PRESCRIBING &
CLINICAL EFFECTIVENESS
NEWSLETTER
Supporting the Derbyshire Health Community
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JAPC Update

The Joint Area Prescribing Committee (JAPC) is a countywide group covering Derbyshire County PCT and Derby City PCT. It provides recommendations on drugs and medicines management issues.
RED drugs are those where prescribing responsibility lies with a hospital consultant or a specialist. AMBER drugs are those that are initiated within a hospital/specialist setting but are suitable for shared care with a GP under a shared care agreement. GREEN drugs are regarded as suitable for primary care prescribing. BROWN drugs are those that JAPC does not recommend for use, except in exceptional circumstances, due to lack of data on safety, effectiveness, and/or cost-effectiveness.

The most recent updates are in the table below; the full list is available at
http://www.derbyshirecountypct.nhs.uk/guidelines/default.asp
The guidelines, formulary chapters, newsletters, etc can now be found via this link.

Drug	Date considered	Decision
Clodronate sodium oral	June 2009	GREEN (specialist recommendation only)
Exenatide	June 2009	AMBER
Qlaira (estradiol + dienogest)	June 2009	BROWN
Sekivar (olmesartan + amlodipine)	June 2009	BROWN
Ustekinumab	June 2009	RED

Clopidogrel and PPIs – stop press

Further to the article in last month's newsletter, the MHRA and CHM have issued the following advice for healthcare professionals[1]:

- The need for PPI therapy in patients who are also taking clopidogrel should be reviewed at their next appointment: only use these medicines concomitantly when essential
- Prescribe PPIs strictly in line with their licensed indications
- Check that patients who are taking clopidogrel are not buying over-the-counter omeprazole.

1. Drug Safety Update Volume 2, Issue 11 June 2009

Re-evaluating blood glucose control in type 2 diabetes

Further to the article on sensible HbA_{1c} targets in the April edition, another editorial provides a call to re-evaluate the emphasis given to tight control of blood glucose in type 2 diabetes[1]. The authors suggest that an HbA_{1c} target of 7% to 7.5% is a reasonable aspiration for many patients and may be feasible to attain without increasing the risk of harm and the need for multiple hypoglycaemic agents. However, importantly, this will not apply to all people with type 2 diabetes. Blood glucose targets should be agreed with the patient and can be adjusted – up or down – according to the burden of treatment, side effects, and the patient's context, values and preferences. For

most people, keeping blood glucose levels below about 10mmol/L will prevent symptoms associated with hyperglycaemia. This is equivalent to an HbA_{1c} of about 9%, and the authors suggest that it may be more desirable for policy makers to use HbA_{1c} >9% as an indicator of possible inadequate care, rather than setting targets which may encourage less patient-centred care.

The NPC recommends the following action[2]:
"Health professionals and people with type 2 diabetes should prioritise lifestyle interventions (losing weight, healthy diet, stopping smoking if relevant), blood pressure control as well as taking a statin, aspirin if cardiovascular disease is present, and metformin. We should follow NICE guidance and agree individual targets for HbA_{1c}, which could be above 6.5%, taking into account patient preferences and the balance of likely benefits and burden of treatment."

See the new JAPC guideline on glucose control in type 2 diabetes.

1. Glycemic control in type 2 diabetes: time for an evidence-based about-face? www.annals.org/cgi/content/full/0000605-200906020-00118v1
2. www.npci.org.uk/blog/?p=336

Stroke risk in paroxysmal atrial fibrillation

A recent study investigated whether there are differences in stroke risk between paroxysmal AF and permanent AF[1]. All patients treated for both types of AF during 2002 at one of Scandinavia's largest hospitals were followed up for 3.6 years regarding incidence of stroke.

The incidence of ischaemic stroke was similar in paroxysmal AF and permanent AF - 26 vs 29 events/1000 patient years (HR 1.09 [95% CI 0.71 to 1.61]). The hazard ratio (HR) for any stroke, ischaemic or haemorrhagic, was 0.89 (CI 0.61 to 1.30). Compared with the general population, ischaemic stroke was twice as common as expected in paroxysmal AF after standardisation for age and sex. Paroxysmal AF patients who took warfarin had approximately half as many ischaemic strokes as those who did not take warfarin (HR 0.44 [CI 0.30 to 0.65]).

