

NEWSLETTER

Supporting the Derbyshire Health Community

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JAPC Update

The Joint Area Prescribing Committee (JAPC) is a countywide group covering Derbyshire County PCT and Derby City PCT. It provides recommendations on drugs and medicines management issues.

RED drugs are those where prescribing responsibility lies with a hospital consultant or a specialist. AMBER drugs are those that are initiated within a hospital/specialist setting but are suitable for shared care with a GP under a shared care agreement. GREEN drugs are regarded as suitable for primary care prescribing. BROWN drugs are those that JAPC does not recommend for use, except in exceptional circumstances, due to lack of data on safety, effectiveness, and/or cost-effectiveness.

The most recent updates are in the table below; the full list is available at

<http://www.derbyshirecountypct.nhs.uk/guidelines/default.asp>

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

Drug	Date considered	Decision
Prasugrel	May 2009	BROWN
U500 Humulin R insulin	May 2009	BROWN
Bicalutamide 50mg/150mg tabs	April 2009	AMBER (with Derby hospitals)
Melatonin	April 2009	AMBER
Fentanyl patch/tablet/lozenge	March 2009	GREEN (third-line use only)
Fluticasone furoate nasal spray (Avamys)	March 2009	BROWN
Ranolazine	March 2009	BROWN
Tadalafil 2.5mg and 5mg tablets (Cialis once-a-day)	March 2009	BROWN

Clopidogrel and PPIs – part 2

Further to the article in the March issue, another study has now been published¹. This also was a retrospective cohort study, involving all patients with acute MI or unstable angina as documented by standard electrocardiographic criteria, elevated troponin levels, and other clinical evidence, discharged from any 1 of 127 VHA medical centres between October 1, 2003, and January 31, 2006, and prescribed clopidogrel at hospital discharge.

Death or rehospitalisation for ACS occurred in 20.8% (n=615) of patients prescribed clopidogrel without PPI and 29.8% (n=1561) of patients prescribed clopidogrel plus PPI. In multivariable analysis, use of clopidogrel plus PPI at any point in time was associated with an increased risk of death or rehospitalisation for ACS compared with use

of clopidogrel without PPI (adjusted OR [AOR], 1.25; 95% confidence interval [CI], 1.11-1.41). In multivariable analysis, use of clopidogrel plus PPI remained significantly associated with a higher risk of recurrent ACS (AOR, 1.86; 95% CI, 1.57-2.20) and revascularisation procedures (AOR, 1.49; 95% CI, 1.30-1.71) compared with use of clopidogrel without PPI; however, there was no association between use of clopidogrel plus PPI and all-cause mortality (AOR, 0.91; 95% CI, 0.80-1.05) compared with use of clopidogrel without PPI.

There was no obvious dose response relationship between PPI dose and adverse outcomes (OR, 1.00; 95% CI, 0.99-1.01 for each 1mg increment). However, each 10% increase in the proportion of time taking clopidogrel plus PPI during follow-up was associated with a higher risk of death or rehospitalisation for ACS (OR, 1.07; 95% CI, 1.05-1.09). In evaluating individual PPI agents, there was a consistent association between omeprazole (OR, 1.24; 95% CI, 1.08-1.41) and rabeprazole (OR, 2.83; 95% CI, 1.96-4.09) with adverse outcomes. The association among the other PPIs (ie, lansoprazole and pantoprazole) was not explored given the small numbers of patients taking these medications.

When patients were not taking clopidogrel after hospital discharge, a prescription for PPI was not associated with death or rehospitalisation for ACS (AOR, 0.98; 95% CI, 0.85-1.13), supporting the hypothesis that the interaction of PPI and clopidogrel, rather than PPI itself, was associated with increased adverse outcomes.

This study suggests that concomitant use of clopidogrel and PPI may be associated with an attenuation of the benefits of clopidogrel after hospitalisation for ACS. The findings were consistent in sensitivity analyses and using a nested case-control study method. It appears that the increased risk is primarily due to recurrent hospitalisation for ACS. The authors state that mechanistic and translational studies suggest a biological mechanism supporting the findings of this study. These medications share common metabolic pathways mediated by cytochrome P450 isoenzymes in the liver.

Omeprazole (and possibly rabeprazole) was strongly associated with adverse outcomes but use of other PPIs was too low to allow analysis. The authors ask for further studies to assess the risk with other PPIs.

They found that longer duration of treatment with clopidogrel plus PPI was associated with adverse outcomes, suggesting that time receiving the combination is important.

As the authors acknowledge, this epidemiological study cannot confirm a causal relationship, and cannot address the individual patient benefits of PPI therapy with clopidogrel after hospitalisation for ACS. That would require a randomised, controlled trial. They suggest that, pending additional evidence, PPIs should be used for patients with a clear indication for the medication, such as history of GI tract bleeding, rather than routine prophylactic prescription. Alternative GI tract medication regimens may also be considered until additional data becomes available.

Both of these studies have now been discussed at JAPC. Both studies agreed that histamine H2-receptor antagonists such as ranitidine did not pose a risk. There appears to be no certainty that any PPI is safe.

