

NEWSLETTER

Supporting the North Derbyshire Health Community

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PACEF update

The current Traffic Lights list can be accessed via your PCT website (www.chesterfieldpct.nhs.uk, www.highpeakanddalespct.nhs.uk, or www.northeasternderbyshirepct.nhs.uk) or the PACEF ntranet 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>
Atimos Modulite (formoterol cfc-free MDI)	June 2006	GREEN
Letrozole	June 2006	AMBER
Acamprosate	April 2006	AMBER (moved from RED)
Ivabradine	April 2006	BROWN
Nebivolol	April 2006	BROWN
Revatio (sildenafil 20mg tablet for PAH)	April 2006	RED
Inhaled insulin (Exubera)	April 2006	RED
Fosavance (alendronate + vitamin D3)	March 2006	BROWN
Hedrin lotion	March 2006	GREEN (not first line)
Zonisamide	February 2006	AMBER (moved from RED)
Rasagiline	January 2006	BROWN
Oxcarbazepine	January 2006	GREEN (not first line)
Midodrine	January 2006	RED

4Ulcercare

"Breaking News – 4Ulcercare – As seen on ITVs This Morning, and other national press is the first static magnetic product available through the doctor and paid for by the NHS" is a headline on the Magnopulse website, www.magnopulse.com (accessed April 06).

This product is a magnetic leg band worn below the knee and promoted to aid the healing of leg ulcers. The PPA has added 4Ulcercare to the Drug Tariff. According to the Magnopulse website "4Ulcercare accelerates healing by promotion of the so-called injury current, by increasing the growth and functional capacity of connective tissue cells and by enhancing blood perfusion and circulation".

The website also offers a magnetic pet coaster because "given the choice your pet will usually choose to drink magnetic water, they can tell the difference"! Or you might like to try the mn8, "a small, powerful, drug free magnetic device, which discreetly attaches to your underwear"?

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The evidence for 4Ulcercare appears to be a small pilot study with 26 patients¹, and a customer survey. PACEF consider that this is not conclusive evidence and does not recommend 4Ulcercare.

1. Journal of Wound Care 2005; 14: 64-7

Tuberculosis guideline

NICE has produced a guideline on TB (No. 33) and although we are not an area with high incidence, PACEF agreed that this is a useful document and primary care needs to know about it.

NICE identifies the following as key priorities for implementation:

Management of active TB

- A 6-month, four-drug initial regimen (6 months of isoniazid and rifampicin supplemented in the first 2 months with pyrazinamide and ethambutol) should be used to treat active respiratory TB in:
 - adults not known to be HIV-positive
 - adults who are HIV-positive
 - children.
- Patients with active meningeal TB should be offered:
 - a treatment regimen, initially lasting for 12 months, comprising isoniazid, pyrazinamide, rifampicin and a fourth drug (for example, ethambutol) for the first 2 months, followed by isoniazid and rifampicin for the rest of the treatment period
 - a glucocorticoid at the normal dose range
 - ❖ adults – equivalent to prednisolone 20-40 mg if on rifampicin, otherwise 10-20 mg
 - ❖ children – equivalent to prednisolone 1-2 mg/kg, maximum 40 mgwith gradual withdrawal of the glucocorticoid considered, starting within 2-3 weeks of initiation.

Improving adherence

- Use of directly observed therapy (DOT) is not usually necessary in the management of most cases of active TB. All patients should have a risk assessment for adherence to treatment, and DOT should be considered for patients who have adverse factors on their risk assessment, in particular:
 - street or shelter-dwelling homeless people with active TB
 - patients with likely poor adherence, in particular those who have a history of non-adherence.
- The TB service should tell each person with TB who their named key worker is, and how to contact them. This key worker should facilitate education and involvement of the person with TB in achieving adherence.

New entrant screening

- New entrants should be identified for TB screening from the following information:
 - Port of Arrival reports
 - new registrations with primary care
 - entry to education (including universities)
 - links with statutory and voluntary groups working with new entrants.

