

## 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. This would normally be under a shared care agreement. GREEN drugs are regarded as routine for primary care prescribing. BROWN drugs are those that JAPC 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.

The most recent updates are in the table below:

<b>Drug</b>	<b>Date considered</b>	<b>Decision</b>
Colesevalem	February 2008	DARK BROWN
Hyaluronic acid injection	February 2008	RED
Apraclonidine eye drops	January 2008	RED
Cabergoline (hyperprolactinaemia only)	January 2008	LIGHT BROWN
Co-proxamol (unlicensed)	January 2008	DARK BROWN
Ezetimibe	January 2008	LIGHT BROWN
Fostair	January 2008	LIGHT BROWN
Hedrin lotion	January 2008	GREEN
Omalizumab	January 2008	RED
Sativex spray (unlicensed)	January 2008	DARK BROWN
Erdosteine	December 2007	DARK BROWN
Exenatide	December 2007	LIGHT BROWN

### Ezetimibe: NICE guidance

NICE has issued technology appraisal guidance 132: ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia. The guidance relates only to primary hypercholesterolaemia, and not to primary or secondary prevention of cardiovascular disease. Ezetimibe is not licensed for primary or secondary prevention of CV events, as there are no published outcome studies that examine this.

Ezetimibe<sup>▼</sup> has an extremely limited role, as defined by NICE, for those with excessively high concentrations of cholesterol (unfortunately not defined by NICE) **despite** being prescribed (and, importantly, taking) an evidence-based dose of an evidence-based statin, i.e. simvastatin 40mg daily.

The guidance advises that ezetimibe<sup>▼</sup> monotherapy is an option for the treatment of adults with primary hypercholesterolaemia who would otherwise be initiated on statin therapy but who are unable to do so because statins are contraindicated or they were unable to tolerate them.

Ezetimibe<sup>▼</sup> may also be used in combination with a statin in some limited circumstances in adults with primary hypercholesterolaemia. This option should be considered **only** where statin therapy has not appropriately controlled serum total or LDL-cholesterol despite appropriate statin dose titration (or in people who cannot tolerate higher doses of statin) **and** consideration is being given to changing from the initial statin used to an alternative statin.

“Intolerance” was defined by NICE as the presence of **clinically significant** adverse effects from statin therapy that are considered to represent an **unacceptable risk** to the patient or that may result in compliance with therapy being compromised. Adverse effects include new-onset muscle pain (often associated with levels of muscle enzymes in the blood indicative of muscle damage), significant gastrointestinal disturbance or alterations of liver function tests.

NICE guidance does not state what “appropriate control of cholesterol concentrations” should be, but says this should be based on “individualised risk assessment”. **The great majority of patients will achieve a good reduction in their total cholesterol, and meet the Quality and Outcomes Framework standard and national target of 5 mmol/L total cholesterol or less, on simvastatin 40 mg a day alone.** This is widely tolerated and has a low acquisition cost to the NHS.

The guidance defines hypercholesterolaemia just as the presence of high concentrations of cholesterol in the blood and does not relate this to any level of CV risk. Those with familial hypercholesterolaemia (FH) do not need a risk assessment and should be considered for treatment as they are at high risk. Consider FH if cholesterol >7.5 mmol/l (LDL-C >4.9) and there is family history of either early MI or raised cholesterol. The presence of tendon xanthoma in the patient or a relative is pathognomonic. The majority of people with cholesterol >9 mmol/l, and normal triglycerides, will have FH.

For those with non-familial (not due to a genetic cause) hypercholesterolaemia, a formal risk assessment would seem to be the appropriate approach. Individuals likely to be at high risk are those with a family history of premature CVD (i.e. a father or brother who had a vascular event before the age of 55, or a mother or sister before the age of 65), clinical signs of hyperlipidaemia, those originating from the Indian subcontinent, smokers, and hypertensives. For family history or Indian subcontinent descent multiply the calculated risk by 1.5.

Remember, ezetimibe<sup>▼</sup> is a “black triangle” drug under intensive surveillance by the MHRA. Health care professionals (and patients) are therefore requested to report **all suspected adverse reactions** from it to the MHRA.

