

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>
Erdosteine	February 2007	BROWN
Lidocaine 5% medicated plaster	February 2007	BROWN
Armour thyroid	January 2007	BROWN
Melatonin	January 2007	AMBER (moved from RED)
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

PACEF and PAG (in the south of the county) have now had their final meetings. A new county-wide group has been formed. The Clinical Effectiveness, Prescribing, and Prioritisation Committee (CEPPaC) will have its first meeting this month.

Initiation of Insulin Therapy in Type 2 Diabetes

Contributed by Dr Rob Robinson, Consultant Diabetologist, Chesterfield Royal Hospital Foundation Trust.

Once the decision to start insulin has been made, insulin choice can be confusing as there are a large number of insulin products available. When deciding insulin choice, a number of factors need to be considered including: current local and NICE guidelines, risks of hypoglycaemia, a plan for both short and long term insulin management, the efficient use of NHS resources, patient preference and choice.

Generally, people with diabetes should have treatment tailored to their needs, and realistic glycaemic targets set. Increasingly, glycaemic targets are being lowered due to the fact that data from the DCCT and UKPDS trials suggest there is no “threshold value” for HbA1c below which further risk reduction cannot be achieved with improved control. Current NICE guidelines state “HbA1c levels of between 6.5% and 7.5% are generally recommended”. This being the case, many patients with Type 2 diabetes who are on maximal doses of oral hypoglycaemic agents are being started on insulin once the HbA1c level has climbed to 7.5%.

In Chesterfield and the surrounding area there is a wide variation in type of insulin therapy chosen for insulin naïve Type 2 diabetic patients. Many patients with Type 2 diabetes are being started on night-time long-acting analogue insulin, and quite rapidly progressing onto a basal bolus regime. This approach is not appropriate in many cases, and unlikely to be cost-effective.

Current guidance from NICE suggests that long-acting insulin analogues are not recommended for routine use for people with Type 2 diabetes mellitus. They should be considered for the following:

- those who require assistance from a carer or healthcare professional to administer their insulin injections
- those whose lifestyle is significantly restricted by recurrent symptomatic hypoglycaemic episodes.

Many of the studies comparing NPH (isophane) insulin with long-acting analogue insulin when added to oral hypoglycaemic agents have shown equivalent improvements in glycaemic control when patients are “treated to target”. The main difference between these two therapies is risk of hypoglycaemia, with benefit generally shown in favour of analogue insulins. However, risk of hypoglycaemia is low for type 2 patients who have only recently started insulin therapy. The risk does increase with increasing duration of insulin therapy; therefore, it is logical to alter glycaemic targets according to the patient. For example, early in the course of insulin therapy glycaemic targets could be “tighter” than if a patient has had insulin treatment for a number of years, and is suffering frequent problematic hypoglycaemic episodes.

Patients who are no longer achieving their glycaemic target and who are on maximal oral hypoglycaemic agents should be considered for the following algorithm (also see page 8):

1. Night-time NPH (isophane) insulin, such as Insulatard, should be started first line, in addition to the patient’s oral hypoglycaemic agents (glitazones should be stopped). Insulin dosage should be started at 8 to 12 units at night, and titrated upwards using a rapid titration regimen. An example of such a regimen would be to increase the dose by 2 units every 3 days if the fasting blood glucose is greater than 5.5mmol/l on each day. The dose should be cut back if the patient suffers nocturnal hypoglycaemia. One advantage of night-time insulin is that usually patients only need check their fasting blood glucose, unless feeling unwell at other times.
2. If the patient is unable to achieve a fasting glucose of < 7mmol/l due to problematic nocturnal hypoglycaemia, a basal insulin analogue should be considered. Nocturnal hypoglycaemia is an indication for long-acting analogues. To change from NPH (isophane) insulin to a long-acting analogue a “same dose” change is reasonable.
3. If the patient’s HbA1c starts to climb, despite having optimal fasting sugars of 4-7 mmol/l, the next step would be to change to a twice-daily biphasic insulin mixture (Mixtard 30, Humulin M3, or Insuman Comb 25). At this stage, sulphonylurea medication should be stopped, but metformin continued.
4. If a patient has delayed insulin initiation for any reason, such as occupation, and their HbA1c pre-insulin is greater than 9.5%, they should be started on a twice-daily mixture as first line.