BCG vaccination

- Neonatal BCG vaccination for any baby at increased risk of TB should be discussed with the parents or legal guardian.
- Primary care organisations with a high incidence of TB should consider vaccinating all neonates soon after birth.

Advice about contact tracing is available from the Health Protection Agency (01623 819000).

Top 5 cost savings in prescribing

These have been derived from the top 20 most costly drugs of the North Derbyshire PCTs.

Atorvastatin

Consider switching all atorvastatin 10mg prescriptions to simvastatin 40mg – they provide the same amount of LDL-C lowering. If you follow the statin policy, few patients will need more than 40mg of simvastatin anyway. Atorvastatin 10mg at £234 per year is more than four times as expensive as simvastatin 40mg (£55 per year).

PPIs

Make sure all prescriptions are for lansoprazole or omeprazole. Aim for 70% to be on maintenance doses. Encourage on demand rather than every day usage by patients.

Blood glucose testing strips

Consider reducing or eliminating use in non-insulin users. Dr Sutherland's practice in Killamarsh can advise how this can be done (see PACE Newsletter December 05 or Practical Diabetes International October 05).

Fluticasone / Salmeterol / Seretide

If asthma, do they still need to be at step 3? Have you tried step down? Beclometasone is the ICS of choice. If COPD, Seretide appears to be no better than either fluticasone or salmeterol on their own. Tiotropium is likely to be a better option anyway.

Clopidogrel

Audit combination use with aspirin. Make sure there is a stop date and that it has not passed. Very few people should need long-term combination antiplatelet therapy with aspirin + clopidogrel.

Trimethoprim and renal function

An incident has occurred locally where the prescription of trimethoprim to a patient with impaired renal function had serious consequences.

Renal impairment is listed as a caution for trimethoprim in the BNF. Trimethoprim can reversibly increase serum creatinine concentration and reduce creatinine clearance without decreasing glomerular filtration rate. The mechanism is probably competitive inhibition of tubular secretion of creatinine and does not signify deterioration in renal function. Thus, a small increase in serum creatinine at the beginning of treatment is not necessarily indicative of impaired renal function. However, trimethoprim can cause nephrotoxicity but this is extremely rare.

Yellow card reports for trimethoprim (alone) are as follows:

Nephritis interstitial	3
Renal failure	5
Renal failure acute	5
Renal impairment	5 (1 death)
Renal tubular necrosis	1

Considering how widely trimethoprim has been used and for how long, these are very low numbers, indicating low incidence.

There is a case report from the BMJ in 1994¹. A 79-year-old woman developed hyperkalaemia with non-oliguric renal failure shortly after starting trimethoprim. After stopping the drug and treating the hyperkalaemia, the results of serum biochemistry and renal function returned to normal.

Appendix 3 of the BNF 50, for *prescribing purposes*, arbitrarily divides renal impairment into 3 grades:

<i>Grade</i>	<i>GFR</i>
Mild	20-50ml/minute
Moderate	10-20ml/minute
Severe	<10ml/minute

For trimethoprim it recommends the following specific dosage adjustments in renal impairment:

- Use half normal dose after 3 days if creatinine clearance 15-30 ml/minute
- Use half normal dose if creatinine clearance less than 15ml/minute
- Avoid if creatinine clearance less than 10ml/minute (unless plasma trimethoprim concentration monitored)

1. BMJ 1994; 308:454

Estimated glomerular filtration rate (eGFR)

The NSF for Renal Services recommended that measurement of kidney function should include a formula-based estimation of GFR. The Department of Health have recommended that all clinical biochemistry labs should routinely report eGFR by April 1st 2006.