### **Fostair 100/6 pMDI**

Fostair is the first combination inhaler to use the first-line inhaled steroid (beclometasone) with a LABA. Each metered dose contains 100mcg of beclometasone (extrafine) and 6mcg of formoterol. It is licensed for regular treatment of asthma where use of a combination product is appropriate. Fostair is less costly than Seretide and Symbicort but only has a 3-month shelf left after dispensing. Also it is not dose equivalent to Clenil Modulite and cfc-containing beclometasone MDIs as the beclometasone is extrafine (like Qvar).

**Fostair has been discussed at JAPC and was not recommended for first-line use when a combination inhaler is needed and classified as LIGHT BROWN.**

### **Sativex oromucosal spray**

Sativex is an unlicensed, cannabis-based medicine used for relief of spasticity in people with multiple sclerosis. It is supplied on a named patient basis. The MHRA has recently produced a large public information report on Sativex spray (access at [www.mhra.gov.uk](http://www.mhra.gov.uk)).

The MHRA concluded that evidence of efficacy is not considered to be sufficient at present and a positive risk-benefit has not been sufficiently demonstrated. **JAPC does not recommend use of Sativex and it is classified DARK BROWN.**

### **Appropriate use of amiodarone**

Last month's PACE Newsletter highlighted thyroid function abnormalities during amiodarone therapy. Six-monthly checks of thyroid function are recommended. The SPC also recommends six-monthly checking of liver function.

According to the SPC amiodarone combined with the following drugs is not recommended:

- Beta-blockers, diltiazem and verapamil; potentiation of negative chronotropic properties and conduction slowing effects may occur.
- Stimulant laxatives e.g. senna, which may cause hypokalaemia thus increasing the risk of torsades de pointes; other types of laxative should be used.
- Caution should be exercised over combined therapy with drugs that may also cause hypokalaemia and/or hypomagnesaemia, e.g. diuretics, systemic corticosteroids.

In cases of hypokalaemia, corrective action should be taken and the QT interval monitored.

Warfarin and digoxin doses need reducing when amiodarone is initiated and it is recommended not to exceed a dose of 20mg daily with simvastatin when co-prescribed with amiodarone.

Eight GP practices in Derbyshire recently took part in an audit of the monitoring and use of amiodarone.

Some of the results are of potential concern:

TFT recorded in the last 6 months	65%
TFT recorded in the last 12 months	84%
LFT recorded in the last 6 months	60%
LFT recorded in the last 12 months	76%

Patients taking any of beta-blockers/diltiazem/verapamil/stimulant laxatives	48%
Patients taking greater than 20mg simvastatin daily	23%
Patients taking diuretic	68%

The audit results have been discussed at JAPC and **it is recommended that all practices consider undertaking this audit, should follow the amiodarone monitoring protocol and re-audit in 12 months time.**

### **Statins for people with diabetes**

The first priority in the statin policy is secondary prevention – “These patients are at highest risk of a vascular event: history of myocardial infarction (MI), angina, or coronary revascularisation, peripheral vascular disease (PVD), transient ischaemic attack (TIA) or ischaemic stroke, and patients with diabetes over 40 years of age. These patients do not need a formal coronary risk assessment because they are at a high enough risk to warrant treatment.” This recommendation was driven by the results of the Heart Protection Study<sup>1</sup>.

A meta-analysis of the effect of statins in people with diabetes (1,466 with type 1 and 17,220 with type 2) has recently been published<sup>2</sup>. The statins used in the trials were simvastatin 20-40mg, pravastatin 40mg, and atorvastatin 10mg (also some fluvastatin and lovastatin). In people with diabetes statin therapy reduced mortality, coronary death, MI, coronary revascularization, and stroke. After 5 years, 42 fewer people had major vascular events per 1000 allocated statin therapy.

The authors concluded that present guidelines might need to be revised to ensure that a statin regimen which is sufficient to produce a substantial reduction in LDL cholesterol is considered for all people with diabetes, irrespective of whether vascular disease has developed and irrespective of lipid profile. Fortunately the statin policy does not need changing and this meta-analysis supports its recommendation. Simvastatin 40mg daily was the most effective and cost effective regimen used in the trials.

The Association of British Clinical Diabetologists has recently published a position statement on the use of lipid modifying drug therapy in diabetes<sup>3</sup>:

*Type 2 diabetes* – the vast majority over 40 years of age should receive statin therapy as they have a >20% 10-year CVD risk (often due to other CVD risk factors, e.g. hypertension etc).

