

## 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 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, 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:

<b>Drug</b>	<b>Date considered</b>	<b>Decision</b>
Adefovir	June 2008	RED
Dabigatran	June 2008	RED
Disofrol	June 2008	BROWN
Fulvestrant	June 2008	RED
Lamivudine	June 2008	RED
Nebido injection (only on consultant recommendation)	June 2008	GREEN
Retapamulin 1% ointment	June 2008	BROWN
Tenofovir	June 2008	RED
VSL#3 (pouchitis only)	June 2008	AMBER
Virulite CS cold sore machine	April 2008	BROWN
Eucreas (vildagliptin + metformin)	April 2008	BROWN
Vildagliptin	April 2008	BROWN
Suboxone (buprenorphine + naloxone)	April 2008	BROWN

### Post-trial drug supply

If a patient is given a new drug in a clinical trial, are they guaranteed to continue to receive the drug once the trial is completed? We were asked to discuss this issue at JAPC.

There is no obligation on a PCT to fund the trial drug after completion of the research. When a clinical trial is planned, patient expectations should not be raised that when the trial ends the treatment will be continued with NHS funding. Ethics and Research & Development Committees have a responsibility to ensure that this information is included in the trial protocol, patient information leaflet and the consent form.

JAPC does not support the continued use of trial drugs after the trial had finished unless this had been specifically agreed beforehand.

## Lipid lowering

**There are no cholesterol targets, simply offer simvastatin 40mg daily to the defined high risk groups.**

The NICE clinical guideline on lipid modification has now been published. This is not a mandatory document and is currently being considered by the PCTs. It is the responsibility of the PCTs to set their own local priorities. This guideline does not provide any new trial evidence beyond that already appraised by the PCTs.

If a statin is indicated, NICE recommends simvastatin 40mg daily. Despite rumours to the contrary this guideline does **not** set a new national target for cholesterol of <4 or LDL-C target if <2. It says "In people taking statins for secondary prevention, consider increasing to simvastatin 80 mg or a drug of similar efficacy and acquisition cost if a total cholesterol of less than 4 mmol/litre or an LDL cholesterol of less than 2 mmol/litre is not attained. Any decision to offer a higher intensity statin *should take into account informed preference, comorbidities, multiple drug therapy, and the benefit and risks of treatment.*"

The statement highlighted in italics is crucial. If the clinician explains to the patient that there is no evidence that simvastatin 80 reduces clinical outcomes more than simvastatin 40 but increases the risk of adverse events<sup>1</sup>, why would any person want to take it? NICE is quite clear that the use of any other option to simvastatin 80 (e.g. atorvastatin 80) would not be cost-effective.

The key message from the PCTs is that the Statin Policy still stands and should continue to be followed.

1. JAMA 2004; 292: 1307-16

## ACE inhibitors in CV disease – unbeatable?

ACE-inhibitors have been shown to be effective in reducing the risk of cardiovascular (CV) events and death in patients at high risk of these events. The evidence for angiotensin receptor blockers (ARBs) either alone or added to an ACE-inhibitor is less clear. The ONTARGET study compared the ARB telmisartan 80 mg/day, ramipril 10 mg/day and the combination of both drugs in patients at high risk of CV events but who did not have heart failure<sup>1</sup>.

After a median follow-up of 56 months, there was no significant difference in the rates of the primary outcome (a composite of death from cardiovascular causes, MI, stroke or hospitalisation for heart failure). The rate was 16.5% in the ramipril group, 16.7% in the telmisartan group (RR compared to ramipril 1.01, 95% confidence intervals [CI] 0.94 to 1.09) and 16.3% in the combination group (RR compared to ramipril 0.99, 95%CI 0.92 to 1.07).

More patients in the ramipril group than in the telmisartan group stopped treatment due to cough (4.2% vs 1.1%, RR 3.8, Number Needed to Harm [NNH] 32) or angioedema (0.3% vs 0.1%, RR 3, NNH 500) but more patients in the telmisartan group stopped treatment due to hypotensive symptoms (2.7% vs 1.7%, RR 1.6, NNH 100). Patients taking the combination therapy were more likely than those taking ramipril alone to discontinue treatment due to hypotensive symptoms (4.8% vs 1.7%, RR 2.8, NNH 32), diarrhoea (0.5% vs 0.1%, RR 5, NNH 250) and renal impairment (1.1% vs 0.7%, RR 1.58, NNH 250).

