

## 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/clinical-guidelines-and-referral-guidelines.asp>

The guidelines, formulary chapters, newsletters, etc can now be found via this link.

Drug	Date considered	Decision
Full Marks solution spray	October 2009	BROWN
Lacosamide	October 2009	AMBER (moved from RED)
Tredaptive	October 2009	BROWN
Xamiol scalp gel	October 2009	GREEN
n-Acetylcysteine tabs	August 2009	AMBER
Degarelix injection	August 2009	BROWN
Fluticasone furoate nasal spray (Avamys)	August 2009	GREEN (after consultant initiation)
Liraglutide injection	August 2009	RED
Histrelin implant	August 2009	RED

### Generic clopidogrel

Generic versions of clopidogrel are now available but are different salts and do not have the same licence as the branded drug Plavix due to a patent protection issue. The licensing authorities are satisfied that the generic products are bioequivalent to Plavix. JAPC recommends that as the clopidogrel preparations are deemed to be bioequivalent, prescribers should continue to prescribe generically for all indications and prescribe the most cost-effective salt once that option is available on the prescribing system.

### Treating acute otitis media

An observational follow-up study to an RCT found that children prescribed amoxicillin for AOM were about 50% more likely to have recurrence of AOM over the following three years than those given placebo<sup>1</sup>. Three years after randomisation, AOM had recurred in 63% of children in the amoxicillin group compared with 43% in the

placebo group (RR 1.5 [95% CI 1.1 to 2.0]). The absolute risk increase was 20%, giving a NNH of 5. In other words, for every 5 children like those in the study given antibiotics for AOM, one developed AOM in subsequent years who would not have done so had they all been given placebo.

The NPC recommends the following action<sup>2</sup>:

“Health professionals should follow NICE guidance on management of upper respiratory tract infections. They should try to agree a no-antibiotic or delayed-antibiotic strategy for most children with AOM, and generally prescribe antibiotics **only** to children with AOM who are systemically very unwell or at high risk of serious complications because of pre-existing co-morbidity, or who appear unwell with symptoms and signs suggestive of mastoiditis. Depending on clinical assessment of severity, an immediate antibiotic prescription could be **considered** for children with otorrhoea or children younger than two years with bilateral AOM, but it is important to weigh the likely benefits against the possible risk, including side effects. The NPCi [patient decision aids](#) relating to AOM specifically and upper respiratory tract infections generally may be helpful in some consultations.”

1. BMJ 2009; 338:b2525
2. [www.npci.org.uk/blog/?p=495](http://www.npci.org.uk/blog/?p=495)

### **Reducing antibiotic prescribing**

Use of a booklet on respiratory tract infections in children within primary care consultations leads to important reductions in antibiotic prescribing and reduced intention to consult without reducing satisfaction according to a recently published study<sup>1</sup>.

This was a pragmatic cluster randomised controlled trial undertaken in 61 general practices in England and Wales. Clinicians in the intervention group were trained in the use of an interactive booklet on respiratory tract infections (see [www.equipstudy.com](http://www.equipstudy.com) or contact me for a copy) and asked to use the booklet during consultations with recruited patients (and provide it as a take home resource). Clinicians in the control group conducted their consultations as usual.

The participants were 558 children (aged 6 months to 14 years) presenting to primary care with an acute respiratory tract infection (7 days or less). Children with suspected pneumonia, asthma or a serious concomitant illness, or needing immediate hospital admission were excluded. Antibiotics were prescribed at the index consultation to 19.5% of children in the intervention group and 40.8% of children in the control group (absolute risk reduction 21.3%). This gives an NNT of 4 to 5. In other words, for every 4 to 5 consultations where the booklet was used there was one less prescription for antibiotics. There was also a significant reduction in the proportion of patients who said they would consult in the future if their child developed a similar illness (OR 0.34 [0.20 to 0.57]).

The authors comment that this was an adequately powered randomised controlled trial and the results are highly generalisable to UK general practice. They suggest that routine use of this intervention in primary care should now be considered along with other effective interventions such as delayed prescribing.