5. If control is not optimal, and if pre-tea BM stix are high, but pre-lunch BM stix readings low, making it impractical to titrate up the morning dose a third injection could be added pre-lunch, starting at a low dose, and titrating upwards.
6. Some patients with Type 2 diabetes will benefit from basal bolus insulin therapy. This could be considered if concordant patients are failing to achieve good control due to significant hypoglycaemia.
7. Some lean patients with Type 2 diabetes may have "slow burn" Type 1 diabetes and may be better suited to a basal bolus regimen.

This guidance has been ratified by PACEF and now forms part of the Guideline for the management of people with type 2 diabetes, which you can find on the PACEF website.

Long-term alendronate treatment

There is a limited difference in clinical outcomes between five years' and ten years' treatment with alendronate in women with post-menopausal osteoporosis, according to the results of a randomised open-label trial (FLEX)¹ – a long-term follow-up extension to the Fracture Intervention Trial (FIT). Bisphosphonates are released slowly from bone once they have been incorporated. They have a terminal half-life of over ten years and may therefore have an effect after treatment stops.

1,099 women, with an average age of 73 who have received at least three years' alendronate treatment (average five years) during FIT were randomised to receive daily alendronate 10mg, 5mg, or placebo for a further five years, and offered daily calcium plus vitamin D supplements. Primary outcome was hip bone mineral density (BMD); fracture incidence was a secondary outcome.

60% of participants had a history of fractures since menopause. Compared to those continuing alendronate therapy, placebo recipients had a:

- Modest decline in hip BMD (-2.4%; [95% CI -2.9% to -1.8%]; p<0.001), and spine BMD. Levels remained at or above pre-treatment levels of ten years earlier.
- Small increase in risk of vertebral fracture (5.3% for placebo vs 2.4% for alendronate; RR 0.45; [0.24 to 0.85]). There was no difference in the rates of morphometric vertebral fractures (those causing change in the shape of a bone) or hip fractures.

There were no significant differences between the groups in adverse effects, and no reports of jaw osteonecrosis. The authors conclude that women who stopped alendronate after five years showed a modest increase in bone loss, and in clinical vertebral fractures, but no increase in other fractures. They suggest that for many women, stopping alendronate after five years will not significantly increase their fracture risk. Those at very high risk of clinical vertebral fractures may benefit from continued treatment.

1. JAMA 2006; 296: 2927-2938

Average or lowest blood pressure?

NICE Clinical Guideline 34 on the management of hypertension says that several BP readings need to be taken before classifying someone as hypertensive. The guideline advises that if BP is raised, to ask the patient to return for at least two more appointments and check BP twice on each occasion, under the best conditions available.

What BP reading do you then use to assess the overall cardiovascular risk? At a recent seminar with GPs on hypertension, two-thirds said they used the average and one-third the lowest reading. I was asked to check which is correct!

NICE doesn't seem to make it clear but PRODIGY says, "Take the **average** of at least two readings (more recordings are needed if marked differences are found between initial measurements)." I hope this clears it up.

Heavy menstrual bleeding

NICE has issued clinical guideline No. 44 on the management of heavy menstrual bleeding. It says that heavy menstrual bleeding has a major impact on a woman's quality of life, and any intervention should aim to improve this rather than focusing on menstrual blood loss. The guideline makes recommendations on a range of treatment options for heavy menstrual bleeding. The key priorities for implementation are as follows.

Impact on women

- For clinical purposes, heavy menstrual bleeding (HMB) should be defined as excessive menstrual blood loss, which interferes with the woman's physical, emotional, social and material quality of life, and which can occur alone or in combination with other symptoms. Any interventions should aim to improve quality of life measures.

History taking, examination and investigations

- If appropriate, a biopsy should be taken to exclude endometrial cancer or atypical hyperplasia. Indications for biopsy include, for example, persistent intermenstrual bleeding, and in women aged 45 and over treatment failure or ineffective treatment.
- Ultrasound is the first-line diagnostic tool for identifying structural abnormalities.

