

NEWSLETTER

Supporting the Derbyshire Health Community

Volume 6: Issue 7

October 2007

| | | |
|------------------------------|---------------|--|
| Further in this issue | Page 2 | UTI in children, Chronic fatigue syndrome 2007 update to the British Asthma Guideline |
| | Page 3 | Painful diabetic neuropathy Switching from atorvastatin to simvastatin |
| | Page 4 | Fall in simvastatin prices |
| | Page 5 | Continence appliance prescribing guidelines |
| | Page 6 | Drug safety update |
| | Page 7 | NPCi has now been launched |
| | Page 8 | Human papillomavirus (HPV) vaccine More on CV risk with glitazones |

CEPPaC update

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 CEPPaC does not recommend for use (DARK BROWN) or only in restricted circumstances (LIGHT BROWN) due to lack of data on safety, effectiveness, and/or cost-effectiveness. *All BROWN drugs are non-formulary.*

The most recent updates are in the table below:

| Drug | Date considered | Decision |
|-----------------------------|------------------------|--|
| Nicorandil | October 2007 | GREEN (3 rd or 4 th line) |
| Celluvisc eye drops | September 2007 | GREEN (not first line) |
| Lymecycline 408mg caps | September 2007 | GREEN (second line for acne) |
| N-acetylcysteine 600mg tabs | September 2007 | RED |
| Minocycline | September 2007 | DARK BROWN |
| Cerazette | August 2007 | GREEN |
| Evra patch | August 2007 | LIGHT BROWN (if oral COC not suitable) |
| Yasmin | August 2007 | LIGHT BROWN (if other oral COC not suitable) |
| Rotigotine patches | August 2007 | LIGHT BROWN (if oral dopamine agonists not suitable) |

Appropriate oral antibiotic use for acne

Oral minocycline is no more effective than other oral tetracyclines in treating acne and the risk of rare but serious adverse effects make it less suitable for use than other drugs in its class¹. CEPPaC has reviewed the available options for oral antibiotics in the management of moderate to severe acne and recommended that minocycline be no longer used (DARK BROWN drug). This is the recommended algorithm for choosing an oral antibiotic in acne. Please consider this for new patients and treatment failures.

First line: doxycycline capsules 50-100mg daily (or oxytetracycline tablets 250mg, 2 twice daily, if the patient can manage this regime)

Second line: lymecycline capsules 408mg daily

Third line: erythromycin tablets 250mg, 2 twice daily

Cost for 3 months supply (Drug Tariff October 2007):

Doxycycline capsules 50-100mg daily - £12.60

Lymecycline capsules 408mg daily - £21.50

Erythromycin tablets 250mg, 2 twice daily - £36.70

1. BMJ 2007; 334:154

UTI in children

NICE have issued Clinical Guideline No. 54 on the diagnosis, treatment and long-term management of UTI in children. The quick reference guide can be found here at <http://guidance.nice.org.uk/CG54/quickrefguide/pdf/English>

A BMJ editorial on this says, “New NICE guidelines emphasise prompt diagnosis and treatment but more restrained imaging”¹. There are two key issues raised by this guideline according to the editorial. “The statement that the routine prescription of prophylactic antibiotics is no longer supported will surprise many, but evidence is accumulating that prophylactic antibiotics do not significantly decrease the risk of recurrent urinary tract infections and may increase the risk of resistant organisms”.

“The imaging strategies will provoke even more debate. Much relies on using non-invasive ultrasound to determine the status of the urinary tract. In children who are systemically well, only those under 6 months or with recurrent infections need an ultrasound scan. Routine imaging to identify vesicoureteric reflux is not recommended, and only in children under 6 months should a micturating cystourethrogram be requested when there is severe or atypical illness, or recurrent urinary tract infections.”

1. BMJ 2007; 335:356-7

Chronic fatigue syndrome

NICE have also issued Clinical Guideline No. 53 on the diagnosis and management of CFS/ME in adults and children. The quick reference guide can be found at <http://guidance.nice.org.uk/CG53/quickrefguide/pdf/English>

The guideline recommends that the following strategies should NOT be used for CFS/ME:

- Advice to undertake unsupervised, or unstructured, vigorous exercise (such as simply ‘go to the gym’ or ‘exercise more’) – this may worsen symptoms
- Specialist management programmes delivered by practitioners with no experience of the condition
- Do not use the following drugs for the treatment of CFS/ME:
 - monoamine oxidase inhibitors
 - glucocorticoids (such as hydrocortisone)
 - mineralocorticoids (such as fludrocortisone)
 - dexamphetamine
 - methylphenidate
 - thyroxine
 - antiviral agents

2007 update to the British Asthma Guideline (BAG)

BAG is regularly updated to incorporate the results of the latest research. An update to the pharmacological management section has recently been released. A major review of the entire guideline, with publication of a revised paper copy is planned to take place in early 2008.