Statin therapy for younger type 2 diabetes needs further clarification and should currently be restricted to those at highest CVD risk.

*Type 1 diabetes* – treat if age >50 years, >40 years with complications, and for 18-39 year-olds selective assessment based on other risk factors and complications, including poor glycaemic control and long duration of diabetes, or first degree relative with early onset CVD is recommended.

1. Lancet 2002; 360: 7-22
2. Lancet 2008; 371: 117-25
3. Pract Diab Int Nov/Dec 2007; 24(9): 458-62

### **Drug safety update**

Drug safety update can be found at [www.mhra.gov.uk/mhra/drugsafetyupdate](http://www.mhra.gov.uk/mhra/drugsafetyupdate)

The January issue majors on statins.

### ***Statins: interactions, and updated advice for atorvastatin***

Drug interactions may increase the risk for adverse effects, or reduce the effectiveness of statin treatment. Updated prescribing advice for atorvastatin provides detailed recommendations for dose restrictions when used with some other drugs.

<b>Interacting drug or food</b>	<b>Simvastatin prescribing advice</b>	<b>Atorvastatin prescribing advice</b>
Potent CYP3A4 inhibitors, including itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, and HIV protease inhibitors	All are contraindicated with simvastatin	Avoid if possible: consider temporary suspension of atorvastatin if interacting drug is taken for short period.  <b>Itraconazole:</b> do not exceed 40 mg atorvastatin daily <b>Clarithromycin:</b> do not exceed 20 mg atorvastatin daily <b>HIV protease inhibitors:</b> monitor lipid levels to ensure lowest necessary dose of atorvastatin is used
Ciclosporin*	Do not exceed 10 mg simvastatin daily	Do not exceed 10 mg atorvastatin daily
Danazol	Do not exceed 10 mg simvastatin daily	No restriction in Summary of Product Characteristics
Verapamil, amiodarone	Do not exceed 20 mg Simvastatin daily	Monitor lipid levels to ensure lowest necessary dose of atorvastatin is used
Diltiazem	Do not exceed 40 mg simvastatin daily	Monitor lipid levels to ensure lowest necessary dose of atorvastatin is used
Grapefruit juice	Avoid grapefruit juice	Limit intake of grapefruit juice to very small quantities (or avoid altogether)
Warfarin/coumarins†	Monitor INR before starting treatment and regularly during treatment, especially with dose changes	Monitor INR before starting treatment and regularly during treatment, especially with dose changes
Fibrates†	Increased risk of myopathy when used with fibrates: do not exceed 10 mg simvastatin daily (except with fenofibrate); gemfibrozil increases systemic exposure to simvastatin	Increased risk of myopathy when used with fibrates; gemfibrozil increases systemic exposure to atorvastatin
Ezetimibe†	Additive risk of myopathy cannot be ruled out	Additive risk of myopathy cannot be ruled out

\*Ciclosporin interacts with all statins and is contraindicated with rosuvastatin.

†Warfarin/coumarins, fibrates, and ezetimibe are important potential interactions to consider for all statins.

### **Bisphosphonates and musculoskeletal pain**

The U.S. FDA has recently highlighted the possibility of severe and sometimes incapacitating bone, joint, and/or muscle (musculoskeletal) pain in patients taking bisphosphonates. They comment that the association between bisphosphonates and severe musculoskeletal pain may be overlooked by healthcare professionals, delaying diagnosis, prolonging pain and/or impairment, and necessitating the use of analgesics.

The severe musculoskeletal pain may occur within days, months or years after starting a bisphosphonate. Some patients have reported complete relief of symptoms after discontinuing the bisphosphonate, whereas others have reported slow incomplete resolution. The risk factors for and incidence of severe musculoskeletal pain associated with bisphosphonates are unknown.

This severe musculoskeletal pain is in contrast to the acute phase response characterized by fever, chills, bone pain, myalgias, and arthralgias that sometimes accompanies initial administration of intravenous bisphosphonates and may occur with initial exposure to once-weekly or once-monthly doses of oral bisphosphonates. The symptoms related to the acute phase response tend to resolve within several days with continued drug use.

They recommend that healthcare professionals should consider whether bisphosphonate use might be responsible for severe musculoskeletal pain in patients who present with these symptoms and consider temporary or permanent discontinuation of the drug.

