

## NEWSLETTER

Supporting the Derbyshire Health Community

Volume 6: Issue 4

July 2007

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### 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  |
|-----------------------------------|-----------------|---|
| Eflornithine cream                | July 2007       | DARK BROWN  |
| Etoricoxib/lumiracoxib/valdecoxib | July 2007       | DARK BROWN  |
| Ibandronate 150mg tablet          | July 2007       | DARK BROWN  |
| Rimonabant                        | July 2007       | DARK BROWN  |
| Rosuvastatin                      | July 2007       | DARK BROWN  |
| Eplerenone                        | July 2007       | LIGHT BROWN (when spironolactone not tolerated)   |
| Fentanyl lozenges                 | July 2007       | LIGHT BROWN (for breakthrough pain only when fentanyl patches indicated i.e. oral route not possible) |
| Metformin SR                      | June 2007       | GREEN (2 <sup>nd</sup> line use only)   |
| Disulfiram                        | June 2007       | AMBER   |
| Exenatide injection               | June 2007       | DARK BROWN  |
| Sitagliptin                       | June 2007       | DARK BROWN  |
| Testosterone patch (Intrinsa)     | May 2007        | DARK BROWN  |

### Travelling abroad with controlled drugs

Apologies but a ' / ' inadvertently replaced a full stop in the URL for the website with the information on controlled drug quantity limits in last month's newsletter.

The correct link is

[www.drugs.gov.uk/publication-search/drug-licences/travellers-controlled-drug-list](http://www.drugs.gov.uk/publication-search/drug-licences/travellers-controlled-drug-list) .

## **HPV vaccine**

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.

## **Feverish illness in children**

NICE has issued clinical guideline No. 47 'Feverish illness in children – assessment and initial management in children younger than 5 years'. One of the key priorities for implementation is 'antipyretic agents do not prevent febrile convulsions and should not be used specifically for this purpose'. Another recommendation is 'do not use paracetamol and ibuprofen at the same time, but consider using the alternative agent if the child does not respond to the first drug'.

The 'Quick reference guide' with all the key points can be found at <http://guidance.nice.org.uk/CG47/quickrefguide/pdf/English>

## **Aspirin dose for the prevention of CV disease**

For most patients with established atherosclerotic disease, aspirin is indicated and provides considerable benefit in terms of mortality. There is also clear reduction in risk of both MI and stroke. In the primary prevention setting, the situation is much less clear. Aspirin lowers the risk of MI but not stroke in men without a history of clinical atherosclerotic CV disease and seems to lower the risk of stroke but not MI in similarly healthy women. An effect on CV mortality has been difficult to document and continues to be debated<sup>1</sup>.

When it is indicated, what dose of aspirin should be used? A recent systematic review provides us with the answer<sup>2</sup>. The objective was to review the mechanism of action of aspirin and the clinical literature for relationships among aspirin dosage, effectiveness, and safety. The authors found that the available evidence, predominantly from secondary prevention studies, supports that dosages greater than 75mg to 81mg/day do not enhance effectiveness, whereas larger doses are associated with an increased incidence of bleeding events, primarily related to GI tract toxicity. They conclude that currently available clinical data do not support the routine, long-term use of aspirin dosages greater than 75-81mg/day in the setting of CV disease prevention. Higher doses do not better prevent events but are associated with increased risks of GI bleeding.

**Key point:** when indicated for CV prophylaxis, the recommended dose of aspirin is 75mg/day.

1. Arch Intern Med 2007; 167:535-6
2. JAMA 2007; 297:2018-24

## **Reducing stroke risk in AF**

Adjusted-dose oral anticoagulation and antiplatelet drugs are effective for the reduction of stroke risk in patients with non-valvular AF. However, oral anticoagulation is more effective according to the results of a recent meta-analysis<sup>1</sup>.

- Compared with control, adjusted-dose warfarin reduced the relative risk of stroke by 64% [95% CI 49% to 74%]. Absolute risk reductions were 2.7% per year (number needed to treat [NNT] for one year = 37) for primary prevention and 8.4% per year (NNT for one year = 12) for secondary prevention.
- Antiplatelet therapy reduced relative risk by 22% compared to control when data from all trials were included. When just data from aspirin trials were analysed (three quarters of the total), the relative risk reduction with aspirin compared to placebo was 19%; [-1% to 35%] and the absolute risk reductions 0.8% (NNT for one year = 125) for primary prevention and 2.5% (NNT for one year = 40) for secondary prevention.