Summary of 2007 changes

1. Section 4.2.2 Safety of inhaled steroids in children

Clinical adrenal insufficiency has been identified in a small number of children who have become acutely unwell at the time of intercurrent illness. Most of these children had been treated with high doses of inhaled corticosteroids. The guideline notes that the dose or duration of inhaled steroid treatment required to place a child at risk of clinical adrenal insufficiency is unknown.

The guideline now contains a good practice point stating “*Specific written advice about steroid replacement in the event of a severe intercurrent illness should be part of the management plan for children treated with ≥ 800 mcg per day of BDP or equivalent. Any child on this dose should be under the care of a specialist paediatrician for the duration of the treatment.*”

2. Section 4.2.3 Comparison of inhaled steroids

There is limited published evidence regarding the clinical benefit of the new inhaled steroid, ciclesonide, as the exact efficacy to safety ratio compared to other inhaled steroids has not been fully established. The guideline does not make specific recommendations about ciclesonide.

3. Section 4.2.4 Smoking

There is a new section about the effect of smoking on the efficacy of inhaled steroids. The guideline now recommends that *“Clinicians should be aware that higher doses of inhaled steroids may be needed in patients who are smokers/ex-smokers.”*

4. Section 4.7.1 Onset of exacerbation of asthma

The guideline looks at the evidence of adjustable dosing of inhaled steroids and concludes that in adults doubling the dose of inhaled steroids at the time of exacerbation has not been shown to be effective. However, studies in which the dose of a combination inhaler budesonide/formoterol is adjusted according to symptoms have shown good levels of asthma control, although as it is not clear if this is superior to the use of more conventional stable dose of inhaled steroids and long-acting beta-2 agonists, no specific recommendations have been made.

5. Section 4.8 Anti IgE monoclonal antibody

There is a new section about the anti IgE monoclonal antibody, omalizumab. The guideline summarises the latest evidence and concludes that as there are no active comparative studies it is not possible to place omalizumab in the stepwise treatment of asthma.

Importantly the British Asthma Guideline has not recommended the Symbicort SMART regime. Despite this, a ‘Change Page’ article in a recent BMJ favours the SMART approach¹. This has been discussed again at CEPPaC (see PACE Newsletter of July 07 for previous discussion) and again the decision was not to recommend Symbicort SMART, unless there is revision of national policy.

1. BMJ 2007; 335:513

Painful diabetic neuropathy

A recent systematic review investigated treatments for symptoms of painful diabetic neuropathy¹. Clinical success was defined as a 50% reduction in pain. Withdrawal due to adverse events was a secondary outcome. The review found that tricyclic antidepressants were most effective in reducing pain by 50% (OR 31.73), followed by traditional anticonvulsants (sodium valproate, carbamazepine) (OR 7.59), and the newer generation anticonvulsants (gabapentin, oxcarbazepine, pregabalin) (OR 3.25). The newer generation anticonvulsants were most likely to cause withdrawals due to adverse events, followed by TCAs and the traditional anticonvulsants (OR 2.98, 2.32, 1.51 respectively). In the analysis of the effects of tramadol the odds ratio for withdrawal due to adverse events was higher than the OR for 50% pain relief.

The authors’ proposed treatment algorithm has a TCA first line, or if there are contraindications to TCA, sodium valproate or carbamazepine.

As the accompanying editorial points out, patients’ beliefs and perceptions of the pain and its cause, coping strategies, mood changes, disturbed sleep, and anxiety all need to be addressed. If, despite these measures, the pain persists and is so severe that pharmacological treatment is indicated, TCAs seems the best first step².

1. BMJ 2007; 335:87-96
2. BMJ 2007; 335:57-58

Switching from atorvastatin to simvastatin

Further controversy on drug switching has been fuelled by findings of a Pfizer sponsored study presented at the annual European Society of Cardiology congress recently (and featured in several newspapers) suggesting that patients switching from atorvastatin to generic simvastatin were at an increased risk of major cardiovascular events.

