

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:

Drug	Date considered	Decision
Ambrisentan	July 2008	RED
Aripiprazole	July 2008	GREEN (only on consultant recommendation)
Olanzapine	July 2008	GREEN (only on consultant recommendation)
Quetiapine	July 2008	GREEN (only on consultant recommendation)
Anastrozole	July 2008	GREEN (only on consultant recommendation)
Exemestane	July 2008	GREEN (only on consultant recommendation)
Letrozole	July 2008	GREEN (only on consultant recommendation)
Fesoterodine	July 2008	BROWN
Melatonin prolonged-release (Circadin)	July 2008	BROWN
Rimonabant	July 2008	GREEN (as per NICE guidance)
Sustanon injection	July 2008	GREEN (only on consultant recommendation)
Testim gel	July 2008	GREEN (only on consultant recommendation)
Testogel	July 2008	GREEN (only on consultant recommendation)
Venlafaxine	June 2008	GREEN (as per depression guideline)

Revised British Asthma Guideline

The British Thoracic Society and the Scottish Intercollegiate Guidelines Network have jointly published a new British Guideline on the Management of Asthma.¹ Significant changes have been made to the section on diagnosis and monitoring, and sections on non-pharmacological and pharmacological management have been updated to reflect current evidence. A new topic of 'difficult asthma' is included; topics of asthma in pregnancy and occupational asthma are unchanged. Other sections have been re-organised and updated to create a section on organisation and delivery of care, and audit, and another on patient education and self-management. Guidance on the content of personalised written action plans is included.

A useful summary of the changes can be found at

www.nelm.nhs.uk/Documents/BT5%202008%20Asthma%20final.doc?id=593261

The new guidance states that:

In adult patients at step 3 who are poorly controlled, the use of budesonide/formoterol in a single inhaler as rescue medication instead of a short-acting beta-2 agonist, in addition to its regular use as a controller treatment (i.e. Symbicort SMART), is an effective treatment option. Before instituting this management careful patient education is required.

It is important to note that the guidance says this is an **option** for **patients at step 3** who are **poorly controlled**. This refers to patients who have already moved from step 2 to step 3 (i.e. they have previously needed to move from regular inhaled steroid alone to regular inhaled steroid plus regular long-acting beta-2 agonist, and whose asthma is uncontrolled with this regime, as an alternative to moving to step 4. Note also that not all patients respond to LABAs, in which case an alternative approach is required (see the guideline).

Regular review of patients, and stepping down, is essential. Before adding or changing treatment practitioners should check compliance with existing therapy, check the patient's inhaler technique and eliminate trigger factors. Most patients can be managed successfully at step 2 (regular inhaled steroid plus reliever inhaler when required), at least most of the time.²

SIGN and BTS have made a joint statement about certain drug advertisements. They say that it has come to their attention that a number of advertisements have appeared in the medical press which could, erroneously, imply to clinicians that the new asthma guideline has recommended, or endorsed, specific (named) pharmaceutical products. Moreover, these advertisements do not accurately summarise the guideline in the way they purport to do. **BTS and SIGN stress that the new asthma guideline does not recommend any specific products.**

1. www.sign.ac.uk/pdf/sign101.pdf
2. www.npci.org.uk/blog/?p=114

eGFR and CKD

For sometime now laboratories have been providing an eGFR result routinely when biochemistry has been ordered on a blood sample. The problem is how to use this information. We want to avoid over diagnosing CKD.

In the data from the modification of diet in renal disease study that were used to generate the eGFR equations, samples were taken from predominantly fasting subjects.¹ In clinical practice, however, samples are taken in situations where the patient's recent dietary intake is not usually considered.