The authors concluded that it is important to increase the use of anticoagulants among paroxysmal AF patients in accordance with current guideline recommendations. They also noted "our study confirms earlier studies regarding the efficacy of the $CHADS_2$ scoring system for the proper identification of patients at high-risk as well as low-risk for ischaemic stroke".

A reminder of the $CHADS_2$ scoring system:

- $CHADS_2$ assigns 2 points to a history of stroke or TIA and 1 point each for any of the following: confirmed diagnosis of heart failure, history of hypertension, age 75 or older, and diabetes mellitus. Hence the acronym:
  - C CHF
  - H Hypertension
  - A Age over 75
  - D Diabetes
  - S_2 Stroke/TIA (2 points)

- E.G. An 82 year-old (+1) with hypertension (+1) and a prior stroke (+2) would have a $CHADS_2$ score of 4.

- $CHADS_2$ score — Adjusted stroke rate per 100 patient years

$CHADS_2$ score	Adjusted stroke rate per 100 patient years
0	1.9
1	2.8
2	4.0
3	5.9
4	8.5
5	12.5
6	18.2

Someone with a $CHADS_2$ score of 3 or more should be offered warfarin. For a score of 0 they are suitable for aspirin. For a score of 1 or 2, aspirin or warfarin may be suitable and the options discussed with the patient.

NNTs from the $CHADS_2$ Score
These may aid discussion with the patient.

$CHADS_2$ Score	Adjusted annual stroke rate	20% RRR with aspirin	60% RRR with warfarin
0	1.9%	1.5%	0.76%
1	2.8%	2.24%	1.12%
2	4.0%	3.2%	1.6%
3	5.9%	4.7%	2.36%
4	8.5%	6.8%	3.4%
5	12.5%	10.0%	5.0%
6	18.2%	14.56%	7.28%

NNT to prevent a stroke over one year for aspirin or warfarin, compared to no treatment, for each $CHADS_2$ score.

$CHADS_2$ Score	Aspirin NNT	Warfarin NNT
0	250	88
1	179	60
2	125	42
3	83	28
4	59	20
5	40	13
6	27	9

It is reasonable to assume that the risk of bleeding from drug therapy is independent of the $CHADS_2$ score. If warfarin is used instead of aspirin, for every 1,000 people treated for a year, there will be nine more major bleeds. This gives a NNH of 111. Hence, one can estimate the risk/benefit ratio for using warfarin instead of aspirin for each $CHADS_2$ score.

1. Eur Heart J advance access published January 27, 2009 doi:10.1093/eurheartj/ehn599

Anticoagulation intensity and outcomes
The purpose of anticoagulant therapy is to reduce the risk of thrombosis with the lowest possible risk of bleeding. A systematic review and meta-analysis has sought to determine the association between anticoagulation intensity and the risk of haemorrhagic and thromboembolic events[1]. Nineteen studies were included.

They found a strong association between anticoagulation intensity and the risk of haemorrhage and thromboembolic events. The risk of haemorrhage significantly increased when the INR exceeded 3. The risk of thromboemboli was greatest when the ratio was below 2. Overall, patients were safest with a ratio of 2-3.

When both haemorrhagic and thromboembolic events are considered, their data showed that patients were safer with a ratio slightly above, rather than below, the therapeutic range of 2-3. The authors advise “Physicians should be aware of this finding and should adjust their clinical practices accordingly by aggressively correcting sub therapeutic ratios and avoiding overreaction to ratios that narrowly exceed 3”.

1. CMAJ 2008; 179:235-44

Clopidogrel plus aspirin in AF
Warfarin reduces the risk of stroke in patients with AF but is unsuitable for some patients and aspirin is recommended instead. Would aspirin plus clopidogrel be a better option? ACTIVE W has previously compared aspirin plus clopidogrel with oral anticoagulation[1]. Oral anticoagulation was shown to be superior to aspirin plus clopidogrel. ACTIVE A compared aspirin plus clopidogrel with aspirin alone in patients with AF who were at increased risk for stroke and for whom therapy with a vitamin K antagonist was considered unsuitable[2].

