

NEWSLETTER

Supporting the Derbyshire Health Community

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PACEF update

The current Traffic Lights list can be accessed via the PACEF intranet site
www.nodyis.nhs.uk/guidelines/pacef%20web.htm.

RED drugs are those where prescribing responsibility would normally lie with a hospital consultant or a specialist. AMBER drugs are those that although usually initiated within a hospital setting, could appropriately become the responsibility of the GP. This would normally be under a shared care agreement. GREEN drugs are regarded as routine for primary care prescribing. BROWN drugs are those that PACEF does not recommend for use (or only in restricted circumstances) due to lack of data on safety, effectiveness, or cost-effectiveness.

<u>Drug</u>	<u>Date considered</u>	<u>Decision</u>
Dexibuprofen	November 2006	BROWN
Valganciclovir	November 2006	RED
Efalizumab	September 2006	RED
Rituximab	September 2006	RED
Clenil Modulite (beclometasone cfc-free MDI)	August 2006	GREEN Prescribe by brand name
Celluvisc eye drops	August 2006	GREEN
Natalizumab	August 2006	RED
Rimonabant	August 2006	BROWN
Desloratidine	July 2006	BROWN
Levocetirizine	July 2006	BROWN
Pegaptanib injection	July 2006	RED
Rotigotine patch	July 2006	BROWN
Zaleplon	July 2006	BROWN
Zolpidem	July 2006	BROWN
Zopiclone	July 2006	BROWN
Formoterol cfc-free MDI (Atimos Modulite)	June 2006	GREEN
Letrozole	June 2006	AMBER

Success of the statin policy

There is a new national NHS indicator, which grades PCTs on their levels of low cost statin prescribing (simvastatin and pravastatin). The best PCT in the country is North Eastern Derbyshire PCT with 84% (see BMJ of 28/10/06, p. 873). Not far behind is Chesterfield PCT at number 6 with 81%. High Peak and Dales PCT is a little further behind at number 46 (out of 303) with 72%. This is because of the influence of hospitals outside North Derbyshire and we are trying to tackle this. As the BMJ points out, £millions will be saved if all

PCTs achieve our levels of simvastatin prescribing. So, a big thank you to one and all who have helped us to achieve this success.

But we must not take our eye off the ball. Rumors abound that we have new national targets for cholesterol and LDL-C of 4 and 2. This is not true. JBS2 have suggested these targets but they do not set national policy. The Department of Health has confirmed that the targets are still 5 and 3 as per the NSF for CHD. This will only be revised if there is an amendment that arises from the NICE guideline due in December 2007. The standard included in the QoF for 07/08 for total cholesterol will remain at 5mmol/l.

The JBS2 targets are not exactly evidence based. Almost all published clinical trials examined fixed doses of statins and no published trial examined titrating statin therapy to the proposed new LDL-C levels. The LDL-C level of 2 was the mean achieved in the trials that used atorvastatin 80mg. This means that about half the patients did not reach this level!

A recently published review analysed all controlled trials, cohort studies, and case-control studies that examined the independent relationship between LDL-C and major cardiovascular outcomes¹. No high-quality evidence could be found that suggests that titrating lipid therapy to recommended LDL-C targets is superior to empirically prescribing doses of statins used in clinical trials for all patients at high cardiovascular risk. They conclude that clear, compelling evidence supports near-universal empirical statin therapy in patients at high cardiovascular risk (regardless of their LDL-C level), but current clinical evidence does not demonstrate that titrating lipid therapy to achieve proposed low LDL-C levels is beneficial or safe.

A colleague of mine has calculated that to achieve JBS2 targets would require an uplift on the prescribing budget of 42%! Another calculated that it would double the current NHS deficit! There are much more effective and efficient interventions to spend scarce resources on.

The statin policy is the right approach and simvastatin 40mg is the cost-effective, evidence-based choice for empirical therapy.

1. Ann Intern Med 2006; 145:520-30

Combination antithrombotics and bleeding risk

Aspirin is the mainstay of prophylactic antiplatelet treatment in patients with atherosclerotic disease. However, serious GI ulcer complications are 2- to 4-fold more common in patients who take 75 – 300mg/day of aspirin compared with controls. Whereas all doses of aspirin are associated with increased risk of GI bleeding, the risk is dose related¹.