Chronic kidney disease (CKD) affects about 10% of the population and is often asymptomatic until renal function is severely reduced. Mild CKD is also important as it represents a significant risk factor for coronary heart disease. Once identified patients with progressive CKD can be actively treated to preserve remaining renal function and to manage potential complications such as cardiovascular disease. The introduction of estimated glomerular filtration rate (eGFR), based on serum creatinine measurement and application of a formula, will enable GPs to create a register of patients with CKD stages 3-5 and identify patients who require referral to renal services, while continuing to manage the majority of patients with stable CKD themselves.

In adults (≥ 18 years old) eGFR will be calculated by the laboratory using the 4-variable Modification of Diet in Renal Disease (MDRD) equation. The four variables are:

- Serum creatinine concentration
- Age
- Sex
- Ethnic origin (for African-Caribbean people only, eGFR multiplied by 1.21).

The ethnicity correction only applies to African-Caribbean patients. Laboratory reports should indicate whether a correction has been applied.

The eGFR will be reported as ml/min/1.73 m². When eGFR exceeds 89 ml/min/1.73 m² values will be reported as ≥ 90 ml/min/1.73 m².

The equation is only an estimate and is not validated for use in:

- Children
- Acute renal failure
- Pregnancy
- Oedematous states
- Muscle wasting disease states
- Amputees
- Malnourished patients

In the UK Caucasian population, the equation seems to work quite well. It may not perform so well in all other ethnic groups. The MDRD formula should not be used in children. When required, eGFR can be calculated using the Schwartz formula, which requires knowledge of height (length) of the child. Whilst such estimates may be used in specialist settings, they will not be routinely produced and reported on samples received from children in a primary care setting.

The following indicates the relationship between eGFR and the stages of kidney disease with suggested frequency of retesting to be adopted:

Stage	ml/min/1.73 m²	Frequency of testing
1 Normal GFR*	>90	Annually
2 Mild impairment*	60-89	Annually
3 Moderate impairment	30-59	6-monthly
4 Severe impairment	15-29	3-monthly
5 Established	<15	3-monthly

*The terms stage 1 and stage 2 CKD are only applied when there is a structural abnormality, as determined by renal ultrasound, such as polycystic kidney disease or a functional abnormality such as persistent proteinuria or microscopic haematuria. If there is no such abnormality, a GFR of 60-89 ml/min/1.73 m² is not regarded as abnormal.

There is a decline in eGFR as people age, which is predominantly related to disease. In CKD the eGFR falls at a predictable rate related to the disease process. Monitoring trends in eGFR, with identification of increased rates of decline, will provide an important indicator of need for intervention in CKD patients.

eGFR calculated using the MDRD formula should be used with caution when calculating doses of drugs as the vast majority of published drug dosing information is based on estimation of creatinine clearance using the Cockcroft and Gault formula, so patients may be incorrectly dosed by switching. It may be prudent, in patients with moderate or severe renal failure, to continue using C&G estimates of creatinine clearance to determine drug dosing.

Further information can be accessed at www.renal.org/eGFR/eguide.html. In addition, the NHS has produced a document 'eGFR Frequently Asked Questions', which I can email to you if you want a copy. Just ask. The East Midlands Renal Network Guidelines for adults with chronic kidney disease are available on the PACEF intranet site.

Calcium and vitamin D and falls

A previous meta-analysis showed that supplementation with vitamin D should prevent more than 20% of falls in older persons¹. The evidence base has been added to with the recent publication of a study investigating the effect of calcium and vitamin D supplementation on the risk of falling in ambulatory older individuals living in the community².

This was a 3-year double-blind placebo-controlled trial of men and women aged 65 years or older (mean 71). Participants were subdivided for analysis into two activity levels, with participants being classified as less physically active if their activity level was below the median of average physical activity. Falls were defined as "unintentionally coming to rest on the ground, floor, or other lower level". Participants were randomly assigned to receive cholecalciferol (vitamin D₃) 700 IU/day plus calcium citrate malate 500mg/day or identical placebo, taken once daily at bedtime.