ACTIVE A was a randomised, double-blind, multicentre trial performed at 580 centres in 33 countries. By means of an interactive telephone system, patients in ACTIVE A were randomly assigned in equal numbers, in blocks of

varying sizes, to receive clopidogrel at a dose of 75 mg or matching placebo once daily, in a double-blind fashion. All patients also received aspirin (recommended dose, 75 to 100 mg per day). The primary study outcome was any major vascular event (stroke, non-central nervous system systemic embolism, myocardial infarction, or death from vascular causes). The most important secondary outcome was stroke.

Results

- A total of 7,554 patients were enrolled and were randomly assigned to receive clopidogrel (3,772) or placebo (3,782) in addition to aspirin.
- The median duration of follow-up for both groups was 3.6 years.
- The mean age was 71 years; 58.2% were men. AF was permanent in 63.7%, persistent in 14.0%, and paroxysmal in 22.1%. The mean $CHADS_2$ score was 2.0.
- Rates of discontinuation of the study medication were 16.3% and 15.2% for clopidogrel and placebo, respectively, at 1 year, increasing to 39.4% and 37.1% at 4 years. All patients were receiving aspirin at the time of randomisation, with use decreasing in both groups to 92.9% at 1 year and 81.1% at 4 years.
- The primary end point occurred in 832 patients receiving clopidogrel (22.1%) as compared with 924 patients receiving placebo (24.4%) (RR, 0.89; 95% confidence interval [CI], 0.81 to 0.98; P=0.01). This is an NNT of 43.
- The reduction in the risk of major vascular events in the clopidogrel group was primarily due to a reduction in the incidence of stroke. Stroke occurred in 296 patients receiving clopidogrel (7.8%) and 408 patients receiving placebo (10.8%) relative risk, 0.72; 95% CI, 0.62 to 0.83; P<0.001). This is an NNT of 33.
- There was no reduction in MI (RR 0.78 [0.59 to 1.03]), non-central nervous system systemic embolism (RR 0.96 [0.66 to 1.40]), death from vascular causes (RR 1.00 [0.89 to 1.12]), or death from any cause (RR 0.98 [0.89 to 1.08]).
- Major bleeding occurred in 251 patients receiving clopidogrel as compared with 162 patients receiving placebo (6.7% vs. 4.3%; RR 1.57; 95% CI, 1.29 to 1.92; P<0.001). This is an NNH of 42.
- Minor bleeding occurred in 10.8% and 4.6%, respectively; RR 2.42 (2.03 to 2.89), p<0.001. This is an NNH of 16.
- With the combination of major vascular events (the primary outcome) and major haemorrhage, there was no significant difference between the overall event rate with aspirin plus clopidogrel and the rate with aspirin alone (968 vs. 996 events; RR 0.97; 95% CI, 0.89 to 1.06; P=0.54).

Discussions/implications

- The paper reports the results as "the addition of clopidogrel to aspirin reduced the rate of major vascular events from 7.6% per year to 6.8%. This was primarily due to a reduction in the rate of stroke. The rate of major haemorrhage increased with the addition of clopidogrel, from 1.3% to 2.0% per year."
- When the NNTs and NNHs are compared, they are similar and appear to cancel each other out.
- ACTIVE A does not provide strong enough evidence to recommend clopidogrel plus aspirin instead of aspirin alone for patients with AF unsuitable for oral anticoagulation.

Key point: JAPC does not recommend the combination of aspirin + clopidogrel for people with AF.