Education and information provision

- A woman with HMB referred to specialist care should be given information before her outpatient appointment. The Institute's information for patients ('Understanding NICE guidance') is available from www.nice.org.uk/CG044publicinfo

Pharmaceutical treatment

- If history and investigations indicate that pharmaceutical treatment is appropriate and either hormonal or non-hormonal treatments are acceptable, treatments should be considered in the following order:
 - levonorgestrel-releasing intrauterine system provided long-term (at least 12-months) use is anticipated
 - tranexamic acid or non-steroidal anti-inflammatory drugs (NSAIDs) or combined oral contraceptives
 - norethisterone 15mg daily from days 5 to 26 of the menstrual cycle, or injected long-acting progestogens
- If hormonal treatments are not acceptable to the woman, then either tranexamic acid or NSAIDs can be used.

Non-hysterectomy surgery

- In women with HMB alone, with uterus no bigger than a 10-week pregnancy, endometrial ablation should be considered preferable to hysterectomy.

Hysterectomy

- Taking into account the need for individual assessment, the route of hysterectomy should be considered in the following order: first-line vaginal; second-line abdominal.

Also included in the guideline are these recommendations.

The following investigations are not recommended:

- Direct or indirect menstrual blood loss measurements
- Serum ferritin test
- Female hormone testing
- Thyroid testing
- Saline infusion sonography as first-line diagnostic investigation
- MRI as first-line diagnostic investigation
- Dilatation and curettage (D and C)

The following treatments are not recommended:

- Oral progestogens in the luteal phase only
- Danazol
- Etamsylate
- Dilatation and curettage (D and C)

Rosiglitazone and fractures

In last month's PACE Newsletter I reviewed the ADOPT trial. I didn't mention that in the published paper there is a note added in proof: "While this article was in production, further examination of data on adverse events identified a higher rate of fractures in the group receiving rosiglitazone. This was an unexpected event that was not part of the prespecified analysis plan". Hence my reason for not mentioning it.

However, Glaxo SmithKline has notified healthcare professionals in the US of these data via a letter. The letter says:

"A review of the safety data in ADOPT was consistent, in general, with the known safety profile of rosiglitazone. However, significantly more female patients who received rosiglitazone experienced fractures than did female patients who received either metformin or glyburide. The observed incidence of fractures for male patients in ADOPT was similar among the three treatment groups.

The majority of fractures observed in female patients who received rosiglitazone during ADOPT were in the upper arm (humerus), hand, or foot. These sites of fracture are different from those associated with post-menopausal osteoporosis (e.g., hip or spine). In ADOPT, the number of female patients with a hip or spine fracture was low and similar among the three treatment groups.

At GSK's request, an independent safety committee reviewed an interim analysis of fractures in another large ongoing, long-term, controlled rosiglitazone clinical trial. The primary purpose of that study is to investigate cardiovascular endpoints in patients with type 2 diabetes mellitus. The results of the preliminary analysis were reported to GSK as being consistent with the observations from ADOPT. The independent safety committee also recommended that the study continue without modification. Final results of this study are anticipated to be available in 2009.

Presently, our understanding of the clinical significance of the findings from these two long-term trials is incomplete, and the mechanism(s) for the observed increase in fractures is uncertain. Further evaluation of these observations is ongoing. GlaxoSmithKline believes the risk of fracture should be considered in the care of patients, especially female patients, with type 2 diabetes mellitus who are currently being treated with rosiglitazone, or when initiation of rosiglitazone treatment is being considered. In these patients, as with all patients with type 2 diabetes mellitus, attention should be given to assessing and maintaining bone health according to current standards of care."

In ADOPT, 9.3% of women experienced a fracture on rosiglitazone, compared with 5.1% on metformin and 3.5% on glyburide (glibenclamide); $p < 0.01$ for both comparisons with rosiglitazone. This calculates as a NNH of 17-24.