There are now some indications for dual antiplatelet therapy and it is increasingly being used. However, the net benefit from using dual antiplatelet therapy in high-risk vascular disease patients comes with the cost of increased GI complications. A recent population based case-control study has assessed the risk of serious upper GI bleeding (admitted to hospital) with combined antithrombotic therapy².

	Adjusted OR for association between antithrombotic drug use and serious upper GI bleeding (95% CI)	Number of treatment years to produce one excess case of serious upper GI bleeding (95% CI)
Aspirin alone	1.8 (1.5 to 2.1)	1040 (725 to 1641)
Aspirin and clopidogrel	7.4 (3.5 to 15)	124 (54 to 312)
Aspirin and vitamin K antagonist	5.3 (2.9 to 9.5)	184 (93 to 407)
Dipyridamole and aspirin	2.3 (1.7 to 3.3)	595 (348 to 1201)

The authors concluded that combined antithrombotic treatment confers particular risk and is associated with a high incidence of GI bleeding. The combination of aspirin and clopidogrel was associated with a 7-fold increase in the odds of bleeding compared with a 5-fold increase for the combination of aspirin and warfarin. The effect reflects a true synergism, that is, the effect of combined treatment is more than a simple addition of the effects of individual drugs².

The MeReC Rapid Review of this study concludes that it adds to the evidence that any possible benefits of treatment with clopidogrel plus aspirin may be outweighed by an increased risk of bleeding, especially with prolonged use³. It concludes that combination antithrombotic regimens should only be used with caution for conditions where it has been established that the benefits outweigh the increased risk of bleeding, and then only for a limited time. The combination of aspirin plus warfarin should only be used under specialist supervision³.

1. Circulation 2006; 113: e655 – e658
2. BMJ, doi:10.1136/bmj.38947.697558.AE (published 19/9/06)
3. MeReC Rapid Review, Issue No. 3, 11/10/06

New indication for clopidogrel

Clopidogrel is now licensed for the prevention of atherothrombotic events in ST segment acute myocardial infarction (STEMI), in combination with aspirin, in medically treated patients eligible for thrombolytic therapy. It is already licensed for combination therapy for non-ST segment elevation acute coronary syndrome (NSTEMI), where it is given for up to 12 months and then stopped.

For STEMI the SPC says “combined therapy should be started as early as possible after symptoms start and continued for at least four weeks. The benefit of the combination of clopidogrel with aspirin beyond four weeks has not been studied in this setting”. Two studies provide the evidence for the use of clopidogrel (in addition to aspirin) in STEMI. In CLARITY TIMI 28¹ clopidogrel was given for a maximum of 8 days and in COMMIT² it was given for up to 4 weeks (mean 15 days).

PACEF has agreed that after a STEMI, clopidogrel treatment is for 14-28 days and this course is supplied by the hospital. It should not be continued in primary care. The PACEF clopidogrel guideline has been updated.

1. N Engl J Med 2005; 352 : 1179-89
2. Lancet 2005; 366 : 1607-21

Human Papillomavirus Vaccine (Gardasil)

This vaccine has recently been launched and is licensed for the prevention of high-grade cervical dysplasia, cervical carcinoma, high-grade vulvar dysplastic lesions, and external genital warts causally related to Human Papillomavirus (HPV) types 6, 11, 16 and 18. The indication is based on the demonstration of efficacy of Gardasil in adult females 16 to 26 years of age and on the demonstration of immunogenicity of Gardasil in 9 to 15-year old children and adolescents. Protective efficacy has not been evaluated in males.

The efficacy of Gardasil was assessed in 4 placebo-controlled, double-blind, randomised Phase II and III clinical studies including a total of 20,541 16 to 26-year old women, who were enrolled and vaccinated without pre-screening for the presence of HPV infection. Cervical intraepithelial neoplasia (CIN) grade 2/3 (moderate to high-grade dysplasia) was used in the clinical trials as a surrogate marker for cervical cancer.

The primary analyses of efficacy were conducted in the per-protocol efficacy population (n= all 3 vaccinations within 1 year of enrolment, no major protocol deviations and naïve to the relevant HPV type(s) prior to dose 1 and through 1 month postdose 3 (month 7). Efficacy was measured starting after the month 7 visit. Overall, 73% of subjects were naïve (PCR negative and seronegative) to all 4 HPV types at enrolment.