1. Lancet 2006; 367:1903-12
2. N Engl J Med 2009; 360: 2066-78

Colesevelam

DTB has recently reviewed the evidence for colesevelam[1]. This is their conclusion:

"Small short-term studies indicate that ▼colesevelam, a treatment for primary hypercholesterolaemia, lowers LDL-cholesterol in a dose-dependent manner both as monotherapy and also in combination with statins. The reduction on monotherapy is substantially less than that with statins alone (even when they are taken at suboptimal doses). Also, published studies of colesevelam have not assessed clinical outcomes and there is no longer-term safety data, so no firm conclusions can be drawn on colesevelam's role in decreasing cardiovascular risk. Like other bile acid sequestrants, the drug can cause gastrointestinal unwanted effects and may aggravate hypertriglyceridaemia. Also, the need to take a large number of colesevelam tablets daily may compromise adherence. For all these reasons, we cannot recommend colesevelam in the management of patients with hypercholesterolaemia".

1. DTB 2009; 47(5):53-55

Update on treatments for headlice

Here is the conclusion of a recent review by DTB[1]:

"Treatments for head lice include conventional insecticides (e.g. malathion, phenothrin); medical devices (e.g. fine tooth louse combs); and topical preparations working by a physical rather than chemical mode of action (e.g. dimeticone). None of these treatments eradicate head lice in all users. Potential disadvantages of conventional insecticides include unwanted effects and the development of resistance by lice, and combing regimens are time-consuming. Recent data on dimeticone 4% (Hedrin) showed similar efficacy to that in previously published studies (around 70%), so it remains a reasonable first-line alternative to chemical insecticides.

Isopropyl myristate 50% in cyclomethicone solution (Full Marks solution) is a new treatment option for head lice infestation with a physical mode of action, which requires a 10-minute treatment time. This is much shorter than the standard contact times of several hours for conventional insecticides or dimeticone. The product has a physical rather than a chemical mode of action and therefore lice are less likely to develop resistance to it than to conventional neurotoxic insecticides. Published studies of the treatment have suggested a cure rate of up to 82%. However, it has not been directly compared with other insecticides generally used for the treatment of patients with head lice in the UK, with dimeticone or with wet combing methods such as Bug Busting. Until such comparative data are available, it cannot be recommended in preference to established treatments for patients with head lice."

1. DTB 2009; 47 (5): 50-52

Olive oil treatment for cradle cap- can it worsen the condition?

This question has been answered by a UK Medicines Information Q&A[1].

Summary

- Cradle cap in infants is a form of seborrhoeic dermatitis. Treatment is often unnecessary but suggested management options include the use of baby oil, baby shampoo, or vegetable oils, such as olive oil.
- The cause of seborrhoeic dermatitis is unknown but *Malassezia* yeasts, in particular *Malassezia furfur* have been implicated.
- *Malassezia* yeasts thrive in oily environments, especially vegetable oils. It has been suggested that olive oil can encourage the proliferation of *Malassezia furfur* and worsen the condition.
- No evidence has been found that the use of olive oil for cradle cap leads to a worsening of the condition in clinical practice, and there seems no reason to change current recommendations. If the condition is not improving however, it may be preferable to use an alternative baby oil based on mineral oils.

Limitations

These recommendations relate solely to the management of cradle cap in healthy, immunocompetent infants. The data in this area are limited and of poor quality.

1. UKMi Q&A 264.1

Drug safety update

This can be found at www.mhra.gov.uk/publications/safetyguidance/drugsafetyupdate/index.htm

Here are some key points from the May issue.

Aliskiren (Rasilez▼): risk of angioedema and renal dysfunction

Angioedema may occur with use of aliskiren and it should not be used in patients who have previously had angioedema after using it. Aliskiren should be used with caution in patients taking NSAIDs, or in patients who may be at increased risk of acute renal failure such as patients with renal artery stenosis or with risk factors for renal dysfunction.

Advice for healthcare professionals:

- Aliskiren should not be used for the management of high blood pressure in patients who have previously had angioedema when using it.