The authors (all Pfizer staff plus a statistician from a biostatistics company) analysed the GP records of 2511 patients switched from atorvastatin to simvastatin and matched them with 9009 controls. Records were obtained from a UK primary care database (THIN). Importantly the last data collection was June 2005. There were some key imbalances in baseline characteristics between switched patients and controls – for example, total cholesterol was 0.5mmol/L higher and there were more smokers in switched patients. There were also baseline differences in other cardiovascular drugs prescribed to the different groups.

Switching treatment was associated with a statistically significant increase in the risk of death or major cardiovascular events (MI, stroke or coronary revascularization) compared with patients who did not switch (HR 1.30, 95%CI 1.02 to 1.64; P = 0.03). Although this P value achieves the conventional level of statistical significance, this result could have occurred by chance with a marginally greater probability than the likelihood of throwing a double six in a board game (and we've all seen that happen). Looking at these results in more detail, there was no statistically significant difference between the two groups in the rate of death. The set of outcomes labelled "major cardiovascular events" occurred more frequently in the switch group but looking at these outcomes individually, only stroke occurred statistically significantly more frequently in the switch group: there was no difference in rates of MI or revascularisation. Patients who switched were also more likely to stop taking their statin than those who did not switch (HR for discontinuation 2.15, 95%CI 1.96 to 2.36, P<0.001).

The reasons for switching statins in this cohort were not available, nor were the doses of atorvastatin or simvastatin prescribed. These are two very important factors that could affect the results. Since the time of switching pre-dates NHS switching programmes it's reasonable to assume that the switches here involved people who were non-responders, poor compliers, side effect sufferers etc (and so likely to discontinue treatment) and not the sort of people who have been switched as a result of the Better Care Better Value indicator, the Bogle & Moon BMJ editorial and the work of medicines management teams.

This type of study is inherently prone to bias and confounding – not least because of the identified imbalances in baseline characteristics. As the report itself indicates these results should be hypothesis generating. This study fails to provide adequate evidence that atorvastatin has advantages over generic alternatives that are less costly to the NHS and offer value for public money.

You may be interested in some of the comments on this study from the medical BLOGs.

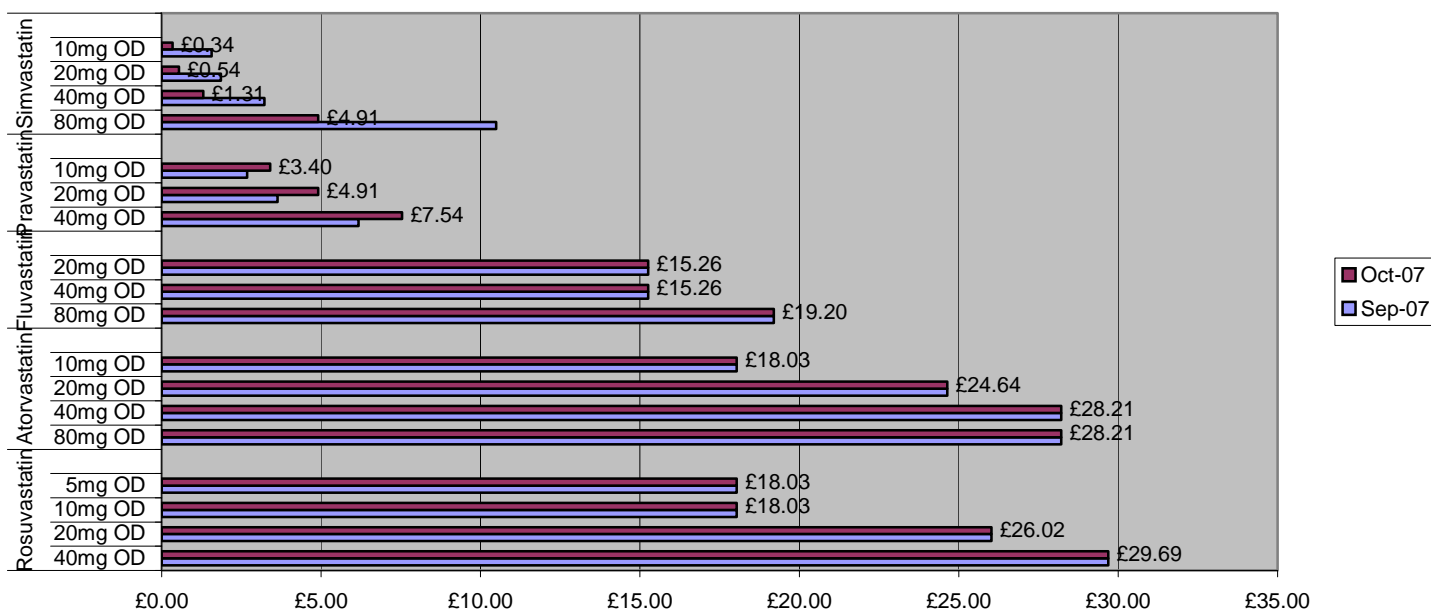
<http://hcrenewal.blogspot.com/2007/09/why-might-switching-statins-be-bad-for.html>