	Gardasil		Placebo		%Efficacy (95% CI)
	N	Number of cases	N	Number of cases	
HPV 16- or HPV 18-related CIN 2/3 or AIS*					
Protocol 005	755	0	750	12	100.0 (65.1, 100.0)
Protocol 007	231	0	230	1	100.0 (<0.0, 100.0)
Protocol 013	2200	0	2222	19	100.0 (78.5, 100.0)
Protocol 015	5301	0	5258	21	100.0 (80.9, 100.0)
<i>Combined protocols</i>	8487	0	8460	53	100.0 (92.9, 100.0)

* AIS = adenocarcinoma in situ

In the modified intention to treat (ITT) population, defined as women who received at least one vaccination regardless of baseline HPV status at day 1 with case counting starting at 1 month postdose 1, the results are summarised below. This population approximates to the general population of women with respect to prevalence of HPV infection and disease at enrolment.

Endpoints	Gardasil or HPV 16 L1 VLP vaccine		Placebo		% Reduction (95% CI)
	N	Cases	N	Cases	
HV 16/18-related CIN 2/3 or AIS#	9831	122	9896	201	39.0 (23.3, 51.7)
HPV 16/18-related VIN 2/3*	8954	7	8962	18	61.0 (2.1, 86.2)
HPV 6/11/16/18 related genital warts*	8954	58	8962	184	68.5 (57.5, 77.0)

Protocols 005, 007, 013 and 015 combined.

* Protocols 007, 013, and 015 combined.

In the placebo group of the per-protocol population (PPP) the number of cases of CIN 2/3 or AIS was low at 0.626%. Although the efficacy was 100%, the NNT is 160.

In the modified ITT population there were more cases in the placebo group (2.03%) but the reduction in cases was only 39%. The NNT calculates at 127.

In the PPP the NNT to prevent a case of genital warts was 88, and in the ITT population the NNT was 71.

The primary vaccination series consists of three separate 0.5ml doses administered at 0, 2, and 6 months. The cost of this course is £241.50. In the USA, HPV vaccine is apparently only recommended for girls aged 11-12 years. In the UK there are an estimated 1,250 girls of this age per 100,000 population. Vaccinating this group of girls alone would cost Derbyshire County PCT £2.1 million!

We do not yet know what the Joint Committee on Vaccination and Immunisation will recommend for the use of Gardasil. We need direction from the Department of Health on the cost-effectiveness and funding of this new vaccine. **This was discussed at PACEF and the advice is that Gardasil should not be prescribed in primary care, either on the NHS or privately, until we have instructions from the JCVI.**

More on eGFR and CKD

Last month's article has stimulated some discussion. One GP asked "if GFR falls with age anyway aren't we just medicalising old age?" This may well be so and is supported by a letter in the BMJ of 28th October from a Consultant Nephrologist. He says "patients older than 40 generally lose between 0.8-1 ml/min of glomerular filtration rate per year due to nephron loss as a normal ageing process. Hence one cannot assume that an estimated glomerular filtration rate of less than 60 ml/min/1.73 m² is indicative of chronic kidney disease in elderly patients. Higher rates of loss (>4ml/min/1.73 m²) would be suggestive of progressive chronic kidney disease or precipitating factors such as hypertension. Hence an 80 year old may be normally expected to have an estimated glomerular filtration rate of 45-50 ml/min/1.73m². With this in mind, for general practitioners the registry of chronic kidney disease would have to include all their elderly patients who need regular monitoring. This may overwhelm their service and detract from the management of other patients."

Another letter from a GP, in the same edition of the BMJ says "the introduction of routine reporting of eGFR with every serum creatinine requested seems to have led to three outcomes in general practice: worried patients, increased workload, and confused clinicians". She adds that eGFR is not a population screening test but rather should be used to give further information about patients already known to be at risk of renal disease.