A small study investigated the impact of meals on creatinine concentration and eGFR by having blood samples taken before and after normal helpings of meat-containing meals supplied by the hospital canteen. Median eGFR fell from 84.0 pre-prandially to 59.5, 1-2 hours after eating ($p < 0.0001$) and 64.0, 3-4 hours after eating ($p < 0.0001$). This led to apparent changes in staging of CKD. The authors concluded that the risk of misdiagnosis or incorrect staging of CKD is high after a meal containing cooked meat. They recommend that serum creatinine measurement should be carried out when a patient has fasted or specifically avoided a cooked meat meal on the day of blood sampling.²

The advice from Paul Masters, Consultant Clinical Pathologist, is that strictly speaking samples should be fasting. People on the borderline of CKD3 on a random sample should have a repeat sample to confirm, and ideally this should be fasting. Alternatively, people should be advised not to eat meat for 12 hours before the test.

This has been discussed at JAPC and the recommendation is that **if the initial test result suggests CKD3, then the test should be repeated using a fasting sample or after advising the person to eat no meat or meat products for 12 hours before the test.** Just make sure that the patient still drinks though and does not become dehydrated.

The recently published SIGN guideline on CKD³ gives similar advice: 'staging of chronic kidney disease should not be based on samples collected after consumption of meals containing cooked meat. Confirmatory samples should be taken in the fasting state.' It also says 'as single aberrant results are relatively common the abnormality should be present for at least three months.'

1. Bandolier 156, 14(2), February 2007
2. BMJ 2006; 333: 1072
3. <http://www.sign.ac.uk/guidelines/fulltext/103/index.html>

Treatment of nausea and vomiting in pregnancy

In the absence of any good-quality clinical evidence in this area, updated guidance from CKS (formerly known as Prodigy) provides pragmatic advice for the management of women with nausea and vomiting in pregnancy.¹

Symptoms (nausea, vomiting or both) normally manifest before nine weeks of gestation in almost all affected women and are usually mild and self-limiting. However, a minority of women, for whom symptoms are more severe, will require further assessment. This group includes women with hyperemesis gravidarum, which commonly presents with:

- Persistent vomiting not related to other causes (the guidance has advice on what other causes to consider)
- Weight loss (usually at least 5% of pre-pregnancy body weight)
- Signs of acute starvation (usually large ketonuria).

The guidance recommends reassurance and simple lifestyle measures (e.g. diet, rest) in the first instance. Women should be informed of the circumstances when they should seek further medical advice. Over the counter (OTC) remedies are not recommended, but prescribed drug treatment may be considered if initial simple measures have failed and the woman has persistent, severe symptoms that prevent daily activities, or increased urine ketone levels.

Where drugs are necessary, promethazine (or cyclizine) is the first-line antiemetic; second-line choices are prochlorperazine or metoclopramide. It is important that, where drug treatments are prescribed, patients are followed up after 24 hours. Suggested dosing regimens are provided. None of these drugs are licensed for use in pregnancy; they should be given for the shortest time necessary to manage symptoms.

- Either promethazine hydrochloride or promethazine teoclate may be used:
 - Promethazine hydrochloride: give up to 25mg as one dose at bedtime, and repeat in the morning if necessary. The 10mg tablets can also be titrated up to a dose that gives optimal effect.
 - Promethazine teoclate: give 25mg at bedtime. The dose may be increased to 100mg daily.
- Cyclizine: prescribe 50mg up to three times a day.
- Prochlorperazine oral tablets: give up to 10mg three times a day.
- Prochlorperazine buccal tablets: give 3mg to 6mg twice a day.
- Metoclopramide: prescribe 10mg tablets three times a day.

Non-pharmacological measures²

There are a number of non-pharmacological measures that may help initially, though there is little published evidence regarding the efficacy of dietary changes:

- Small, frequent, high-carbohydrate, low-fat cold meals.
- Plain or ginger biscuits about 20 minutes before getting up if suffering from 'morning' NVP. Ginger has been shown to reduce nausea and vomiting in pregnancy but the dose and form varied greatly across the trials.
- Glucose tablets to help prevent blood sugar levels from dropping, as low blood sugar may cause nausea.
- Drink little and often.
- Avoiding any food or smells that trigger symptoms.