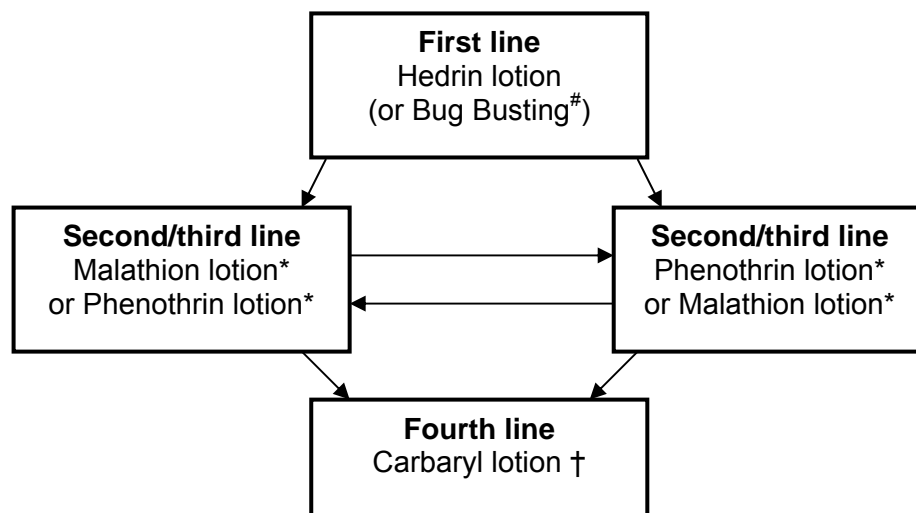
[www.fda.gov/cder/drug/infopage/bisphosphonates/default.htm](http://www.fda.gov/cder/drug/infopage/bisphosphonates/default.htm)

### **Hedrin lotion now a first-line option**

A recent RCT compared 4% dimeticone lotion (Hedrin) with 0.5% malathion liquid (Derbac-M) for treating confirmed head louse infestation<sup>1</sup>. The primary outcome was elimination of head lice using two applications of treatment 7 days apart. Dimeticone was significantly better than malathion with an NNT of 2-3.

JAPC has updated the treatment algorithm for treating head lice infestation accordingly.

**Treatment should not be used unless a living, moving louse is detected.**



<sup>#</sup> Bug Busting requires meticulous use; 30 minutes each time over the whole scalp at 4-day intervals for a minimum of 2 weeks.

\* Aqueous liquid for young children or those with asthma/eczema.

† Prescription only medicine.

#### **With each treatment choice:**

- Use two applications seven days apart (12 hours/overnight contact time).
- 2-3 days after final application of insecticide: check hair thoroughly with a plastic detector comb.
- If adult lice are present, then go on to next choice of treatment. Always thoroughly investigate the reasons for treatment failure e.g. incorrect use.

## **Prevention of infection in patients with absent spleens**

An updated Derbyshire-wide guideline on the prevention of infection in patients with absent spleens has been ratified by JAPC. There are changes in the vaccinations required and in the antibiotic doses for children. To obtain a copy contact your Medicines Management team or me.

## **Clopidogrel plus aspirin**

A Cochrane review has been published that quantifies the effects (both benefit and harm) of adding clopidogrel to standard long-term aspirin therapy for preventing cardiovascular events in people at high risk of CV disease and those with established CV disease<sup>1</sup>. Only two RCTs were found, CURE and CHARISMA.

The CURE trial, confined to people with acute non-ST segment coronary syndromes, showed evidence of benefit from treatment. For every 1,000 people treated for an average of 9 months, 23 events (mainly non-fatal MI) would be avoided and 10 major bleeds would be caused. Data from the study suggest that the main benefit of combination therapy is in the initial period.

In the CHARISMA trial that randomised patients at high CV risk defined either in terms of pre-existing CV disease or risk factors, the effects of treatment were less marked and were consistent with the play of chance. For every 1,000 patients treated for an average of 28 months, 5 CV events would be avoided and 3 major bleeds would be caused.

### **The authors conclude:**

“Clinicians should not add clopidogrel to standard long-term aspirin therapy for preventing cardiovascular disease in people at high risk of cardiovascular disease and in those with established cardiovascular disease. In patients with acute non-ST coronary syndromes there is evidence of benefit outweighing harms caused by major bleeding and combination treatment should be considered.”