Another GP asked in reference to the use of ACE inhibitors "do we take them off it or put them on it?". The BNF in Appendix 3 says of ACEIs 'mild to moderate impairment – use with caution and monitor response'. The renal guidelines from the East Midlands Renal Network has a list of risk groups which includes long-term NSAIDs but also ACEIs/ARBs. The leaflet from the Royal College of GPs, "Introducing eGFR – promoting

good CKD management”, advises that if eGFR is less than 60ml/min to review medication, particularly recent additions e.g. NSAIDs, antibiotics, mesalazine, diuretics, ACEIs/ARBs. The UK guidelines on CKD in adults from the Renal Association also highlight ACEIs and ARBs as potentially nephrotoxic drugs.

The Renal Association guidelines make the following recommendations for using ACEIs/ARBs in patients with CKD:

- ‘Dual blockade’ with combinations of ACEIs and ARBs should usually only be initiated under specialist supervision.
- Serum creatinine and potassium concentration should be checked prior to starting ACEIs and/or ARBs, within two weeks of starting, and within two weeks after subsequent increases in dose; during severe intercurrent illness, particularly if there is a risk of hypovolaemia; and at annual intervals thereafter, or more frequently if indicated, according to kidney function.
- A rise of serum creatinine concentration of >20% or fall in estimated GFR of >15% after initiation or dose increase should be followed by further measurements within two weeks; if deterioration in kidney function is confirmed, a specialist opinion should be sought (not necessarily by formal referral) on whether the drug treatment should be stopped or the patient subjected to investigation for renal artery stenosis.
- Hyperkalaemia (serum potassium >6.0 mmol/L) should result in stopping of concomitant nephrotoxic drugs (eg NSAIDs), reduction or cessation of potassium-retaining diuretics (amiloride, triamterene, spironolactone), and reduction of loop diuretic dosage if there is no sign of congestion. If hyperkalaemia persists, the ACEI or ARB should be stopped.

So the decision to start or stop an ACEI/ARB has to include an assessment of the risk/benefit ratio. Careful monitoring is mandatory and a key aspect of safe use is that they don’t cause a sustained fall in eGFR of >15%.

Meticulous control of blood pressure is recommended in the management of CKD. The Royal College of GPs leaflet and the Renal Association guideline recommend that an ACEI should be included in the regimen for all patients with proteinuria (PCR>100mg/mmol) and for diabetic patients with microalbuminuria, not for everyone.

The CKD patient information leaflet is published again on the final page.

Review of non-selective NSAIDs

As part of its continuous monitoring of medicines, the European Medicines Agency (EMA) has reviewed cardiovascular safety data on non-selective NSAIDs. It has concluded that the overall benefit-risk balance of these medicines remains positive. No conclusion has yet been reached for the NSAID piroxicam, for which a review is still ongoing.

The EMA’s Committee for Medicinal Products for Human Use (CHMP) recommended that doctors continue to prescribe, and patients continue to use, the lowest dose of NSAIDs for the shortest possible duration to control symptoms. They should base their choice of NSAID on the patient’s underlying conditions and the safety profiles of the medicines.

Based on the information available, the CHMP concluded that:

- non-selective NSAIDs are important treatments for arthritis and other painful conditions,
- it cannot be excluded that non-selective NSAIDs may be associated with a small increase in the absolute risk for thrombotic events, especially when used at high doses for long-term treatment,
- the overall benefit-risk balance for non-selective NSAIDs remains favourable when used in accordance with the product information.

For the NSAID piroxicam, the balance of benefits and risks is still being assessed in a separate ‘Article 31’ referral procedure by the EMA.

Advice for patients and prescribers for NSAIDs remains as follows:

- Patients and prescribers should use NSAIDs as necessary at the lowest effective dose for the shortest possible duration to control symptoms.

- Doctors should continue to decide which NSAID to prescribe on the basis of the overall safety profiles of the medicines, as set out in the product information, as well as the patient's underlying conditions, including those affecting the gastrointestinal system (stomach and bowel), the cardiovascular system (heart and blood vessels) and the kidneys.
- Doctors should not switch patients from one NSAID to another without careful consideration of the overall safety profile of the medicines and the patient's underlying conditions and preferences. Patients should not switch between NSAIDs without talking to their doctor or pharmacist.