1. www.cks.library.nhs.uk/nausea_vomiting_in_pregnancy
2. www.nelm.nhs.uk/Documents/162.1FINAL.doc?id=587891

Drug safety update

This can be found at www.mhra.gov.uk/drugsafetyupdate Here are some key points from the June issue.

Nicorandil: gastrointestinal ulceration

Nicorandil is associated with a risk of gastrointestinal ulceration, including perianal ulceration. Healthcare professionals should consider nicorandil treatment as a possible cause in patients who present with symptoms of gastrointestinal-tract ulceration.

Advice for healthcare professionals:

- GPs and other healthcare professionals should consider nicorandil treatment as a possible cause in patients who present with symptoms of gastrointestinal ulceration.
- Ulcers that result from nicorandil are refractory to treatment; they respond only to withdrawal of nicorandil.
- Nicorandil withdrawal should take place only under the supervision of a cardiologist.

Ezetimibe: new data from the ENHANCE trial

In April 2008, the ENHANCE trial (Ezetimibe and Simvastatin in Hypercholesterolaemia Enhances Atherosclerosis Regression) suggested no benefit from the addition of ezetimibe to simvastatin on the rate of atherosclerosis progression compared with simvastatin with placebo. ENHANCE was a 2-year clinical trial in 720 patients with familial hypercholesterolaemia – a disorder characterised by high LDL cholesterol and increased risk of premature coronary artery disease. Patients were randomly assigned to simvastatin plus placebo, or to simvastatin plus ezetimibe. The primary endpoint was mean change in intima-media thickness of the carotid artery, as measured by ultrasonography as a surrogate marker for progression of atherosclerosis and risk of cardiovascular adverse events.

To date, no data from large clinical outcomes trials are available for ezetimibe. The ongoing IMPROVE-IT trial (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial) is evaluating the clinical benefit – in terms of cardiovascular morbidity and mortality – of ezetimibe combined with simvastatin compared with simvastatin alone in about 10,000 patients with acute coronary syndromes. However, the results are not expected to be available in the next 4 years.

The MHRA, together with other regulatory agencies in the European Union, is currently reviewing the results of the ENHANCE trial to establish their clinical significance and potential effect on the balance of benefits and risks for ezetimibe. We will inform healthcare professionals of any changes to prescribing advice as soon as these reviews have been completed.

Tramadol with SSRIs and the serotonin syndrome

There is a risk of development of serotonin syndrome following concomitant use of tramadol with SSRIs. Serotonin syndrome occurs as a result of excess agonist activity at central and peripheral nervous system serotonin receptors. Excess serotonergic activity produces a spectrum of clinical findings from barely perceptible to lethal.

Serotonin syndrome is characterised by three groups of symptoms:

1. neuromuscular hyperactivity – hyperreflexia, clonus, myoclonus, tremor and rigidity;
2. autonomic hyperactivity – hyperreflexia, tachycardia and diaphoresis;
3. altered mental-state – agitation, anxiety, hypomania and confusion.

Patients with mild manifestations may present with subacute or chronic symptoms, whereas severe cases may progress rapidly to death.

Groups of drugs that have been associated with serotonin syndrome include monoamine oxidase inhibitors, SSRIs, tricyclic antidepressants, opiate analgesics and certain antibiotics.

Tramadol is a centrally acting analgesic structurally related to codeine and morphine. Tramadol is an agonist of the μ opioid receptor. In addition tramadol inhibits serotonin reuptake and norepinephrine reuptake, enhancing inhibitory effects on pain transmission in the spinal cord. Tramadol may cause serotonin syndrome particularly when it is used at high doses or in combination with other agents that increase serotonin levels.

The manufacturer of tramadol states that co-administration with serotonergic drugs, e.g. SSRIs, triptans or with monoamine oxidase inhibitors may lead to an increase of serotonin-associated effects, which can include serotonin syndrome.