1. Cochrane Database of Systematic Reviews 2007, Issue 3

## **Anticoagulant plus antiplatelet for PAD?**

Although antiplatelet therapy is routinely recommended for patients with peripheral arterial disease, it is unknown whether adding an oral anticoagulant would improve outcomes. A recent study identified 2417 adults between the ages of 35 years and 85 years with documented symptomatic lower extremity vascular disease or carotid artery disease (recent transient ischemic attack or stroke, carotid endarterectomy, or carotid stenosis >50%). Patients were then given antiplatelet agent (aspirin, ticlopidine, or clopidogrel at the discretion of their physician) and an oral anticoagulant (warfarin in 5 countries, acenocoumarol in 2 countries) for a 2-week to 4-week run-in period.

The 2161 who were compliant, agreed to continue, and achieved a stable international normalized ratio between 2.0 and 3.0 were randomized with concealed allocation to receive either antiplatelet therapy alone or antiplatelet therapy plus oral anticoagulation. The patients' mean age was 64 years, 74% were men, and 82% had lower extremity vascular disease. Participants were followed for an average 3 years, and although patients and physicians were not masked, outcomes were assessed by an independent team masked to treatment assignment.

There was no difference between groups in either of the 2 composite outcomes (1. MI, stroke, or cardiovascular death, or 2. MI, stroke, severe coronary or peripheral ischemia, or cardiovascular death). However, there were more episodes of life-threatening bleeding (4.0% vs 1.2%;  $P < 0.001$ ; number needed to treat to harm [NNH]=36) or moderate bleeding (2.9% vs 1.0%;  $P = 0.002$ ; NNH=53) in the oral anticoagulant group.

### **Key message: the combination of antiplatelet and anticoagulant is not recommended in PAD**

1. N Engl J Med 2007; 357:217-27

## **Asthma in children**

Children presenting with wheeze are likely to have either atopic asthma or episodic viral wheeze; distinguishing between these has important implications for management. A recent review of diagnosing asthma in children is helpful<sup>1</sup>.

If one feature consistently points to a diagnosis of asthma, it is wheeze. Wheeze is the end result of narrowing of small airways due to processes that include oedema of the airway wall, contraction of smooth muscle, and mucus plugging. A study of parents of wheezing children found that some thought that wheeze was a sound such as whistling, squeaking, or gasping, whereas others defined it as a different rate, style, or timbre of breathing, and some thought it was the same as coughing. This is an important reminder that reported wheeze might not be wheezing after all.

One area of diagnostic difficulty in childhood asthma is chronic cough. Cough is a common complaint in childhood; up to 10% of preschool and early school aged children have chronic cough without wheeze at some time. Although childhood asthma may present with cough, most children who cough without wheeze do not have asthma. Isolated chronic cough is a poor marker of asthma and without other typical features of asthma, should always raise the strong possibility of an alternative cause.

### ***Summary points from the diagnosis review article:***

- “Childhood asthma” describes several different clinical phenotypes with different management strategies.
- The two most common phenotypes are atopic asthma, more common in school aged children, and episodic viral wheeze, more common in preschool children.
- Wheeze is a poorly understood symptom, and parents should be asked to clarify what they understand it to be.
- Wheeze is commonly associated with asthma, but several other conditions can result in recurrent wheezing and should be considered before a diagnosis is made.

A second review article discussed the management of asthma in children<sup>2</sup>. The authors comment that the management of episodic viral wheeze is controversial. Little evidence exists in the literature to support the use of regular bronchodilators and corticosteroids. A Cochrane review of short acting  $\beta_2$  agonists found eight studies involving 229 patients and found no benefit in episodic viral wheeze and persistent wheeze in children under the age of 2 years.

The benefit of anticholinergics in the management of episodic viral wheeze is similarly unclear. A Cochrane review of six studies involving 321 infants under the age of 2 years showed no impact on symptoms or clinical course of the acute illness. The studies were heterogeneous, however, leaving the possibility of a subgroup that may benefit. Currently, the indiscriminate use of anticholinergics and short acting  $\beta_2$  agonists in the management of acute episodic viral wheeze is not recommended. Although these agents are still used for young children with wheeze, the doctor should ensure that a clear clinical benefit is achieved before they are regularly prescribed.