The reduction in falls in the total sample did not reach statistical significance, OR 0.77 (CI 0.51 – 1.15). However, the results for men and women were different. Calcium and vitamin D significantly reduced the odds of falling in women OR 0.54 (0.30 – 0.97) but not in men. Fall reduction was most pronounced in less active women, OR 0.35 (0.15 – 0.81). The treatment effect increased with time and occurred primarily after 12 months of treatment. InfoPOEMs reports the NNT for 3 years in this study as 7.

The authors concluded that calcium and vitamin D supplementation reduces falls by 46% - 65% in community-dwelling older women, but has a neutral effect on falls in men.

1. JAMA 2004; 291:1999-2006
2. Arch Intern Med 2006; 166:424-30

Glucocorticoid-induced bone loss

Glucocorticoid-induced bone loss is a predictable and debilitating complication of prolonged administration of systemic corticosteroids. Everybody prescribing systemic corticosteroids must be aware of the risk of osteoporosis and ensure that every patient is receiving measures to prevent it. A recent review provides us with the following advice on how to do this¹.

Patients receiving prolonged corticosteroid therapy, defined as longer than 3 months, should be evaluated for prophylactic treatment to decrease the risk of bone loss. For duration of steroid use shorter than 3 months, current literature does not suggest treatment. All patients starting glucocorticoid treatment should be given instruction on general measures for prevention of bone loss (Table 1). Clinicians should assess each patient's risk of osteoporosis and fracture based on known risk factors (Table 2). The total length of treatment with an oral corticosteroid should also be carefully estimated.

Table 1 - General Preventive Measures

Provide 1200 to 1500 mg/d of calcium and 800 IU/d of cholecalciferol (vitamin D) to all patients
Prescribe the lowest possible effective dose of corticosteroid to achieve disease control
Consider topical route of corticosteroid delivery when appropriate
Recommend a good nutritional diet, high in calcium and vitamin D
Recommend regular weight-bearing and cardiovascular exercise
Recommend maintaining body weight and, if possible, increasing muscle mass
Instruct to abstain from the use of tobacco products
Instruct to limit the use of alcohol and caffeine
Assess each patient's risk for falls (consult with physical and occupational therapists if appropriate)
Decide if patient may benefit from referral to physical medicine osteoporosis specialist

Table 2 - Risk Factors for Bone Loss
Advancing age
Postmenopausal status
Low body mass index
White or Asian ethnicity
History of previous low-trauma fracture
Suspected vertebral fracture
Family history of osteoporotic fracture
History of frequent falls
Low levels of physical activity or immobilisation
Smoking
Excess alcohol or caffeine use
Low calcium or cholecalciferol (vitamin D) intake

The Royal College of Physicians produced guidelines for prevention and treatment of glucocorticoid-induced osteoporosis in 2002². They point out that loss of BMD associated with oral glucocorticoid administration is greatest in the first few months of glucocorticoid use. Fracture risk increases rapidly after the onset of treatment and declines rapidly after stopping therapy. Glucocorticoids contribute to the increase in fracture risk over and above the effect on BMD. Thus, for a given BMD, the risk of fracture is higher in glucocorticoid-induced osteoporosis than in postmenopausal osteoporosis.

The evidence base for managing glucocorticoid-induced osteoporosis is not strong. Fracture has not been a primary end-point of any studies of prevention or treatment of glucocorticoid-induced osteoporosis. A reduction in vertebral fracture has been observed in post hoc or safety analyses of trials of etidronate, alendronate and risedronate.

The RCP recommends that those aged 65 years or over and those with a prior fragility fracture should be advised to commence bone-protective therapy at the time of starting glucocorticoid. In other patients in whom it is intended to continue therapy for at least 3 months, bone densitometry should be considered. A T-score of -1.5 or lower may indicate the need for intervention with a bone-sparing agent, although the effect of age on fracture probability should be taken into account.

For those with a T-score between 0 and -1.5, advise following the general preventive measures and repeat BMD measurement in 1-3 years if glucocorticoids continued. Those with a T-score above 0 can be reassured and advised to follow the general measures. A repeat BMD is not indicated unless very high doses of glucocorticoids are required.