- Patients should be advised that they should stop aliskiren and seek medical advice straight away if they develop symptoms of angioedema, such as swelling of the face, eyes, lips or tongue (or both), hands and feet, or difficulty breathing or swallowing
- Extreme caution is required if aliskiren is used in patients with renal artery stenosis or conditions predisposing to kidney dysfunction (such as hypovolaemia, heart disease, liver disease, or kidney disease) because of a risk of acute renal failure. If any signs of renal failure occur, aliskiren should be promptly discontinued
- NSAIDs may reduce the antihypertensive effect of aliskiren
- Elderly patients or patients with compromised renal function may be at risk of further deterioration of renal function if NSAIDs and aliskiren are used together

Aliskiren is a BROWN drug in Derbyshire

ACE inhibitors and angiotensin II receptor antagonists: recommendations on use during breastfeeding

ACE inhibitors and angiotensin II receptor antagonists should not be used by breastfeeding mothers in the first few weeks after delivery because of possible profound neonatal hypotension; preterm babies may be at particular risk. In mothers who are breastfeeding older infants, the use of captopril, enalapril, or quinapril may be considered.

Advice for healthcare professionals:
ACE inhibitors:
- Captopril, enalapril, or quinapril: use in breastfeeding is not recommended in the first few weeks after delivery because of the possibility of profound neonatal hypotension; preterm babies may be at particular risk. Use may be considered when the infant is older if an ACE inhibitor is necessary for the mother; careful follow-up of the infant for possible signs of hypotension is recommended.
- Ramipril, lisinopril, fosinopril, trandolapril, moexipril, or perindopril: use in breastfeeding is not recommended. Alternative treatments with more established safety profiles during breastfeeding are preferable, especially while nursing a newborn or preterm baby.

All angiotensin II receptor antagonists:
- Use in breastfeeding mothers is not recommended. Alternative antihypertensive treatments with more established safety profiles during breastfeeding are preferable, especially while nursing a newborn or preterm baby.

Non-steroidal anti-inflammatory drugs: reminder on renal failure and impairment

Caution should be exercised when using NSAIDs in patients with established, or a risk of, renal impairment.

Advice for healthcare professionals
- Patients at risk of renal impairment or renal failure (particularly elderly people) should avoid NSAIDs if possible. If NSAID treatment is absolutely necessary, then the lowest effective dose for the shortest possible duration should be used to control symptoms. The renal function of such patients should be carefully monitored during NSAID treatment.
- It is important to consider other concomitant disease states, conditions, or medicines that may precipitate reduced renal function when prescribing NSAIDs

<u>Oral salicylate gels for children</u>
The MHRA has reviewed the safety of oral topical salicylate-containing products after publication of a case report of suspected Reye's syndrome associated with use of a dental gel that contained choline salicylate in a 20-month-old child[1].

The review concluded that the symptoms were not consistent with Reye's syndrome and were more likely to reflect salicylate toxicity, but nevertheless showed that substantial systemic levels of salicylate were achievable after overuse of salicylate-containing dental gels. The Commission on Human Medicines acknowledged that although there is only a theoretical risk of Reye's, these products should be contraindicated in those younger than age 16 years in line with other oral salicylate-containing preparations. This decision affects four products currently

licensed in the UK: Bonjela; Bonjela Cool Mint; Dinnefords Teejel Gel (not marketed); and Pyralvex. In those younger than age 16 years, these products are no longer indicated for pain associated with infant teething, orthodontic devices, cold sores, or mouth ulcers.

Advice for healthcare professionals:

- Please advise parents and patients that those younger than age 16 years should use alternative treatments or products. There are several dental gels available which contain a local anaesthetic/mild antiseptic.
- For infant teething, gentle pressure with something cool such as a chilled teething ring may help relieve teething pain.
- For pain associated with orthodontic devices, salt water mouthwashes are recommended for sore areas. For discomfort arising from tooth movement, a paracetamol-based painkiller is recommended.