A combination of agents increasing serotonin by different mechanisms, such as by inhibition of serotonin uptake and serotonin metabolism, is associated with a high risk of the syndrome. The increasing availability of antidepressant agents with serotonergic properties has increased the number of reports of this syndrome in recent years. Symptoms usually occur following initiation of therapy or increases in dose of a drug that can increase serotonin levels.

Other potential causes such as infections, metabolic disturbances, substance abuse, or withdrawal need to be excluded. Differential diagnoses include malignant hyperthermia, anticholinergic poisoning and neuromuscular malignant syndrome.

There is a risk of development of serotonin syndrome following concomitant use of tramadol with SSRIs. This may be more frequent than with other combinations of serotonergic drugs due to inhibition of tramadol metabolism as well as the combined serotonergic effect.¹

The inhibition of the metabolism of tramadol through CYP2D6 by SSRIs and the potential for 10% of the population to be poor metabolisers of CYP2D6 may explain why this reaction seems to be of significance in only a small number of patients.

There are only a limited number of case reports in the literature suggesting the risk may be low, however serotonin syndrome can be serious if undetected and there does not seem to be a strong pattern in determining which patients may be predisposed to the development of serotonin syndrome. In addition, several of the symptoms of serotonin syndrome are non-specific and this may mean the syndrome is largely undiagnosed.

In all case reports, symptoms developed within a few days of addition of the SSRI to tramadol therapy or vice versa, and equally symptoms resolved within days to a few weeks of discontinuation of the serotonergic agents. Patients and healthcare professionals should be aware of the potential for serotonin syndrome and monitor for any of the symptoms of serotonin syndrome on initiation and upwards dose titration of all serotonergic medications.¹

1. [www.nelm.nhs.uk/Documents/QA94-2-TramadolSSRIs\(Final\).doc?id=592217](http://www.nelm.nhs.uk/Documents/QA94-2-TramadolSSRIs(Final).doc?id=592217)

Structured education in type 2 diabetes (DESMOND)

A 6-hour well-constructed educational intervention given to patients with newly diagnosed type 2 diabetes was no better than usual care in improving their overall glucose control over 1 year of evaluation.¹ However, the intervention resulted in a greater average weight loss and prompted more patients to quit smoking, though these results were not the primary goal of the intervention.

The study took place in 207 UK general practices. The practices were randomised so that all patients of each practice received either the education program or usual care (cluster randomisation). The 824 participants were adults who were newly diagnosed with type 2 diabetes. Patients receiving the intervention attended 6 hours of education taught in a nondidactic fashion by 2 educators over 1 day or 2 half-days. The education consisted of a discussion of lifestyle factors, such as food choices, physical activity, and cardiovascular risk factors. The goal of the education program was for participants to understand their own risk factors and to choose a specific behaviour change to work on. Patients in the control group received the diabetes education normally provided at the practice. Diabetes education was ongoing in both groups.

At 12 months following diagnosis, haemoglobin A1c levels had decreased similarly in both groups from a baseline of 7.9% to 8.3% by 1.21% to 1.49%. The intervention group experienced greater weight loss (an average 2.98 kg as compared with an average 1.86 kg in the control group; P=0.027) and were, on average, slightly less likely to be smoking. The lack of effect on HbA1c may be because, as newly diagnosed patients, patients in both groups were highly motivated, independent of the education they received, to achieve good control. Studies of the effect of education on patients with established diabetes have shown a decrease in HbA1c. Also, the lack of masking of both the patients and the clinicians may have prompted clinicians in the control practices to try harder.

The NPC has blogged this study², which makes the following observations:

“NICE recommend that structured patient education is made available to all people with type 1 or 2 diabetes at the time of initial diagnosis and then as required on an ongoing basis, based on a formal, regular assessment of need. From the evidence available, it is still difficult to recommend a specific type of education or provide guidance on the setting for, or frequency of, sessions.