As a minimum, all patients on long-term oral glucocorticoids should be considered for supplementation with calcium and vitamin D. Those at high risk because of previous fragility fracture, age, or low BMD should be considered for bisphosphonate therapy.

1. Arch Dermatol 2006; 142:82-90
2. Royal College of Physicians, 2002. Glucocorticoid-induced osteoporosis.

Choice of antihistamine

Cetirizine and loratidine are the recommended non-sedating antihistamines in the formulary. Cetirizine is first line as it is the cheapest. Levocetirizine and desloratadine are not included and are much more expensive. There are no trials comparing control of hay fever symptoms using levocetirizine/desloratadine rather than their parent drugs and they should be reserved as a last resort if cetirizine and loratidine are not suitable.

Cost of 30 days supply (Drug Tariff May 2006)

Cetirizine 10mg daily	£1.78
Loratidine 10mg daily	£2.39
Levocetirizine 5mg daily	£7.45
Desloratidine 5mg daily	£7.04

Amiodarone and grapefruit juice

Sanofi Aventis has updated the SPC for Cordarone X (amiodarone) to include a warning regarding the potential interaction with grapefruit juice. The warning states that:
'Grapefruit juice inhibits cytochrome P450 3A4 and may increase the plasma concentration of amiodarone. Grapefruit juice should be avoided during treatment with oral amiodarone'.

Metformin increases fertility in PCOS

Metformin and Clomiphene have each been used to increase fertility in women with polycystic ovary syndrome. A study has evaluated them head-to-head¹.

One hundred women between the ages of 20 and 34 years with a BMI of less than 30 were randomly assigned to receive metformin 850mg bd or clomiphene 150mg tds (plus placebos of the opposite drug). Before starting medication, the patients received a progesterone challenge, and medication was then started on the third day of progesterone-induced menstruation.

At the end of 6 months of treatment, 69% taking metformin became pregnant compared with 34% taking clomiphene. We would need to treat 3 women with metformin instead of clomiphene for 6 months for one additional woman to become pregnant. The rate of side effects was similar in each group (approximately 20%).

1. J Clin Endocrinol Metab 2005; 90: 4068-74

What is the drug of choice to manage inadequate lactation?

Having been asked if it is appropriate to prescribe domperidone to increase breast milk supply, I obtained the following advice from the UK Medicines Information Service.

Use of drugs to initiate or augment milk supply

Use of galactagogues (drugs for faltering milk supply) should generally be reserved for situations where a thorough evaluation of treatable causes such as poor attachment and increased frequency of breastfeeding, pumping or hand expression of milk has not been successful.

Indications for the use of galactagogues are:

- increase of a faltering milk supply due to maternal or infant illness and prematurity
- separation of mother and infant
- after a period of milk expression by hand or with a pump when a decline in milk production may occur after several weeks
- adoptive nursing
- relactation (re-establishing milk supply after weaning)

There are no products in the UK that are licensed for use as galactagogues. Such use is "off-label".

Summary

- a health professional should always be involved in the decision to use a galactagogue.
- drugs to manage inadequate lactation should only be used where there is objective evidence to support diagnosis and where non-drug methods have failed.
- there are no drugs licensed in the UK to improve lactation.
- domperidone is considered to be the agent of choice for inadequate lactation because of its superior side effect profile, efficacy, and minimal passage into breast milk.
- the most commonly used regimen for domperidone is 10-20mg, orally, three to four times daily.
- further studies are needed to determine the optimum regimen and duration of treatment.
- there are insufficient data to support the use of herbal remedies.

Limitations

Published reports of drug use in lactation are generally limited to small numbers of subjects or to single case reports. Quantitative reports are often limited to single time point estimations.