- In direct comparisons, warfarin was more effective than antiplatelet therapy (relative risk reduction 37%; [23% to 48%]) and more effective than dual antiplatelet therapy with aspirin plus clopidogrel (RRR 40%; [18% to 56%]).
- Warfarin treatment was associated with an increased risk of intracranial bleeding compared with aspirin, although the absolute risk increase was small at 0.2% per year (NNH = 500). The risk of all-cause mortality was reduced by 26% with warfarin compared to control.

The authors conclude that adjusted-dose warfarin is significantly more effective at reducing stroke risk than antiplatelet agents, although these do have some benefit. Between 10 and 20% of patients with AF receive warfarin plus antiplatelet therapy; however the evidence available so far is insufficient to confirm the safety or efficacy of this approach. Overall, the authors suggest that their results reaffirm recommendations that patients with AF and a high risk of stroke will benefit significantly from adjusted-dose warfarin, with antiplatelet therapy being appropriate for those at low risk and those who cannot tolerate warfarin. Use the CHADS<sub>2</sub> scoring system or the stroke risk stratification algorithm from NICE guideline 36 to determine the level of stroke risk.

1. Ann Intern Med 2007; 146: 857-867

### **Once daily corticosteroid creams in atopic eczema**

A recent BMJ 'change practice' article advises us that the case for changing to once daily application of established topical corticosteroid (e.g. betamethasone valerate) is strong<sup>1</sup>. The author says that patients using moderate, potent, or very potent topical corticosteroids more than once a day should switch to once daily use.

He quotes the UK Health Technology Assessment report as the source of the evidence. Ten RCTs compared once daily versus more frequent application within the same potency group. None of the studies found clear evidence that applying topical corticosteroids more than once a day produced better overall clinical outcomes in eczema.

The key points from the paper are:

- Established topical corticosteroids such as betamethasone valerate have typically been used twice daily or more frequently for treating inflammatory episodes of eczema
- Reducing the frequency of application to once daily does not seem to result in loss of efficacy and could lead to fewer local side effects
- Using topical corticosteroids just once a day may be more convenient for patients and may save costs if established preparations are used

1. BMJ 2007; 334:1272

**Key point:** consider changing the computer defaults to once daily application.

### **Explaining risk reduction**

A study in Norway has compared different methods of describing to patients the risk reduction associated with taking certain medications<sup>1</sup>. They looked at reducing the risk of a heart attack and a hip fracture. The drugs involved were statins and bisphosphonates. Risk reduction was explained either in terms of NNTs (number needed to treat to prevent one event over a defined period), gain in disease-free life expectancy, or postponement of an adverse event. Patients were randomised to one method of explanation.

The use of NNTs resulted in the highest rate of consent to therapy. Smiley face charts and Paling's palette were provided in the January issue of this newsletter to help you explain NNTs and NNHs to patients.

1. Ann Intern Med 2007; 146: 848-56

### **Use of tramadol**

Tramadol has always been a less favoured analgesic by local pain teams. A recent audit of Adverse Drug Reaction (ADR) related admissions to Chesterfield Royal Hospital highlighted several areas for further

investigation. One of these was that admissions due to ADRs with tramadol had become more common in recent years, in parallel with increasing use.

Tramadol is a synthetic opioid that does not fit easily into the WHO 3-step analgesic ladder. Evidence to support the claim that tramadol has fewer opiate side effects and lower addiction potential is scarce and comparisons with other step 2 analgesics suggest tramadol is no more effective.

The most common side effects of tramadol are nausea, vomiting, somnolence, dizziness and constipation. There have been two CSM alerts warning of psychiatric reactions, including hallucinations and confusion (1995) and withdrawal syndrome after chronic use (1995). The CSM has advised that treatment with tramadol should be short-term and intermittent. Great caution is required in patients with a history of addiction or dependence and patients with a history of seizures should only take tramadol if there are compelling reasons to do so.

Tramadol is licensed for moderate to severe pain but is not suitable for control of cancer pain due to difficulties with dose titration – maximum dose of 400mg/day which should not be exceeded due to risk of convulsions – and the availability of other more effective strong opioids. Tramadol is more expensive than alternative Step 2 analgesics e.g. codeine and in view of the issues highlighted above, should not be used as a first choice agent.

A recent systematic review and meta-analysis on the use of tramadol for osteoarthritis found only small benefits for decreases in pain intensity, symptom relief and improved function with tramadol and the tramadol/paracetamol combination<sup>1</sup>.