1. BMJ 2009; 339:b2885

### **Antidiabetic therapies affect risk of pancreatic cancer**

Treatment of diabetes may affect risk of pancreatic cancer, metformin reducing it and insulin and sulphonylureas increasing it, according to the results of a case-control study<sup>1</sup>.

Patients with type 2 diabetes seem to be at increased risk of several cancers, and there is evidence that diabetes may have a role in pancreatic cancer. Other studies have suggested that metformin reduces, and insulin and sulphonylureas increase risk of any cancer, but have not examined the risk of pancreatic cancer specifically.

Data from an existing case-control study, which was started in 2004 to define environmental and genetic factors that contribute to the development of pancreatic cancer, were used to investigate the potential association between diabetes treatment and pancreatic cancer. Cases were patients with newly diagnosed and confirmed pancreatic ductal adenocarcinoma and controls were recruited from spouses and non-blood relatives and friends

of patients with cancers other than gastrointestinal or smoking-related. Neither cases nor controls had a previous cancer history except for non-melanoma skin cancer. Diagnosis of diabetes, and frequencies of use of insulin, insulin secretagogues, metformin, and other antidiabetic medications among patients with diabetes were compared between cases and controls. The risk of pancreatic cancer was then estimated using multivariate unconditional logistic regression analysis.

There were 973 cases (259 with diabetes) and 863 controls (109 with diabetes). After adjustment for potential confounding factors, the following results were reported:

- Diabetes was associated with a 2.37 fold increased risk of pancreatic cancer (95% CI 1.87 to 3.06).
- Patients with diabetes who had taken metformin had a significantly lower risk of pancreatic cancer vs. those who had not (odds ratio 0.38 [95% CI 0.22 to 0.69];  $p=0.001$ ). The association remained present when analysis was restricted to those with a duration of diabetes greater than two years (OR 0.41 [0.19 to 0.87]).
- Patients with diabetes who had taken metformin also had a lower risk of pancreatic cancer than patients without diabetes (0.38 [0.21 to 0.67];  $p=0.001$ ).
- Patients with diabetes who had used insulin or taken insulin secretagogues had a significantly higher risk of pancreatic cancer than those who had not (4.99 [2.59 to 9.61];  $p<0.001$ ; and 2.52 [1.32 to 4.84];  $p=0.005$ , respectively).
- Ever users of a glitazone had a 55% higher risk of pancreatic cancer compared with never users, but the difference was not statistically significant (OR 1.55 [0.78 to 3.07]).

The authors conclude that patients with type 2 diabetes who had used metformin, especially for more than five years, had a significantly reduced risk of pancreatic cancer compared to never-users. Additionally, although the numbers were smaller and the confidence intervals wider, there was also an indication that use of insulin or insulin secretagogues was associated with an increased risk.

The author of the accompanying editorial<sup>2</sup> comments that the observed pancreatic risk reduction associated with metformin use seen in this study is consistent with prior epidemiologic and preclinical data. He adds that the significantly increased risk of pancreatic cancer observed among long-term insulin users may represent an important finding. Insulin has been shown to induce cell proliferation and reduces apoptosis by increasing the bioavailability of insulin-like growth factor-I<sup>2</sup>.

Metformin is already the first-line antidiabetic therapy for people with type 2 diabetes and a possible protective effect on pancreatic cancer may provide an additional incentive to prescribe it for as many as possible (without contraindications) and for patients to take it.

1. Gastroenterology 2009; 137:482-88
2. Gastroenterology 2009; 137:412-30

### **More on glitazone safety**

A prospective cohort study from Canada provides further evidence that treatment with glitazones is associated with an increased risk of fracture compared with treatment with sulfonylureas<sup>1</sup>. The mean age of the patients in the study was 59 years and 43% were women. In this cohort, treatment with a glitazone was associated with a 28% increased risk of peripheral fractures (HR 1.28 [CI 1.10 to 1.48]). The authors concluded that both men and women who take a glitazone could be at increased risk of fractures and pioglitazone may be more strongly associated with fractures than rosiglitazone, although the confidence intervals from the subgroup analyses for the two glitazones overlapped, which prevents us from making a strong conclusion that the two drugs have different fracture risks.