**Despite increased lowering of blood pressure, the combination did not reduce the risk of CV events, as compared with an ACEI, but was associated with additional adverse effects.** As the accompanying editorial says "the ONTARGET study confirms beyond doubt, that ARBs are not better than ACE inhibitors at reducing fatal and nonfatal cardiovascular events".

Taking into account evidence of efficacy, tolerability and cost, the first choice angiotensin-system drug for people at high risk of CV disease, with or without heart failure, is an ACE-inhibitor such as ramipril. ARBs are an alternative in patients truly not able to tolerate ACE-inhibitors due to cough, but note that cough can still occur with ARBs and also that ONTARGET suggests that ARBs are more likely to cause hypotensive symptoms.

1. N Engl J Med 2008; 358: 1547-59
2. N Engl J Med 2008; 358: 1615-16

## Prophylaxis against infective endocarditis

NICE has recently issued a clinical guideline on prophylaxis against infective endocarditis<sup>1</sup>. This guidance represents a major shift from current accepted practice and therefore it is essential that both appropriate and consistent information is provided to healthcare professionals and patients alike. **The guideline recommends that antibiotic prophylaxis is no longer offered routinely for defined interventional procedures.**

## **Summary of recommendations**

### *Adults and children with structural cardiac conditions*

Regard people with the following cardiac conditions as being at risk of developing infective endocarditis:

- acquired valvular heart disease with stenosis or regurgitation
- valve replacement
- structural congenital heart disease, including surgically corrected or palliated structural conditions, but excluding isolated atrial septal defect, fully repaired ventricular septal defect or fully repaired patent ductus arteriosus, and closure devices that are judged to be endothelialised
- hypertrophic cardiomyopathy
- previous infective endocarditis.

### *Advice*

**Offer** people at risk of infective endocarditis clear and consistent information about prevention, including:

- the benefits and risks of antibiotic prophylaxis, and an explanation of why antibiotic prophylaxis is no longer routinely recommended
- the importance of maintaining good oral health
- symptoms that may indicate infective endocarditis and when to seek expert advice
- the risks of undergoing invasive procedures, including non-medical procedures such as body piercing or tattooing.

### *When to offer prophylaxis*

- **Do not offer** antibiotic prophylaxis against infective endocarditis:
  - to people undergoing dental procedures
  - to people undergoing non-dental procedures at the following sites:
    - upper and lower gastrointestinal tract
    - genitourinary tract; this includes urological, gynaecological and obstetric procedures, and childbirth
    - upper and lower respiratory tract; this includes ear, nose and throat procedures and bronchoscopy.
- **Do not offer** chlorhexidine mouthwash as prophylaxis against infective endocarditis to people at risk undergoing dental procedures.

### *Managing infection*

- **Investigate and treat promptly** any episodes of infection in people at risk of infective endocarditis to reduce the risk of endocarditis developing.
- **Offer** an antibiotic that covers organisms that cause infective endocarditis if a person at risk of infective endocarditis is receiving antimicrobial therapy because they are undergoing a gastrointestinal or genitourinary procedure at a site where there is a suspected infection.

Here are two explanatory documents that may be useful in discussion with patients:

[www.nice.nhs.uk/nicemedia/pdf/CG064UNGWord.doc](http://www.nice.nhs.uk/nicemedia/pdf/CG064UNGWord.doc)

[www.nelm.nhs.uk/Record%20Viewing/viewRecord.aspx?id=592059](http://www.nelm.nhs.uk/Record%20Viewing/viewRecord.aspx?id=592059)

1. NICE Clinical Guideline 64, March 2008. [www.nice.org.uk/nicemedia/pdf/CG64NICEguidance.pdf](http://www.nice.org.uk/nicemedia/pdf/CG64NICEguidance.pdf)

## **Long-term pharmacotherapy for obesity**

An updated meta-analysis has shown that the available drugs only have a modest effect on weight reduction<sup>1</sup>. Each has a specific (but different) adverse effect profile. There are no data evaluating the effect of anti-obesity drugs on morbidity and mortality end points.