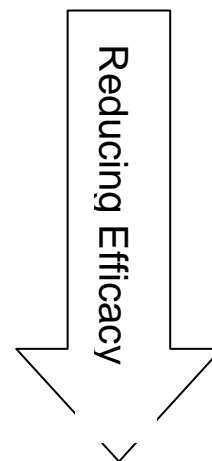
There is little information directly comparing the adverse effects of tramadol with codeine. When tramadol was compared to codeine in 65 patients undergoing elective intracranial surgery, there was a significantly higher incidence of post-operative nausea, vomiting and sedation with tramadol<sup>2</sup>.

The Oxford pain site on the Bandolier website provides interesting reading when considering evidence for analgesics. Acute pain studies into the use of single doses of tramadol 100mg have suggested a NNT (to give a reduction in pain by 50%) of about 4.8 (NNT = 8.3 for 50mg). Similarly codeine when used alone has a very poor NNT. However, when 1g of paracetamol is given with 60mg codeine the NNT is significantly improved (NNT=2.2)<sup>3</sup>.

### ***The Oxford league table of analgesic efficacy***

Number Needed to Treat (NNT) for at least 50% pain relief over 4-6 hours in patients with moderate to severe pain.

|                               |          |
|-------------------------------|----------|
| Paracetamol 1g + Codeine 60mg | NNT 2.2  |
| Diclofenac 50mg               | NNT 2.3  |
| Ibuprofen 400mg, 600mg        | NNT 2.4  |
| Paracetamol 1g                | NNT 3.8  |
| Tramadol 100mg                | NNT 4.8  |
| Codeine 60mg                  | NNT 16.7 |



- the most effective drugs have a LOW NNT of just over 2.
- all opioids work in synergy with paracetamol.
- common side effects of tramadol include nausea (>10%), dizziness (>10%), headache & drowsiness (1-10%).

Here are some of the examples from the ADR admission audit:

- Elderly lady with back pain had tramadol 50mg qds added into paracetamol and diclofenac 14 days prior to admission. Presented with confusion and severe constipation, thought to be due to the tramadol.
- Elderly lady with acute knee pain, taking warfarin, prescribed tramadol 50-100mg qds 6 days prior to admission. On admission the INR > 10. There are documented case reports of increased INRs in patients taking warfarin and tramadol and it is recommended that the INR is monitored with initial tramadol therapy.

- Elderly lady with OA taking co-codamol 30/500 2 qds prn (and also warfarin), prescribed tramadol 50mg qds for pain related to recent fall 3 days prior to admission. Presented with acute confusion, recurrent falls, bruising and pain. The addition of tramadol to codeine is not advisable. This patient had her warfarin switched to aspirin due to the risk of bleeding from falls.

These are the conclusions formed as a result of this audit:

- Codeine remains the first line choice for step 2 analgesia based on current evidence and cost. The overall adverse effect profile is similar to tramadol therefore similar cautions exist.
- Tramadol where appropriate should be added in to regimes containing first line analgesics (e.g. paracetamol or NSAIDs) rather than used alone. Use should be directed by existing guidance.
- Possible ADRs and their likelihood should be considered especially in the elderly. Patients should also be informed of any potential problems when being counselled.
- ADRs that are most commonly quoted in the literature are vomiting, nausea, dizziness and somnolence. These alone are unlikely to cause hospital admissions but may contribute to deterioration of vulnerable patients.
- Tramadol can potentially interact with other medication and should be used in caution in patients with epilepsy.
- The incidence of constipation in patients taking tramadol compared with those taking codeine is debatable. However, tramadol can cause constipation severe enough to warrant a hospital admission and preventative measures should be considered where appropriate.
- The addition of tramadol to codeine is not a recommended practice due to the increased incidence of adverse effects.
- ADRs causing admission to hospital or a prolonged stay should be reported to the MHRA via the yellow card system.

The following related issues about pain management were discussed at a prescribing sub-group meeting and it was agreed that:

- We should encourage patients to try regular, therapeutic doses of paracetamol. Many patients are nervous about taking the maximum dose of eight tablets per day and should be re-assured about the safety of this dose.
- Weak opioids should be added to non-opioids, rather than used alone.
- There are pros and cons of using combined paracetamol and codeine preparations as opposed to separate constituents. Using separate paracetamol and codeine allows the dose of codeine to be titrated, which will minimise side-effects. Using co-codamol 30/500 or 8/500 ensures both paracetamol & codeine are taken and will reduce the risk of codeine abuse, although the patient may end up on a sub-therapeutic dose of paracetamol or take more codeine than necessary.

We have devised a primary care audit for tramadol. Please get in touch if you would like a copy.