<http://www.brandweeknr.com/2007/09/healthcare-jour.html>

Fall in simvastatin prices

There have been substantial falls in the cost of generic simvastatin this month.

Statin prices - cost of 28 days treatment Sept 07/Oct 07 (data labels for Oct 07 shown)



For every patient on atorvastatin 10mg, 14 can be treated with simvastatin 40mg, and for every patient on atorvastatin 80mg, 22 can be treated with simvastatin 40mg.

Contenance appliance prescribing guidelines

A new continence appliance prescribing guideline has been written by the Continence Implementation Group to help health care professionals rationalise prescribing of continence products and to promote good clinical practice. Products have been selected based on cost effectiveness, evidence of efficacy where it exists, manufacturer's literature and practical experience of use. It is expected that prescribers will preferentially use the products included in the guidelines for routine use.

The guidelines have been approved for use in Derbyshire County and Derby City PCTs by CEPPaC and it is also anticipated that the local community and acute hospitals will adopt them. The guidelines were recently launched at a number of events across Derbyshire and a copy along with a wall poster and pocket guide is being sent to all care homes, GP practices, community pharmacies, community hospitals and District Nursing Teams. They can also be accessed via the Prescribing section of the Derbyshire County and City PCTs website or through your medicines management team.

Here are the top 10 prescribing tips for improving compliance with the formulary and reducing problems:

1. Do they really need this appliance?
2. Discuss with client and carers that you would like to change their continence appliances and why
 - Let social services and other care agencies know if necessary.
 - Let appliance contractor know if necessary
 - Leaflets/letters to support change available from the medicine management teams
3. Do a stock take and use up all old stock before changing products over
 - Ask clients to contact District Nursing Services two weeks before current product runs out so the new appliances can be ordered
 - Inform surgery of product change and also get a message put on the script screen to contact District Nursing service when new order necessary
 - Remove old order from script screen
 - Remember to be clear about the new prescription, e.g. whether lever style or slide tap is required for catheter drainage bags
4. Star (*) the Drug tariff/ RDC catalogue to pick out the products to prescribe.
This is as well as knowing where the complete version of the guidelines is kept at your base (this is a useful guide to good practice in general as well as products) and keeping your prescribing leaflet handy in your diary
5. Change catheters and accessories at the same time, only changing one may cause problems with connections
6. Check that a specialist assessment has not taken place, stating that a certain product is advised before using formulary products.
7. Do remember there are a limited number of products available in hospital
(e.g. only 500ml leg bags and only one make of bag with a slide tap and one make with lever tap).
Once home help new patients to select the most appropriate
 - a. size/type of bag or valve
 - b. type of tap
 - c. length of inlet tube
 - d. night drainage system for their needs
 - e. and suspension system to be used
8. Ensure client knows how to empty/ change their drainage system and how frequently it should be changed.
9. Only change sheaths according to guidelines for new patients, or consider guidelines if they are already experiencing problems and need reviewing.
10. Use a problem solving systematic approach if problems occur, find out what the problems are rather than just keep trying different products. Do support client and carers throughout the change over.

Don't try and change everyone all at once. *Don't give up Rome wasn't built in a day!*

Producing prescriptions

- Include full details of product required to ensure the correct size, type, quantity and gender (for catheters).
- The brand and manufacturer should be stated to ensure continuity of supply.
- DO NOT prescribe generically because of the differences between individual products.
- Avoid the term 'original pack' (OP). Pack sizes differ between products and patients may receive inappropriate amounts if the quantity is not stated.
- When new products are being tried, the smallest amount required should be prescribed to minimise wastage.