1. Drug Safety Update, Volume 2 Issue 10, May 2009

Risks with oral anti-cancer medicines

In January 2008 the NPSA issued a Rapid Response Report on the Risks of incorrect dosing of oral anti-cancer medicines. This was to be actioned by 22 July 2008. Following the report JAPC made the decision to classify all oral chemotherapy drugs for the indication of cancer as RED, i.e. for specialist use only. It has been brought to the attention of JAPC that there is continued prescribing of these drugs in primary care. A particular issue is with hydroxycarbamide (hydroxyurea). **JAPC has reiterated that no oral chemotherapy agents for cancer are to be prescribed or dispensed in primary care.**

The term oral anti-cancer medicines include those with direct anti-tumour activity, which currently includes: bexarotene, busulfan, capecitabine, chlorambucil, cyclophosphamide, estramustine, etoposide, fludarabine, hydroxycarbamide, idarubicin, lomustine, melphalan, mercaptopurine, methotrexate, mitotane, procarbazine, tegafur/uracil, temozolomide, tioguanine, treosulfan, vinorelbine. In addition targeted therapies such as the kinase inhibitors: dasatinib, erlotinib, imatinib, sorafenib, and sunitinib are also included. The use of this term does not include hormonal or anti-hormonal therapy used to treat cancer.

The report contained the following advice. Doctors, nurses, pharmacists and their staff must be made aware that the prescribing, dispensing and administering of oral anti-cancer medicines should be carried out and monitored to the same standard as injected therapy. This requires that:

- Healthcare organisations should prepare local policies and procedures that describe the safe use of these oral medicines.
- Treatment should be initiated by a cancer specialist.
- All oral anti-cancer medicines should be prescribed only in the context of a written protocol and treatment plan.
- Non-specialists who prescribe or administer on-going oral anti-cancer medication should have ready access to appropriate written protocols and treatment plans including guidance on monitoring and treatment of toxicity.
- Staff dispensing oral anti-cancer medicines should be able to confirm the prescribed dose is appropriate for the patient, and that the patient is aware of the required monitoring arrangements, by having access to information in the written protocol and treatment plan from the hospital where treatment is initiated and advice from a pharmacist with experience in cancer treatment in that hospital.
- Patients should be fully informed and receive verbal and up-to-date written information about their oral anticancer therapy from the initiating hospital. This information should include contact details for specialist advice, which can be shared with non-specialist practitioners. Written information including details of the intended oral anti-cancer regimen and treatment plan including arrangements for monitoring, taken from the original protocol, should be given to the patient. When shared with pharmacists and dispensing staff, this would enable the above dispensing requirements to be satisfied.
- Full use should also be made of NHS cancer centre web sites to provide information for healthcare staff, patients and carers to ensure the safe use of oral anti-cancer medicines.

"The above guidance is primarily intended to promote the safe use of the medicines listed to treat cancer. Where the use of these medicines is for non-cancer treatment, a risk assessment should be undertaken and the guidance applied as appropriate."

JAPC is in the process of developing appropriate shared care arrangements for selected oral chemotherapy agents for non-cancer indications.

Malaria prophylaxis

As the holiday season fast approaches, I have been asked to include a reminder of the guidance regarding prescribing of malaria prophylaxis.

- The Department of Health issued guidance (FHSL(95)7) that medication for malaria prophylaxis may **NOT** be reimbursed under the NHS.
- Some medicines for the prevention of malaria are available for purchase "over the counter" at community pharmacies.
- Those which are prescription only medicines (POMs) should be prescribed on a private prescription.

(**NOTE :** When issuing a private prescription or if they provide the medication, practices are allowed to charge a fee for one but **NOT** for both).

Advice for travellers

- Local community pharmacists have access to up to date advice about appropriate prophylactic regimes and can advise travellers accordingly.
- Patients should be advised to purchase sufficient prophylactic medicines to cover the period of their travel :
  - commencing one week (two and a half weeks for mefloquine) prior to travel, so that if adverse events occur there will be time to switch to an alternative before departure
  - continuing for at least four weeks on return.

(NOTE : Malarone is an exception being started 1-2 days before travel and stopped one week after return).

- The importance of mosquito nets, suitable clothing and insect repellents to protect against being bitten should be stressed.
- Principles of malaria prevention – no chemoprophylactic regimen can be considered 100% effective.

Remember the ABCD rule:

A. **A**wareness of the risk, by traveller and doctor.
B. Reducing **B**ites from anopheline mosquitoes.
C. Using appropriate **C**hemoprophylactic drugs.
D. Awareness of the residual risk, and prompt **D**iagnosis and treatment of clinical malaria.