26 October 2010.
7. National Prescribing Centre. The management of dyspepsia in primary care. MeReC Briefing; 2006, issue № 32.
8. National Institute for Health and Clinical Excellence. Technology Appraisal 7. Guidance on the use of proton pump inhibitors in the treatment of dyspepsia; July 2000. Available at: http://www.nice.org.uk/nicemedia/pdf/proton.pdf.
9. Thompson A. Emerging Concerns with PPI therapy. The Pharmaceutical Journal 2010; 285: 239.
10. TSO Drug Tariff; January 2010. Available at: http://www.nhsbsa.nhs.uk/prescriptions Accessed 19 January 2011.