### ***Summary points from the management review article:***

- Inhaled corticosteroids, although safe if given at the recommended dose, can have important adverse effects if given above it, including adrenal suppression.
- Long acting  $\beta_2$  antagonists can be used as add-on treatment to avoid further increases in the dose of inhaled corticosteroid but can be associated with increased risk of exacerbations and hospital admission.
- Long acting  $\beta_2$  antagonists should therefore be continued only if a demonstrable response to treatment occurs.
- Inhaled corticosteroids do not prevent the development of asthma.
- Low dose inhaled corticosteroid should not be used as preventive treatment for episodic viral wheeze.
- Referral to a specialist centre should be considered when a child reaches step 4 of the British Thoracic Society (BTS) guideline or earlier, depending on the expertise of the general practitioner and the resources available.

Current UK prescribing trends for asthma medication in children do not follow the BTS guidelines, according to the results of a recent study<sup>3</sup>. Researchers assessed the trends of paediatric asthma prescribing in the UK, and compared them with current BTS guidance. Data from the NHS Information Centre for Health and Social Care were used to estimate community paediatric prescribing figures for asthma medications between the years 2000 and 2006.

The following results were reported:

- The number of prescriptions for bronchodilator syrups decreased by 60% from 2000 to 2006, but this still represents 121,000 prescriptions in 2006 despite minimal recommendations for their use.
- The percentage of steroid inhalers prescribed as combination inhalers of a steroid and a long acting beta-agonist increased from 2.7% in 2000 to 25.3% in 2006. This trend is not consistent with the BTS recommendations that combination inhalers should only be used in patients not controlled on adequate doses of inhaled steroids.
- The prescribing of steroid-alone inhalers gradually declined from 2000 to 2006 although they should be the mainstay for the vast majority of patients with asthma who require controller medications.

The authors conclude “we believe that these numbers point to an overuse of oral  $\beta$  agonists and LABA/steroid combination preparations in children as a group”. They comment “there is a trend towards less prescribing of  $\beta$  agonist syrups, but the increase in combination products is not guideline driven”.

In an internal memorandum, drug safety staff at the FDA in the USA have commented that salmeterol “may have an unfavourable risk-benefit ratio in the treatment of paediatric asthma” and recommend a “more thoroughgoing, formal risk-benefit analysis of salmeterol” for this indication.

The authors of the memorandum state that “adult trial data show an increase in asthma mortality and severe asthma events with salmeterol; available data do not provide any reason to believe that the paediatric population does not share the same risk; and definitive evidence of a protective effect of inhaled corticosteroids is lacking for long-acting beta agonists (LABAs), and in fact there is evidence that inhaled corticosteroids are not protective in paediatric patients receiving formoterol (another LABA)”<sup>4</sup>.

**The current advice from the Commission on Human Medicines (CHM)** appears to apply to patients of all ages. The CHM advise that salmeterol and formoterol should:

- Be added to therapy **only** if regular use of standard-dose inhaled steroids has failed to control asthma adequately.
- **Not be initiated in patients with rapidly deteriorating asthma.**
- Be introduced at a low dose and the effect properly monitored before an increase in dose is considered.
- Be discontinued in the absence of benefit.
- Be reviewed as clinically appropriate: stepping down therapy should be considered when good long term asthma control has been achieved.
- Patients should be asked to report any deterioration in symptoms following initiation of a LABA.

1. BMJ 2007; 335:198-202
2. BMJ 2007; 335:253-7
3. Arch Dis Child doi:10.1136/adc.2007.119834
4. [www.npci.org.uk/blog/?p=43](http://www.npci.org.uk/blog/?p=43)

### **Breastfeeding and thrush**

The Infant Feeding Advisers have asked that health professionals are made aware of the resources available from the Breastfeeding Network available at [www.breastfeedingnetwork.org.uk](http://www.breastfeedingnetwork.org.uk)

In particular, the information and advice available on managing thrush in breastfeeding mothers and breast-fed infants at [www.breastfeedingnetwork.org.uk/thrush-health-professionals.html](http://www.breastfeedingnetwork.org.uk/thrush-health-professionals.html)

You will find fact sheets for mothers, information sheets and a powerpoint presentation for health professionals.