The results of the study do not change existing recommendations. As we keep saying, clinicians and patients should be aware of the importance of managing cardiovascular risk factors in patients with type 2 diabetes. This is likely to include using structured patient education to encourage smokers to stop smoking, and people

who are overweight or obese to lose weight. It is also important that blood pressure is controlled, and consideration should be given to adding a statin (ideally simvastatin 40 mg/day) and aspirin (once blood pressure is controlled). Blood glucose should also be controlled to control symptoms, probably using diet and lifestyle measures along with metformin.”

1. BMJ 2008; 336:491-5
2. www.npci.org.uk/blog/?p=109

Antibiotics for sinusitis-like symptoms

The results of a recent meta-analysis of individual patient data strongly suggest that antibiotics are not needed for most patients with acute rhinosinusitis.¹

The study found that, on average about 15 adult patients with rhinosinusitis-like complaints would need to be treated with antibiotics for one extra patient to be cured (i.e. being free of symptoms). However, taking into account the wide confidence intervals (CIs) around the mean estimate of their effect, the number of patients that would need to be treated to gain benefit could be as low as 7, but it is also possible that no patients benefit and one in every 190 would suffer harm (NNH = 190).

Common clinical signs were unable to identify a subgroup of patients for whom treatment was justified. Only purulent discharge in the pharynx had some prognostic value, although eight patients with this sign still needed to be treated for one patient to benefit. Once again, this has wide CIs; the NNT could be as low as 4 but it is also possible that one in every 47 would suffer harm (NNH = 47).

The authors suggest that antibiotics are not warranted, even when symptoms are present for longer than seven to ten days, which is commonly recommended as a period of watchful waiting before use of antibiotics. They go on to suggest that treatment with antibiotics is only essential if symptoms are suggestive of serious complications (e.g. high fever, periorbital swelling, erythema or intense facial pain). The authors point out that their results do not apply to children or patients with suppressed immune systems.

The NPCi blog² recommends the following action:

“Prescribers should continue to use antibiotics sparingly for the treatment of sinusitis. For most patients providing reassurance that the symptoms will resolve without antibiotic treatment and the use of watchful waiting will be all that is necessary. Only where symptoms are suggestive of serious complications (e.g. high fever, periorbital swelling, erythema or intense facial pain) should they be prescribed immediately”.

The new, Derbyshire-wide antimicrobial treatment guideline is now available. Contact your prescribing adviser if you do not receive a copy soon.

1. Lancet 2008; 371:908-14
2. www.npci.org.uk/blog/?p=82

Antibiotics and antiseptics for venous leg ulcers

A Cochrane review has examined the evidence supporting the use of antibiotics and antiseptics in venous leg ulcers.¹

The authors found that there was no existing evidence to support the routine use of systemic antibiotics to promote healing in venous leg ulcers. However, the lack of reliable evidence meant that they were also not able to recommend the discontinuation of any of the agents reviewed. In terms of topical preparations, they only identified evidence to support the use of cadexomer iodine.

Until there is better quality evidence to support the use of any particular topical or systemic treatment for the infected leg ulcers, and in the absence of NICE guidance, health professionals should consider following the recently revised CKS guidance for the management of venous leg ulcers that are suspected of being infected.² Included in the guidance is the recommendation that a wound swab is taken for all suspected infected venous leg ulcers before prescribing an antibiotic, and prescribing flucloxacillin or erythromycin for 7 days, whilst awaiting swab results. Clarithromycin is an alternative for people who are unable to tolerate erythromycin. Topical antibiotics, which are often associated with sensitivity reactions, are not recommended. The guidance also has recommendations for subsequent follow up, and what to do if the ulcer is not responding to treatment.

1. Cochrane Database of Systematic Reviews 2008, Issue 1
2. www.cks.library.nhs.uk/leg_ulcer_venous#