Thirty trials of one to four years' duration met the inclusion criteria for the meta-analysis. Compared with placebo, orlistat reduced weight by 2.9kg, sibutramine by 4.2kg, and rimonabant by 4.7kg. The NNT for those achieving a 10% weight loss (that which is thought likely to meaningfully reduce risk) was 8 for orlistat, 6 for sibutramine, and 5 for rimonabant.

Patients receiving orlistat are more likely to experience gastrointestinal adverse events and to discontinue because of this. Compared with placebo, sibutramine increased systolic BP by 1.7mmHg and diastolic BP by 2.4mmHg. Insomnia, nausea, dry mouth, and constipation occurred at a frequency of 7-20%. With rimonabant, the most worrying adverse effect was an increased incidence of psychiatric disorders (depression, anxiety, irritability, aggression), which occurred in 6% of patients.

1. BMJ 2007; 335:1194-99

## **Drug safety update**

This can be found at [www.mhra.gov.uk/drugsafetyupdate](http://www.mhra.gov.uk/drugsafetyupdate). Here are some of the key points from the May issue.

**Rimonabant (Acomplia):** depression; psychiatric adverse reactions.

Depressive reactions may occur in up to 10% of patients treated with rimonabant. Rimonabant is contraindicated in patients with ongoing major depression or those taking antidepressants. Prescribers are encouraged to take a detailed history from patients before prescribing rimonabant to assess risk factors for psychiatric reactions, particularly depression. However, depressive reactions may occur in patients who have no obvious risk factors, apart from obesity itself.

*Advice for healthcare professionals:*

- Depressive reactions may occur in up to 10% of patients treated with rimonabant
- Depressive reactions may occur in patients who have no obvious risk factors, apart from obesity itself. Evidence suggests that many patients who develop such reactions will do so within 2 weeks of starting treatment
- Rimonabant is contraindicated in patients with ongoing major depression or those taking antidepressants
- Prescribers are encouraged to take a detailed history from patients before prescribing rimonabant to assess risk factors for psychiatric reactions, particularly depression

**Exenatide (Byetta):** risk of acute pancreatitis.

Spontaneous reports of acute pancreatitis have been received in associated with exenatide. If pancreatitis is suspected, exenatide and other potentially suspect medicines should be discontinued.

*Advice for healthcare professionals:*

- Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain; back pain may also be present
- If pancreatitis is suspected, exenatide and other potentially suspect medicines should be discontinued

## **Self-monitoring of blood glucose**

The question of whether people with type 2 diabetes who do not use insulin should monitor their own blood glucose has been debated over the years in the PACE Newsletter. In 2007, the BMJ published the results of the DiGEM study, performed in general practices in England (see September 07 edition of this newsletter). This study showed that SMBG has little or no effect on medium term blood glucose control in type 2 diabetes not treated by insulin.

A cost effectiveness analysis of the DiGEM study has now been published<sup>1</sup>. Average net annual costs were about twice as high in the SMBG group compared to the no-monitoring group. SMBG was associated with a reduced health-related quality of life at 12 months and there were indications that this was due to increased levels of depression and anxiety. The authors concluded that SMBG is unlikely to be cost effective in addition to standardised usual care.

Some have argued that SMBG would be especially beneficial in people with newly diagnosed type 2 diabetes. This hypothesis has now been tested in the ESMON study<sup>2</sup>.

ESMON found no significant difference in HbA1c between people with newly diagnosed diabetes allocated to blood glucose self monitoring and controls managed according to the same well defined algorithm without self monitoring at 12 months' follow-up. The two groups showed no significant difference in hypoglycaemia. Patients who were allocated to self monitoring reported greater self rated depression than controls.

The NPC blog<sup>3</sup> of these two studies concludes "it is increasingly difficult to justify the use of SMBG other than in very specific circumstances. These specific circumstances include patients with type 2 diabetes treated with insulin who adjust their dose on the basis of SMBG results. Pragmatically, it may also be useful to monitor blood glucose during episodes of intercurrent illness, and self-monitoring might also be useful in people who fast for religious or other reasons (eg during Ramadan) *if* they are at risk of hypoglycaemia (but note not all people are)."