ESPRIT Study (Lancet 2006; 367: 1665-73)

In secondary prevention of stroke, low-dose aspirin is well established because of its well-documented effect, small risk of serious side effects, and minimum costs. However, the effect size is small and only about a quarter of new vascular events are prevented. Alternative antiplatelets, dipyridamole and clopidogrel, have not been shown to be more effective than aspirin. Would combining antiplatelets be better?

Trials have shown that long-term dual therapy with clopidogrel and aspirin does not offer any clear advantages compared with either drug alone. In the ESPS2 study¹, the addition of modified-release dipyridamole 200mg twice daily to aspirin 50mg daily led to a reduction in cerebrovascular events compared with aspirin alone. However, the results were much debated and the view of clinicians on the validity of ESPS2 remains divided. NICE recently recommended that stroke/TIA patients should receive the combination of dipyridamole and aspirin for two years and aspirin alone thereafter². The aim of the ESPRIT study was to try and resolve this uncertainty by comparing aspirin and dipyridamole with aspirin alone in patients with a TIA or a minor ischaemic stroke of presumed arterial origin.

Method

- ESPRIT had an open, non-blinded study design “to assess real-life treatment strategies”. Patients were recruited mainly from Europe (including the UK), with some from Singapore.
- The study does not seem to have been pharmaceutical industry sponsored.
- The primary outcome event was the composite of death from all vascular causes, non-fatal stroke, non-fatal MI, or major bleeding complication, whichever happened first. Major bleeding complication included all intracranial bleeding, any fatal bleeding, or any bleeding requiring hospital admission.
- Patients were randomised to combination therapy or aspirin alone. Dipyridamole was prescribed in a dose of 200mg twice daily, either as a fixed dose combination of aspirin and dipyridamole, or as a free combination. Dipyridamole was preferably used as an extended-release formulation. If no fixed-dose combination was prescribed, the aspirin dose was left to the discretion of local physicians provided it was between 30mg and 325mg per day.

Results

- 1,363 patients were allocated to combination therapy and 1,376 to aspirin alone. Mean length of follow-up was 3.5 years.
- The distribution of prescribed doses of aspirin was similar in both groups, with a median dose of 75mg per day. Of patients allocated to combination therapy, 83% used extended-release dipyridamole.
- During the trial, 34% of those allocated the combination discontinued trial medication, mainly because of adverse effects (26% reporting headache as at least one of the reasons). Of those allocated aspirin alone, 13% discontinued medication, mainly because of a medical reason.
- The primary outcome event occurred in 12.7% assigned to combination therapy versus 15.7% assigned to aspirin alone; HR 0.80 (95% CI 0.66 to 0.98), p-value not stated.
- Death from all causes and death from all vascular causes were not significantly reduced. Bleeding complications were not significantly different between the two groups.

Discussion

- ESPRIT showed a statistically significant 20% relative risk reduction in new serious vascular events for the combination of aspirin and dipyridamole over aspirin alone in patients after non-disabling cerebral ischaemia of presumed arterial origin. The NNT calculates as 33 over 3.5 years.
- The time-to-event curve shows that the event rates separate after about two years and still appear to be diverging at five years.
- In this study treatment was open and not blinded, although the endpoint adjudication process was blinded. The authors claim that reporting bias was unlikely as only major clinical outcome events were recorded, which were unlikely to go unnoticed.
- Combination therapy was difficult to maintain in the long term with at least a quarter stopping the medication because of headache. It is important that if dipyridamole is not tolerated to remember to continue with the aspirin and not leave the patient without antiplatelet therapy.
- ESPRIT provides reasonable additional evidence to support the national policy outlined in NICE TAG 90². ESPRIT also suggests benefit from combination treatment beyond the two-year period currently recommended by NICE. **PACEF agreed that prescribers should be advised to no longer discontinue dipyridamole after 2 years.** Other risk factor and lifestyle modifications should also be addressed.

1. J Neuro Sci 1996; 143: 1-13 2. NICE Technology Appraisal Guidance 90, May 2005