A retrospective cohort study, again from Canada, compared the risk of acute MI, heart failure, and death in patients with type 2 diabetes treated with rosiglitazone and pioglitazone<sup>2</sup>. The median age of the patients was 72 and 52.6% were men. The main outcome measure was a composite of death or hospital admission for either acute MI or heart failure. During the six year study period, the composite outcome was reached in 5.3% of those taking pioglitazone and 6.9% of those taking rosiglitazone. After extensive adjustment for demographic and clinical factors and drug doses, pioglitazone treated patients had a lower risk of developing the primary outcome than did those on rosiglitazone (adjusted HR 0.83 [CI 0.76 to 0.90]). Secondary analyses revealed a lower risk of

death and heart failure with pioglitazone but no significant difference in the risk of MI. One additional composite outcome was predicted to occur annually for every 93 patients treated with rosiglitazone rather than pioglitazone.

The study was designed to explore the comparative safety of the two glitazones and does not assess the safety of pioglitazone relative to other hypoglycaemic agents. The authors stress that their findings should not be interpreted as evidence that pioglitazone is devoid of cardiovascular toxicity. Good evidence exists that both glitazones can cause heart failure. However, the authors do state that given the accumulating evidence of harm with rosiglitazone treatment and the lack of distinct clinical advantage for the drug over pioglitazone, questioning whether ongoing use of rosiglitazone is justified in any circumstance is reasonable; “we believe that clinicians should re-evaluate the appropriateness of new or ongoing treatment with rosiglitazone.”

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

“Health professionals should continue to follow MHRA advice published in October 2007 and December 2007. Neither pioglitazone ▼ nor rosiglitazone should be used in people with heart failure or a history of heart failure. Rosiglitazone should be used in patients with previous or current ischaemic heart disease only after a careful evaluation of the individual patient’s risk. Neither glitazones should be commenced or continued in people at higher risk of fractures.

In people with type 2 diabetes, priority should be given to reducing cardiovascular risk – lifestyle interventions (stopping smoking, losing weight, and taking more exercise as appropriate), controlling blood pressure, taking a statin, and taking metformin. In some patients, additional hypoglycaemic drugs may be considered to control blood glucose. However, NICE guidance should be followed and individual targets for HbA1c should be agreed with each patient. These could be above that of 6.5% (48mmol/mol) set for people with type 2 diabetes in general and should take into account patient preferences and the balance of likely benefits and harms (such as hypoglycaemia) as well as the medicines management issues.”

With regard to the three main safety issues with glitazones: heart failure, myocardial ischaemia and fractures, current MHRA advice is as follows (see Drug Safety Update October 2007 and December 2007).

- Rosiglitazone and pioglitazone ▼ should not be used in people with heart failure or history of heart failure; incidence of heart failure is increased when rosiglitazone or pioglitazone ▼ are combined with insulin. Closely monitor patients during treatment for signs and symptoms of fluid retention, including weight gain or oedema.
- Rosiglitazone might be associated with a small increased risk of cardiac ischaemia, particularly in combination with insulin; rosiglitazone should be used in patients with previous or current ischaemic heart disease only after careful evaluation of individual risk.
- The risk of fracture should be considered in the care of patients, especially women, treated with pioglitazone ▼ or rosiglitazone. NICE recommends that glitazones should not be started or continued in people at higher risk of fractures.

A letter in the BMJ<sup>4</sup> reports that diabetic patients taking a glitazone are more likely to develop diabetic macular oedema. The authors quote two studies to support this. The macular oedema seems to be reversible in many cases on stopping the drug and they recommend that physicians and ophthalmologists caring for patients taking glitazones should be aware of this vision threatening complication and stop glitazone treatment in those developing diabetic macular oedema.