Total healthcare cost of self monitoring may now exceed £100m each year in the UK. This represents a substantial opportunity cost in terms of alternative interventions that might have improved the health of people with diabetes. For patients, self monitoring carries an opportunity cost in terms of the attention that they might have given to more effective disease control measures aimed not just at blood glucose but also at blood pressure, cholesterol, smoking, body weight, and physical activity.

The NPC<sup>3</sup> suggests the following action:

“Patients, health professionals and commissioners of health care should look carefully at the use of SMBG. These two studies cast further doubt on its usefulness in newly diagnosed patients and those with established type 2 diabetes, other than for certain people treated with insulin and, conceivably, in some other very specific circumstances.

More benefit may well come from directing attention to interventions likely to make a difference to patients’ symptoms and cardiovascular risk. It may be worthwhile for commissioners to consider using the resources allocated to SMBG to fund increased focus on support and advice around nutrition, exercise, smoking cessation, foot care, etc.”

These studies have been discussed by JAPC and the agreed message to prescribers is that **SMBG in patients not using insulin is not essential, may not be desirable and may do harm, and patients should be considered for review.**

1. BMJ 2008; 336:1177-80
2. BMJ 2008; 336:1174-77
3. [www.npci.org.uk/blog/?p=102](http://www.npci.org.uk/blog/?p=102)

### **More on glitazones**

The Midlands Therapeutics Review and Advisory Committee (MTRAC) has updated its reviews on rosiglitazone<sup>1</sup> and pioglitazone<sup>2</sup>. The verdicts are:

“Rosiglitazone cannot be recommended for prescribing, based on the current concerns about potential cardiovascular adverse effects and lack of evidence for improved patient-oriented outcomes. Patients already taking rosiglitazone should have their cardiovascular risk re-assessed and their treatment reviewed”

and

“Pioglitazone is suitable for use in primary care by a prescriber with a particular interest in type 2 diabetes who can identify patients likely to benefit from treatment, and monitor for side effects, e.g. heart failure. There is conflicting evidence whether pioglitazone is associated with long-term clinical benefits or harms on cardiovascular outcomes, which dictates caution in its use.”

More evidence has been published showing an association with glitazone use and fracture risk<sup>3</sup>, this study was a nested case-control analysis using the UK General Practice Research Database.

The authors found users of glitazones for approximately 12-18 months had an odds ratio for low-trauma fracture of 2.43 (CI 1.49 to 3.95) compared with non-use. The association was independent of patient age and sex and tended to increase with glitazone dose. No materially altered relative fracture risk was found in association with the use of other oral antidiabetic drugs.

The authors concluded “This analysis provides further evidence of a possible association between longer term use of thiazolidinediones and fractures, particularly of the hip and wrist, in patients with diabetes mellitus”. The

accompanying editorial<sup>4</sup> concludes that the increase in fracture risk seemed to be strong, consistent with other studies, and biologically plausible.

Management priorities for people with type 2 diabetes are to control symptoms of diabetes and reduce the risk of diabetes-related events, in particular cardiovascular disease. Effective drug interventions should be directed towards this, rather than simply showing evidence of reductions in markers of blood glucose control, as the relationship between reductions in HbA<sub>1c</sub> and CV risk is not clear. Currently, only metformin has evidence of

benefits on patient-orientated outcomes (i.e. living longer or better). Follow the 'hand' (see last month's edition).

1. [www.keele.ac.uk/schools/pharm/MTRAC/ProductInfo/verdicts/R/Rosiglitazone3.pdf](http://www.keele.ac.uk/schools/pharm/MTRAC/ProductInfo/verdicts/R/Rosiglitazone3.pdf)
2. [www.keele.ac.uk/schools/pharm/MTRAC/ProductInfo/verdicts/P/Pioglitazone2.pdf](http://www.keele.ac.uk/schools/pharm/MTRAC/ProductInfo/verdicts/P/Pioglitazone2.pdf)
3. Arch Intern Med 2008; 168:820-25
4. Arch Intern Med 2008; 168:793-95

### **COPD treatment algorithm**

JAPC has once again appraised and debated the evidence for drug use in COPD and continues to endorse this treatment algorithm.

### **Algorithm for drug use in COPD**

When prn salbutamol is insufficient -