1. J Rheumatol 2007; 34:543-55
2. Myler's side effects of drugs. [www.elsevier.com](http://www.elsevier.com)
3. Bandolier, Oxford Pain Site. [www.jr2.ox.ac.uk/Bandolier/booth/painpag/index2.html](http://www.jr2.ox.ac.uk/Bandolier/booth/painpag/index2.html)

### **Insulin discontinuations**

Further to the advice given in last month's newsletter, here are some additions. Novo Nordisk will be phasing out the following insulins:

Velosulin (Human insulin) 10ml vial no longer available after 15<sup>th</sup> June 2007.

The following will no longer be available after 31<sup>st</sup> December 2007:

- Mixtard 10(Human insulin), Mixtard 20(Human insulin), Mixtard 40(Human insulin), Mixtard 50(Human insulin)
  - Pork Actrapid (Porcine insulin) 10 ml vial
  - Pork Mixtard 30 (Porcine insulin) 10ml vial
  - Pork Insulatard (Porcine insulin) 10ml vial
- For the few patients who are on Velosulin, they can be switched over to either Human Actrapid or Humulin S, both available in 10 ml vials with Humulin S also available in a 3ml cartridge.
  - Patients managed in secondary care will include a considerable number who are on either Pork insulin (long-standing Type 1 diabetes) or Mixtard 10 and Mixtard 20 (children with Type 1 diabetes) and should have their insulin changed over in the hospital clinic.
  - For those on Pork insulin managed in primary care Wochhardt UK Ltd. have a full range of equivalent Pork insulin (Hypurin Porcine) that is available in both 10ml vials and 3ml cartridges. The recommended pen device is the Autopen classic which is available in the 1 unit pen: 1-21 units or 2 unit pen: 2-42 units (please note that the cartridges are not compatible with the Autopen 24 pen).
  - For adults on Mixtard 10 or Mixtard 20 managed in primary care the recommendation would be to switch over to either Human Insulatard or Mixtard 30. The main reason for this is that those on Mixtard 10 and 20 will be using 3ml cartridges in the Novopen 3 and the Insulatard and Mixtard 30 will still be available in 3ml cartridges. This will make conversion much easier.
  - For those currently struggling to use a Novopen 3, e.g. dexterity problems and deterioration in cognitive function Human Insulatard and Mixtard 30 are also available in the disposable Innolet pen device.
  - For adults on Mixtard 40 a switch to Mixtard 30 would be least problematic. However, Humulin M3 or Humalog Mix50 are other alternatives.
  - For adults on Mixtard 50 switching to Humalog Mix50 (disposable pen or 3ml cartridge) would be the most comparable alternative.

The phasing out of currently available insulin is a commercial decision and the current discontinuations may not be the last. Although, an inconvenience for both patients and Health Care Professionals (HCPs) it should also be viewed as an opportunity to reassess whether the patients affected are on the most appropriate insulin regimen. It would be prudent to assess both glycaemic control and recent history of hypoglycaemia, particularly if severe hypoglycaemia (third party assistance has been required to aid recovery).

In a small number of cases analogue insulin such as Glargine or Novorapid may be deemed necessary e.g. in the presence of hypoglycaemia, particularly severe hypoglycaemia. There may be those that benefit from switching to a multiple dose regimen (basal/bolus) e.g. sub-optimal control on large doses of twice-daily mixed insulin.

Whenever insulin is changed from one type to another a reduction of 10% of the daily dose should be made. This may need to be up to 20% in the presence of severe hypoglycaemia. In those with marked sub-optimal control e.g. HbA1c >9.0% and pre-meal blood sugars mostly >10 mmol/l a reduction in dosage may not be necessary. In all cases where a change of insulin is necessary the solution should be discussed with and agreed by the patient. Where patients do not administer their own insulin then the carer whether it's a relative or HCP should also be involved in the decision making process.

Contributed by Mani Basi, Diabetes Nurse Consultant, Derby City PCT.

### **Choice of angiotensin-II receptor antagonist**

This was discussed at CEPPaC and it was agreed that candesartan should be the first-line A-II RA when one is indicated. A-II RAs are only recommended for use when an ACEI is indicated but truly cannot be tolerated. The most likely indication is for heart failure, where there is no alternative class of drug.