Average quantities to prescribe for ONE month are:

| Product | Type | Monthly Quantity |
|------------|--|---|
| Catheters | Indwelling Foley | ONE (plus ONE spare [initial script and then when used]) |
| | Nelaton reusable catheters for ISC | FIVE (1 pack) |
| | Single use PVC or self lubricating Nelaton catheters for ISC | 125-150 (5-6 packs of 25) |
| Sheaths | All | THIRTY (1 box) |
| Leg bags | Drainable | FIVE (preferable to supply one complete box (10) on a prescription so a box should last 2 months) |
| Night bags | Drainable | FIVE (preferable to supply one complete box (10) on a prescription so a box should last 2 months) |
| | Non-drainable | THIRTY (3 boxes of 10) |

- A copy of the guidelines should be available to prescription clerks so that they can easily monitor prescription requests for continence products.
- Set up a continence product formulary on the computer system so all staff can identify products easily (Please contact a member of the medicines management team if you require assistance with this.)
- Please note that patients have a choice as to whether a community pharmacy or appliance contractor dispenses their prescription.

Drug safety update

This monthly newsletter from the MHRA has replaced the publication 'Current Problems in Pharmacovigilance', which used to be posted to all doctors and pharmacists. 'Drug Safety Update' is only available electronically and you can register for e-mail alerts. It can be found at www.mhra.gov.uk/mhra/drugsafetyupdate
These are some of the highlights from the September issue:

Hormone replacement therapy: updated advice

Before prescribing HRT, healthcare professionals should consider carefully the potential benefits and risks for every woman.

- The decision to prescribe HRT should be based on a thorough evaluation of the potential benefits and potential risks of treatment.
- Healthcare professionals should assess every woman's overall risk, including cardiovascular risk, particularly in those older than 60 years who have increased baseline risk of serious adverse events.
- Evidence for the risks of HRT in women who had premature menopause is limited. However, the baseline risk of adverse events in these younger women is low, and the balance of benefits and risks may be more favourable than in older women.

- Because of the risks associated with long-term use, HRT should be used for prevention of osteoporosis only in women who are unable to use other medicines that are authorised for this purpose.

This section includes a table presenting the absolute risks and benefits of HRT.

Tibolone: benefit risk balance

Increased risk of stroke in older women should be taken into account in prescribing decisions.

- Every woman's overall risk of stroke, breast cancer, and, in those with an intact uterus, endometrial cancer should be assessed carefully, taking into consideration any baseline risk factors, the increased risk due to tibolone use, and her therapeutic preferences.
- Healthcare professionals should refer women who bleed beyond 6 months of treatment, or after stopping treatment, for gynaecological investigation to exclude endometrial malignancy.
- Healthcare professionals should exercise caution in the simultaneous use of tibolone and anticoagulants such as warfarin, especially when starting or stopping tibolone.

Desmopressin nasal spray: removal of nocturnal enuresis indication

Nasal formulations of desmopressin are no longer indicated for primary nocturnal enuresis

- Nasal formulations of desmopressin should not be used for treatment of PNE.
- All patients with PNE should start oral desmopressin at the lowest recommended dose, which should be increased only if necessary to achieve control of symptoms.
- Healthcare professionals and patients should follow closely the advice on fluid intake in the Summary of Product Characteristics and the Patient Information Leaflet to avoid hyponatraemia.

Corticosteroids: early psychiatric side-effects

Risk of early psychiatric side effects is one of several important safety issues for healthcare professionals to discuss with patients and carers. Patients or carers should seek urgent medical advice in the event of any worrying symptoms.

Important information for patients and carers

- All patients (or their carers) should be informed of the important benefits of steroid treatment, and should be warned of the most important safety issues associated with acute and chronic use (see below).
- All patients (or their carers) who receive systemic steroids should receive a Patient Information Leaflet.
- All patients should seek urgent medical advice in the event of worrying symptoms (eg. suicidal thoughts) or illness while taking systemic steroids.
- Patients who take systemic steroids for more than 3 weeks or high-dose inhaled steroids should not stop treatment abruptly, and should be given a steroid card by their doctor or pharmacist.