Attention prescribers: be careful with antibiotics

This is the title of an editorial in a recent Lancet¹. The author reflects on a randomised trial from Belgium².

She writes: "Malhotra-Kumar and co-workers undertook a randomised, double-blind, placebo-controlled study designed to satisfy scientists and persuade even the most disengaged of clinical readers. The effect of two macrolide antibiotics, azithromycin (500 mg once daily for 3 days) and clarithromycin (500 mg twice daily for 7 days), was measured against placebo in four groups of volunteers by use of oral streptococci as model organisms. The researchers recorded a clearly defined effect on commensal pharyngeal streptococci, with both drugs selecting for macrolide resistance."

A previous paper from this group showed a clear correlation on a national level between antibiotic use and the prevalence of resistant organisms³, but now there is evidence from a randomised trial on the individual level. We can be surer that the individual who takes lots of antibiotics may be at personal risk of becoming colonised with resistant organisms.

The commentary ends: "We now have strengthened evidence for the links between antibiotic use and resistance. Our only response to the delay in proving this association should be to get on and do something about it before the antibiotic era finally grinds to its apocalyptic halt."

There are at least two useful tactics in Primary Care to reduce antibiotic prescribing where it is not essential. The first is to ask directly whether the patient is expecting an antibiotic, as they may well not be. The other is to offer a deferred prescription to those who are not toxic, as many upper respiratory infections will clear by themselves.

1. Lancet 2007; 369:442-3
2. Lancet 2007; 369:482-90
3. Lancet 2005; 365:579-87

Combined aspirin and oral anticoagulant therapy?

For patients receiving oral anticoagulant (OAC) therapy, is it worth adding aspirin to their treatment? A recently published systematic review and meta-analysis sought to answer this question¹. They included RCTs with at least 3 months of follow-up that compared aspirin-OAC therapy with OAC therapy alone.

Ten studies were included, totalling 4180 patients. The risk for arterial thromboembolism was lower in patients receiving combined aspirin-OAC therapy compared with OAC therapy alone (OR, 0.66; 95% CI, 0.52-0.84). However, these benefits were limited to patients with a mechanical heart valve (OR, 0.27; 95% CI, 0.15-0.49). There was no difference in the risk of arterial thromboembolism with these treatments in patients with atrial fibrillation (OR, 0.99; 95% CI, 0.47-2.07) or coronary artery disease (OR, 0.69; 95% CI, 0.35-1.36). There was no difference in all-cause mortality with either treatment (OR, 0.98; 95% CI, 0.77-1.25). The risk for major bleeding was higher in patients receiving aspirin-OAC therapy compared with OAC therapy alone (OR, 1.43; 95% CI, 1.00-2.02).

The authors' conclusion was:

“Our findings question the current practice of using combined aspirin-OAC therapy except in patients with a mechanical heart valve, given the questionable benefits in reducing thromboembolic events and the increased risk of major bleeding.”

1. Arch Intern Med 2007; 167:117-24

Do angiotensin receptor blockers increase the risk of MI?

The possibility that ARBs increase the risk of MI came to prominence a couple of years ago (see PACE Newsletter of February 05) and has been debated ever since. Circulation has published two articles, one arguing that ARBs may increase the risk of MI¹ and the other arguing that they do not².

The first group (for the motion) point out that available data indicate that whereas ACEIs produce marked and consistent reduction of MI and CV death across diverse patient populations, the same cannot be said of ARBs. The major ARB trials in high-risk patients have thus far demonstrated almost a complete lack of reduction in MI and mortality despite significant reductions in blood pressure. They agree that there is no consensus on whether ARBs have a tendency to increase MI, but there is also no substantive evidence to indicate that ARBs are able to reduce MI. An ARB-MI paradox exists, they say, that is biologically, pharmacologically, and pathologically plausible. They conclude that evidence dictates that reaching for an ACEI instead of an ARB prevents more MIs and vascular deaths, and ACEIs should be the first choice across the spectrum of cardiometabolic risk reduction.