1. Arch Intern Med 2009; 169:1395-1402
2. BMJ 2009; 339:b2942
3. [www.npci.org.uk/blog/?p=524](http://www.npci.org.uk/blog/?p=524)
4. BMJ 2009; 339: b3856

### **Severe hypoglycaemia and dementia**

According to a recent study, a history of severe hypoglycaemia requiring hospitalisation or an emergency department visit is significantly associated with a diagnosis of dementia in adults with type 2 diabetes<sup>1</sup>.

The study cohort included 16,667 patients, 55 years or older, identified with type 2 diabetes without a prior diagnosis of dementia or cognitive impairment as part of a major diabetes registry initiated in 1994. The registry is

estimated to be greater than 95% accurate in capturing important health-related information. Incident cases included an ICD-9-CM diagnosis of senile, Alzheimer, vascular, and not otherwise specified dementia since January 1, 2003. Exposures included hypoglycaemic episodes occurring from January 1980 through December 31, 2002.

A total of 1822 patients (11%), with a mean age of 64.9 years, were diagnosed with dementia during a mean follow-up of 3.8 years. Cox regression modelling adjusted for other variables including age, education, race, duration of diabetes and its treatment, hyperlipidaemia, hypertension, cardiovascular disease, renal disease, insulin use, and average Hb A1c levels. The remaining attributable risk of dementia for patients with 1 or more severe hypoglycaemic episodes compared with those with no episodes was 2.39% per year. Hazard ratios (HRs) increased proportionally with the number of episodes of hypoglycaemia; at least 1 episode, HR = 1.68; 2 episodes, HR = 2.15; and 3 or more episodes, HR = 2.60. To determine whether preclinical dementia was responsible for the increased likelihood of hypoglycaemic episodes, the authors performed a subanalysis examining the risk in patients whose hypoglycaemic episodes occurred at least 2 years prior to a dementia diagnosis and at least 18 years prior to a diagnosis. Although there were fewer hypoglycaemic events, there was still a significant increased risk for dementia with prior hypoglycaemia (1 or more episodes vs no episodes, HR = 1.32 for 18-year lag time).

The bottom line comment from the Daily POEM review of this study is “Given recent evidence that tight glucose control (an HbA<sub>1c</sub> level less than 7.0) is not beneficial and increases the risk of hypoglycaemia, clinicians and patients should re-evaluate their individual treatment goals”.

1. JAMA 2009; 301:1565-72

### **Diet and the need for antihyperglycaemic drugs**

For people with newly diagnosed type 2 diabetes, their diet can have a very important effect on the need for antihyperglycaemic drug therapy, according to this randomised trial<sup>1</sup>.

The participants were 215 overweight people with newly diagnosed type 2 diabetes who were never treated with antihyperglycaemic drugs and had HbA<sub>1c</sub> levels less than 11%. They were randomised (allocation concealed) to a Mediterranean – style diet (<50% of daily calories from carbohydrates) or a low-fat diet (<30% of daily calories from fat). The MED diet was rich in vegetables and whole grains and low in red meat, which was replaced with poultry and fish, and included olive oil. The low-fat diet was based on American Heart Association guidelines; it was rich in whole grains and restricted additional fats, sweets, and high-fat snacks.

After 4 years, 44% of people in MED diet group and 70% in the low-fat group required treatment with antihyperglycaemic drugs (absolute difference 26%, NNT=4). The hazard ratio was 0.63 (CI 0.51 to 0.86; p<0.001) and was very similar when adjusted for weight change (0.70 [0.59 to 0.90]). Participants assigned to the MED diet lost more weight and experienced greater improvements in some glycaemic control and coronary risk measures than did those assigned to the low-fat diet.

The authors comment that these findings reinforce the message that benefits of lifestyle interventions should not be overlooked despite the drug-intensive style of medicine fuelled by the current medical literature.

1. Ann Intern Med 2009; 151:306-14

### **Monitoring alendronate treatment**

An analysis has found that measuring bone mineral density in postmenopausal women taking alendronate produces unreliable results. Early routine monitoring should be avoided because it has the potential to mislead.