Key safety issues to discuss with patients given systemic steroids and their carers

- **Endocrine:** adrenal suppression, Cushing's syndrome
- **Eye:** cataracts, glaucoma, and papilloedema
- **Gastrointestinal:** ulceration, pancreatitis, candidiasis
- **Immune:** increased susceptibility to infections – especially chickenpox
- **Musculoskeletal:** myopathy, osteoporosis, fractures, growth suppression
- **Neurological:** aggravation of epilepsy
- **Psychiatric:** psychosis; affective (eg, risk of suicide), behavioural, and cognitive disorders

NPCi has now been launched

NPCi is a new and radically different NHS learning resource developed by the National Prescribing Centre specifically for busy health care professionals and managers. The content covers prescribing, therapeutics & medicines management. The information is contained within a virtual building which makes searching for content really intuitive. You can access it here www.npci.org.uk/reception/reception.php Play the introduction movie to see what is on offer.

Human papillomavirus (HPV) vaccine

A second HPV vaccine has been launched by GSK called Cervarix. The DH has agreed in principle to introduce a vaccine against HPV for girls around 12 years of age. This is still subject to independent review of the cost-benefit analysis and any vaccination programme is unlikely to start before autumn 2008. Until this time, the advice issued by Derbyshire County PCT and Derby City PCT in December 2006 still stands.

The PCTs do not recommend HPV vaccine to be prescribed in primary care either on the NHS or privately.

Further information can be obtained from Sue Cohen, Consultant in Public Health, on 01246 514350 for Derbyshire County PCT or Laraine Tuplin, Assistant Director Medicines Management, on 01332 203102 Ext 6335 for Derby City PCT.

More on CV risk with glitazones

Lots more has recently been published about the adverse cardiovascular events that can occur with glitazones.

A systematic review and meta-analysis of the long-term risk of CV events with rosiglitazone¹ found that it significantly increased the risk of MI; RR 1.42 (CI 1.06 to 1.91; p=0.02) with a NNH of approximately 244. Rosiglitazone also increased the risk of heart failure; RR 2.09 (1.52 to 2.88; p<0.001), with a NNH of approximately 125.

The accompanying editorial points out that with many other available oral agents for diabetes, the potential benefit of glitazones requires re-evaluation². The authors also comment that glitazones may allow patients to control their blood glucose levels, but this may be doing patients a disservice if the complications of diabetes are not reduced through better glycaemic control.

In the same issue of JAMA is another meta-analysis evaluating the risk of CV events with pioglitazone³. Serious heart failure was more common in pioglitazone treated patients than in control patients; HR 1.41 (1.14 to 1.76; p = 0.002) with a NNH of approximately 200. The composite endpoint of death, MI or stroke appeared to be reduced; HR 0.82 (0.72 to 0.94; p = 0.005). However, there is a caveat to this result. As the InfoPOEM points out, this analysis was based only on studies provided by and conducted directly by the drug manufacturer. At least 20 other completed trials evaluating pioglitazone but not conducted by the manufacturer were not included in this analysis. In addition, a recent Cochrane review found no evidence of improved patient-orientated outcomes with pioglitazone treatment. Unlike for rosiglitazone, there is currently no evidence that pioglitazone increase the risk of ischaemic heart disease, but it does increase the risk of heart failure. This seems to be a class effect of the glitazones, which has been confirmed in another recent meta-analysis⁴.

Two editorials accompanying this study conclude that the regulatory authorities should be looking at patient-orientated outcomes and not surrogate outcomes^{5,6}. "Improved glycaemic control is not a surrogate for effective care of patients who have diabetes, which should be to reduce disability and increase lifespan"⁵. "Both clinicians and experts must acknowledge that it matters how (i.e. with what agent or agents) we achieve glucose control targets" and "Patients and society may end up paying dearly for drugs that cause more harm than good"⁶.

A reminder of the recommendations from CEPPaC:

- **maximise the use of metformin (initiate at low dose and titrate up slowly, consider using SR if appropriate) and avoid unnecessary use of glitazones**
- **glitazones should only be used as per the NICE guidance (third-line)**
- **and if a glitazone is indicated, pioglitazone would appear to have a better risk/benefit ratio (and is cheaper) and is the glitazone of choice.**

1. JAMA 2007; 298:1189-95
2. JAMA 2007; 298:1216-18
3. JAMA 2007; 298:1180-88
4. Lancet 2007; 370:1129-36
5. Lancet 2007; 370:1103-4
6. Lancet 2007; 370:1104-6