The second group (against the motion) also actually agree that ACEIs remain the agents of choice for reducing MI. They state that ARBs do not increase the risk of MI. The odds ratio for MI for ARBs compared with placebo that they provide is 0.94 (95% CI 0.75 to 1.16). The confidence intervals tell us that this is not a statistically significant difference. MIs were not increased but neither were they reduced!

1. Circulation 2006; 114:838-54
2. Circulation 2006; 114:855-60

Keypoint: ARBs are only indicated when an ACEI is strongly indicated but cannot be tolerated

Care needed when writing insulin doses

Chesterfield Royal Hospital has highlighted that they have had a spate of near misses recently with insulin doses, relating to hospital doctors incorrectly interpreting GP letters (despite quite good handwriting!). Ideally information should be computer generated but if handwriting is unavoidable please be reminded of the following issues

- Separate numerical dose from the word units. i.e. 7 units rather than 7units (u can be interpreted as a zero)
- Avoid abbreviations. If international units abbreviated to iu, i can be interpreted as a number 1); if units abbreviated to u, u can be interpreted as a zero.
- Ensure numbers are clear and legible, in particular continental style 1 can often be interpreted as a 7. If any doubt clarify by writing out in words also.

Standards for Prescribing Antipsychotic Drugs for Older Adults with Dementia

Antipsychotics have been used for many years in attempts to treat troubling behavioural symptoms of dementia such as aggression and agitation, as well as psychotic symptoms e.g. hallucinations or delusions. However, studies have shown that such treatment is often ineffective and likely to cause adverse effects, especially worsening confusion, sedation, hypotension and extrapyramidal side effects leading to reduced mobility and falls. More recently an increased incidence of stroke has been demonstrated during trials involving olanzapine and risperidone in patients with dementia and it is fairly certain that this risk extends to other antipsychotics also.

In line with the recent NICE '[Clinical Guideline 42 – Dementia](#)' and with the Royal College of Psychiatrists Guidance of 2005, '[Atypical antipsychotics & BPSD](#)', Derbyshire Mental Health Services NHS Trust advises that the use of antipsychotics, conventional or atypical, for severe behavioural or psychiatric symptoms of dementia may be appropriate, but only when non-drug interventions have proved ineffective and when the possible risks have been duly weighed against the potential benefits of treatment. Ten standards of good practice have been drawn up to help prescribers minimise risk for this group of difficult to treat patients:

1. Non-drug methods of managing symptoms are considered before prescribing.
2. Information is given to patient and/or carers.
3. Target symptoms are clearly defined.
4. Consideration is given as to whether the patient has mental capacity to consent to medication.
5. Consideration is given to the balance of risks (including risk factors for strokes) and benefits.
6. Consideration is given to baseline investigations.
7. Adverse effects are considered at each review.
8. Medication is reviewed at least weekly during the titration period.
9. Medication is reviewed at least monthly during the first 3 months of stability.
10. Medication is reviewed at least every 3 to 6 months during continuing treatment.

Choice of which antipsychotic to use is left to the prescriber to decide on the basis of the risks v. benefits for an individual patient.

Contributed by Penny Halfpenny, Senior Clinical Pharmacist, Derbyshire Mental Health Services NHS Trust

Minocycline for acne

Acne may require oral antibiotic treatment, particularly in those with moderate to severe disease (an estimated 11% of adolescents). Minocycline is often assumed to be more effective and easier to take than other tetracyclines. A recent review in the BMJ dispels that myth¹.

- Oral minocycline is no more effective than other oral tetracyclines in treating acne.
- The risk of rare but serious unwanted effects with minocycline make it less suitable for use than other drugs in its class. It seems to be unique in causing potentially irreversible slate-grey hyperpigmentation of the skin. It also seems more likely than other tetracyclines to lead to lupus-like syndrome.
- Minocycline is more expensive than most other oral tetracyclines and patients who need treatment with an oral tetracycline should be prescribed doxycycline, lymecycline, or oxytetracycline. Doxycycline is the least costly of these three options.
- Doxycycline and lymecycline are taken once daily, and their absorption is not affected by food.

1. BMJ 2007; 334: 154

Algorithm for initiation of insulin therapy in type 2 diabetes