A letter from the Chairman of the Commission on Human Medicines (CHM) gives the following information:

- Non-selective NSAIDs may be associated with a small increased risk of thrombotic events (such as heart attack or stroke) when used at high doses and for long-term treatment.
- Evidence for diclofenac (particularly at the 150 mg dose) suggests that this drug may have a small thrombotic risk, similar to that of licensed doses of etoricoxib, and possibly other coxibs. These new data are from the MEDAL (Multinational Etoricoxib and Diclofenac Arthritis Long-term) study, which is due to be published soon.
- For ibuprofen, at high doses (e.g. 2400 mg a day) there may be a small thrombotic risk, but overall, at low doses (e.g. 1200 mg or below), epidemiological data do not suggest an increased risk of myocardial infarction.
- Naproxen is associated with a lower thrombotic risk than coxibs and, overall, epidemiological data do not suggest an increased risk of myocardial infarction; however, some increase in risk cannot be excluded on the basis of available evidence.

For all NSAIDs thrombotic risk is likely to be greater when used at high doses and for long-term treatment.

Advice on the use of diclofenac is that “patients who gain effective pain relief by taking diclofenac regularly do not need to switch immediately to another NSAID based on current evidence. At the next routine review, the choice of NSAID can be reviewed as necessary.”

New items on the PACEF intranet site

A new section has been added, which contains the PACEF template practice formulary.

There is a new document – ‘Drug Therapy Monitoring’, which can be found in the alphabetical list or the BNF miscellaneous section. Please let us know if you find this useful or if there are any drugs we have missed off. If you want a paper copy, just get in touch.

There are updated versions of the AF guideline, clopidogrel guidance, and the Nutritional Management guideline for adults. The updated AF guideline standardises the aspirin dose to 75mg daily, in line with other indications.

More on rimonabant

Further to the article on rimonabant in the August edition, a Cochrane review on rimonabant for overweight or obesity has now been published. Four studies evaluating rimonabant 20mg versus rimonabant 5mg versus placebo in addition to a hypocaloric diet lasting at least one year were included in the review.

Compared with placebo, rimonabant 20mg produced a 4.9kg greater reduction in body weight in trials with one-year results. Improvements in waist circumference, HDL-cholesterol, triglyceride levels and systolic and diastolic blood pressure were also seen. Rimonabant 20mg caused significantly more adverse effects both of a general and serious nature, especially of nervous system, psychiatric or gastrointestinal origin. Attrition rates were approximately 40% at the end of one year.

The authors concluded “The observed results should be interpreted with some caution, since the evaluated studies presented some deficiencies in methodological quality. Studies with longer follow-up after the end of treatment and of more rigorous quality should be done before definitive recommendations can be made regarding the role of this new medication in the management of overweight or obese patients”.

Under implications for practice they say “efforts focusing on the prevention of obesity in non-obese people and non-pharmacological management in obese people should remain the cornerstone of obesity therapy”.

Prescribing gabapentin

Be aware of which form (tablet or capsule) and which strength you are prescribing as there are some surprising differences in cost. From the November Drug Tariff:

Gabapentin	100mg capsules x 100	£8.86
“	300mg capsules x 100	£6.66
“	400mg capsules x 100	£15.76
“	600mg tablets x 100	£106.00
“	800mg tablets x 100	£212.41

So 600mg tds could cost you £11.99 per month (as 2 x 300mg capsules) or £95.40 (as 1 x 600mg tablet)! Similarly 800mg bd is £18.91 (as 2 x 400mg capsules) or £127.45 (as 1 x 800mg tablet). Stick with capsules!

And try to avoid pregabalin – 300mg bd will cost £69 per month and 200mg tds is £103.50.

NICE Clinical Guideline 38 – Bipolar Disorder - Implications for Primary Care

Quick Reference Guide can be found at:

www.nice.org.uk/guidance/cg38/quickrefguide/pdf/English

Definition: Bipolar Disorder is characterised by episodes of depression and episodes of either mania (Bipolar I) or hypomania (Bipolar II). In ICD-10 there must be at least two episodes, one of which is mania or hypomania. The guideline refers primarily to Bipolar I.

Indications for specialist assessment:

Urgent referral should be made if there is an acute exacerbation of symptoms, especially mania or severe depression or an increase in the risk to the patient or others.