To evaluate the benefit of BMD monitoring, Australian and US researchers performed a secondary analysis of data from the Fracture Intervention Trial that compared the effect of alendronate and placebo, measuring BMD yearly for 3 years<sup>1</sup>. The researchers used data from all patients to determine differences in BMD over time between different patients but also in the same patient. Most patients receiving alendronate had an increase in BMD of at least 0.019 g/cm<sup>2</sup> (97.5%), meaning that the response is similar between patients and monitoring for individual response is not necessary. More important, the authors found significant variation in BMD over time

within the same individuals, so measurements may be misleading. Extrapolating, the researchers make the case that BMD testing is a poor indicator of adherence to therapy, since variations in BMD may not be at all related to adherence but simply to the imprecision of the test itself. Their suggestion - simply ask the patient if they are taking the drug. Non-adherence is best detected by direct interview and best increased by making patients active participants in their treatment.

The accompanying editorial<sup>2</sup> states that monitoring BMD during antiresorptive treatment for osteoporosis is potentially misleading and a misuse of healthcare resources. This is echoed by the NPC in their review of this study<sup>3</sup>. The NPC comment “Bisphosphonates, or indeed any intervention, can only reduce the risk of fracture: they cannot abolish it. This means that all patients, even if they adhere strictly to their prescribed regimen and also change their lifestyle (e.g. ensuring adequate calcium and vitamin D intake, stopping smoking, moderating alcohol intake, remaining physically active, action taken to reduce the risk of falls) will still have a residual risk of fracture. If a fracture occurs **this does not necessarily mean the drug is ineffective.**”

1. BMJ 2009; 338:b2266

2. BMJ 2009; 338:b1276

3. [www.npci.org.uk/blog/?p=592](http://www.npci.org.uk/blog/?p=592)

### **Treatment blood pressure targets**

A recent Cochrane review has concluded that aiming for blood pressure targets lower than 140/90 mmHg is not beneficial<sup>1</sup>.

### **Plain language summary**

High blood pressure (BP) is linked to an increased risk of heart attack and stroke. High BP has been defined as any number larger than 140 to 160/90 to 100 mmHg and as a result this range of BPs has become the standard blood pressure target for physicians and patients. Over the last five years a trend toward lower targets has been recommended by hypertension experts who set treatment guidelines. This trend is based on the assumption that the use of drugs to bring the BP lower than 140/90 mmHg will reduce heart attack and stroke similar to that seen in some population studies. However, this approach is not proven.

This review was performed to find and assess all trials designed to answer whether lower blood pressure targets are better than standard blood pressure targets. Data from 7 trials in over 22,000 people were analysed. Using more drugs in the lower target groups did achieve modestly lower blood pressures. However, this strategy did not prolong survival or reduce stroke, heart attack, heart failure or kidney failure. More trials are needed, but at present there is no evidence to support aiming for a blood pressure target lower than 140/90 mmHg in any hypertensive patient.

An editorial<sup>2</sup> on this Cochrane review comments that there are limits to the benefits of reducing blood pressure in patients with hypertension and continued efforts to lower it beyond various targets only increases cost and inconvenience for the patient.

1. *Cochrane Database of Systematic Reviews* 2009, Issue 3

2. JAMA 2009; 302:1047-8

### **Guidelines update**

The following guidelines and shared care agreements have recently been ratified by JAPC:

- Medical management of glaucoma
- Stopping long-term amiodarone treatment
- Antipsychotics – recommended physical monitoring
- Osteoporosis guideline (update)
- Antimicrobial treatment guideline (update)
- Management of *C.difficile* infection in primary care
- Drug monitoring recommendations
- n-Acetylcysteine shared care
- Lacosamide shared care
- \*Azathioprine/6-mercaptopurine shared care
- \*Ciclosporin shared care
- \*Hydroxychloroquine shared care
- \*Leflunomide shared care
- \*Methotrexate shared care
- \*D-penicillamine shared care
- \*Sodium aurothiomalate shared care
- \*Sulfasalazine shared care

\* December implementation date