## **Blood pressure device project**

Dr Yasser Chaudhry, an F2 doctor on secondment to the Public Health Department, undertook this project while he was with us. Here is the background and his conclusions:

Blood pressure monitoring devices are widely used in primary care in the diagnosis and monitoring of a wide range of conditions. As such their maintenance is an important part in maintaining a high level of care to patients and treating their conditions appropriately. The gold standard in blood pressure measurement are mercury-based sphygmomanometers. However their use is no longer recommended due to environmental concerns. Most modern blood pressure devices can be divided into two types; aneroid or electronic. Increasingly automated blood pressure devices are used and these have variable accuracy. The British Hypertension Society (BHS) is currently involved in assessing the accuracy of these devices and provides a list of approved devices.

The Department of Health recommends yearly maintenance of blood pressure devices in accordance with manufacture's guidance. Purchasers of these devices are encouraged to review the pros and cons of each device and ensure adequate training of staff.

The aims of this project were:

- To gather information of the number of blood pressure devices throughout North Derbyshire.
- To determine the model and manufacturer of these devices
- To determine who services these devices and how often.
- To determine the number of people who have had formal training in blood pressure measurement.
- To determine if practices are aware of the approved list of these devices by the BHS.
- To determine if practices have different cuff sizes available.

A questionnaire was devised and e-mailed to all practice managers in the north of Derbyshire. The questionnaire was returned by e-mail for analysis. Two attempts were made to contact non-responders.

### *Results*

The response rate was only 38%.

- Omron was the most popular manufacturer (68%)
- Only 56% of devices in total were approved by the BHS
- Only 61% had a regular servicing contract
- The service at Newholme Hospital was the most popular provider of BP device servicing (46%).
- 3% of devices were serviced 6-monthly, 31% yearly, and 66% 2-yearly

### *Conclusion*

Due to the low responder rate of 38% the results may not be generalisable and the issue of responder bias is a possibility. There may be a difference in those practices that chose to respond and those that did not.

On average there were 13 blood pressure monitoring devices per practice with 83% of staff formally trained to use these devices. However, the results show that only 56% of the devices were approved by the BHS, whereas 94% of people were aware of the BHS list of approved devices. This is an area that needs further investigation as practices may be using inaccurate equipment.

The majority of servicing (46%) was conducted at Newholme hospital. This service is one commissioned by the PCT. However only 61% of practices had a regular servicing contract. Current recommendations are for once yearly servicing, although some practices performed servicing on an ad-hoc basis. It would make sense to have the same company servicing the equipment each time.

All of the practices have different cuff sizes available for the measurement of blood pressure. Although the questionnaire did not specify if every machine had a different size cuff, it was deemed acceptable as long as one was available for use.

Even though the response rate was low, this project highlights potential areas for improvement. It seems that the majority of practices are aware of the BHS list of approved devices, but for an unknown reason this has not

been reflected in their purchase of these devices. It should be emphasised that accurate measurement of blood pressure is key to managing conditions effectively and is in the patients' and practices' best interest.

The telephone number to contact Medical Engineering at Newholme Hospital is 01629 817917.

### Is use of Symbicort smart?

Symbicort is now licensed as maintenance and reliever therapy for adult asthma patients suitable for combination inhaler treatment. It is known as Symbicort SMART (**Symbicort Maintenance And Reliever Therapy**) and is being heavily promoted by the manufacturer. Use of Symbicort in this way is not in line with the British Asthma Guideline nor with the recent advice from the Commission on Human Medicines on the safe use of long-acting beta-agonists in asthma (see PACE Newsletter of January 2007).

The evidence was discussed at CEPPaC. It was agreed to await revision of national policy, the British Asthma Guideline, which is due later this year. In addition, Symbicort SMART only seems to have been trialed in select groups of high-risk patients. A key study was published in the Lancet last year<sup>1</sup>. Patients had to have had more than one severe asthma exacerbation in the 12 months before entry to the study; they were not your average asthma patients.

They all received Symbicort 160/4.5 (equivalent to 200/6) twice daily (is this a high enough inhaled corticosteroid [ICS] dose for someone with severe exacerbations?) and randomised to one of three as needed treatments: Symbicort 160/4.5, formoterol 4.5mcg (equivalent to 6mcg), or terbutaline 0.4mg. Symbicort SMART reduced severe exacerbations over one year compared with formoterol (NNT = 24 [16 to 65]) and terbutaline (NNT = 11 [9 to 16]) but is this surprising given that they received more ICS?

1. Lancet 2006; 368: 744-53

**Key point:** stick with the British Asthma Guideline recommendations

### Use of ICS in COPD

Further to the articles on COPD in the May issue of this newsletter, I have been asked to clarify the NICE guidance on the place of inhaled corticosteroids in COPD. I include the algorithm again with the relevant information added in the lower right-hand box. Nothing else has changed.

If prn salbutamol is insufficient –