For new presentations a specialist referral should be made when the current episode of overactive or disinhibited behaviour lasts four or more days or when there is a history of such symptoms with three episodes of depression. For existing Bipolar Disorder consider referral when a patient first registers with a practice, experiences a decline in function, a poor treatment response, treatment adherence problems, co-morbid drug or alcohol misuse or considers stopping prophylactic treatment.

Some General Principles in Drug Treatment of Bipolar Disorder:

The guideline acknowledges the use of a range of preparations, several of which are not licensed for Bipolar Disorder. Combination drug therapies may often be necessary. Antidepressants should not be used long-term and not without an anti-manic drug (as they can precipitate switch into mania) and should be stopped at the onset of a manic episode. The Quick Reference Guide gives more detail about specific drug treatments.

Psychological and Social Care should include regular reviews of mental state and personal and social functioning, review of written treatment plans, clear delineation of individual professional responsibilities and inclusion in a practice SMI register.

Physical Care requires a baseline health assessment including smoking status, alcohol use, BP, FBC, U&E, TFT, LFT, glucose, lipid profile, weight and height. Further investigations including drug screen, serum prolactin, ECG should be arranged as clinically indicated. An annual physical review should be offered. At least BP, weight, glucose and lipids should be monitored; especially important when antipsychotics are prescribed. (See also Monitoring Drug Therapy and Antipsychotic Shared Care Agreements on local website). When lithium is prescribed patients should be aware that erratic concordance or abrupt discontinuation may precipitate relapse. Serum lithium, U&E, TFT and LFT must be monitored, ECG and FBC if indicated (see also Shared Care Agreement).

Women of child-bearing potential must be given contraceptive advice as mood stabilisers (particularly Valproate which should not therefore be used), may damage the foetus. Mental Health Trust advice is that long acting reversible contraceptive methods are preferred. When carbamazepine is used, combined oral contraception should contain at least 50mcg of oestrogen (progesterone only preparations should not be used). Paroxetine should also be avoided as it may harm the foetus.

Children and Adolescents have slightly different diagnostic and treatment criteria and should normally be managed by specialist clinicians.

Contributed by:

Dr Mark Whittingham, Chair for Drug and Therapeutics Committee, Derbyshire Mental Health Trust.

CKD PATIENT INFORMATION LEAFLET

What is chronic kidney disease?

Kidneys take waste out of the blood, which then leaves the body in urine. The kidneys also play a role in controlling your blood pressure. Chronic kidney disease means that for some reason this is not working as well as expected. Our kidney function gets less efficient as we get older anyway but CKD is deterioration in kidney function faster than would be normally expected for age. There is a big reserve of kidney function – you usually only start to feel unwell if it falls below one-third of its normal amount.

How do you know about chronic kidney disease?

Most people with kidney disease have no symptoms. It is usually diagnosed after blood or urine tests. A new blood test now makes it much easier to recognise a problem with the kidneys. There are 5 stages of CKD but it is only at stage 4 or later that you are likely to notice any symptoms.

How common is chronic kidney disease?

About five per cent of the population have kidneys that show signs of damage. Most of these people have mild kidney damage.

What causes chronic kidney disease?

For many people the cause is not known but it is more common in people who have diabetes, high blood pressure or heart problems. It can also be caused by inflammation or swelling in the kidneys or a past history of urine infections.

Will it get worse?

Kidney damage is usually permanent but most people with kidney disease will find it gets worse very slowly. A small number of people will get much worse and need dialysis or a transplant.

Why does it matter?

People with kidney disease are more likely to have heart attacks and strokes so it is important to do things that help prevent this. This includes lowering blood pressure, lowering cholesterol, taking aspirin and not smoking. It is also important to avoid certain drugs that can damage the kidneys and you should always tell your pharmacist about your kidney problem if you are buying medication over the counter.

Will I need to go to hospital?

Most people can be looked after by their GP with regular blood tests, blood pressure checks and a review of any symptoms. A small number of people such as those whose kidney function is getting worse will need out patient hospital assessment.

Do I need a special diet?

Depending on your blood test results, a dietician may advise you on a special diet. A diet that is low in salt can also help in controlling blood pressure and problems with fluid retention. Most people need this. You may also be asked to restrict the potassium and/or phosphate in your diet.