This is the agreed advice, which is supported by cardiologists at Chesterfield and Derby:

1] is the clopidogrel still required i.e. is the JAPC [clopidogrel guidance](#) being followed?

2] if yes, is gastroprotection actually required i.e. is the patient at high risk of bleeding e.g. history of GI tract bleeding?

3] if yes, ranitidine 300mg twice daily, not a PPI, would appear to be the safest option and of equivalent efficacy². Although ranitidine is not specifically licensed for gastroprotection, its use in this situation is supported by JAPC.

The first question is very important. Here is the relevant extract from the clopidogrel guidance:

Acute coronary syndrome (NSTEMI)

- The CURE study compared the combination of clopidogrel with aspirin to aspirin given alone in patients admitted with ACS. Most were at high risk with raised troponin levels and / or ECG changes but without ST-segment-elevation.

- The addition of clopidogrel reduced the risk of a non-fatal MI but **the NNT was 48**, i.e. 48 patients have to be treated with clopidogrel plus aspirin, instead of aspirin alone, to prevent one event.
- The duration of clopidogrel therapy after an NSTEMI is controversial. However, NICE now recommends 12 months.
- Despite exclusion of patients judged at 'high risk of bleeding', the addition of clopidogrel significantly increased the absolute rate of major bleeding (defined as substantially disabling bleeding, intraocular bleeding leading to loss of vision, or bleeding necessitating transfusion of at least 2 units of blood) by 1%. **That is, of 100 people treated for about 9 months, one would suffer severe harm associated with the addition of clopidogrel (NNH = 100).**
- **After an ACS, patients will be discharged with 28 days supply and primary care will be responsible for prescribing the rest of the course. It is imperative that a stop date for the clopidogrel is noted and acted upon. It is advised to include this on the prescription so that the stop date appears on the label e.g. 'Take one daily until 31st October 2008 and then stop.'** It is sensible to involve the patient in the decision to continue the clopidogrel for more than 3 months, bearing in mind the NNT and the NNH. From 3 months to 12 months little additional benefit over aspirin alone is seen, with an NNT of 500.

1. JAMA 2009; 301: 937-44

2. Prevention of NSAID-induced gastroduodenal ulcers. *Cochrane Database of Systematic Reviews* 2002, Issue 4

Antidiabetes drugs and the risk of lactic acidosis

Metformin plays a pivotal role in the treatment of people with type 2 diabetes. Unlike other hypoglycaemic agents metformin has positive patient-orientated outcome evidence and may prolong life. Its use needs to be maximised.

A quoted potential complication of metformin use is lactic acidosis. Studies to date have shown that lactic acidosis is extremely rare in people taking metformin. A recent study adds to our knowledge base.

This study was a nested case-control analysis using the UK General Practice Research Database¹. Patients with type 2 diabetes who used oral antidiabetes drugs were identified and all cases of lactic acidosis and hypoglycaemia identified. Among the study population of 50,048 type 2 diabetes subjects, 6 cases of lactic acidosis during current use of oral antidiabetes drugs were identified, yielding a crude incidence rate of 3.3 cases per 100,000 person years among metformin users and 4.8 cases per 100,000 person years among users of sulphonylureas.

Five of the 6 cases of lactic acidosis suffered from acute worsening of known risk factors for lactic acidosis (acute heart failure, urosepsis, hypovolaemia, seizure, acute renal failure). The authors suggest that diabetes, rather than metformin, may be a leading risk factor for lactic acidosis. The results support previous evidence that metformin-associated lactic acidosis is rare and is observed in association with an acutely worsening clinical condition.

Use of sulphonylureas was associated with a materially elevated risk of hypoglycaemia. The adjusted odds ratio for current use of sulphonylureas was 2.79 (CI 2.23 to 3.50) compared with current metformin use.

The authors advise 'Considering morbidity of severe hypoglycaemia and the low absolute risk of lactic acidosis associated with metformin use, clinicians must carefully ensure that risks outweigh benefits when withholding metformin from patients with type 2 diabetes.'

1. Diabetes Care 2008; 31:2086-91

Fracture risk with glitazones

More information on the fracture risk with glitazones is now available with the publication of a meta-analysis¹. Rosiglitazone and pioglitazone approximately double the risk of fractures in women, but not in men.

This meta-analysis of ten RCTs of people with type 2 diabetes or impaired glucose tolerance (total n=13,715) found that the odds ratio (OR) for fractures with glitazones compared with control (placebo or other oral hypoglycaemic drugs) was 1.45 (95%CI 1.18 to 1.79, P<0.001). Five RCTs (11,401 patients) provided data on

fractures by gender and found a statistically significant increased risk of fractures among women (OR 2.23, 95%CI 1.65 to 3.01; P<0.001) but not among men (OR 1.00, 95%CI 0.73 to 1.39; P=0.98). It was estimated that if 55 women at low-risk of fracture took a glitazones for one year, then one fracture would occur (NNH=55). Among women at high risk, one fracture would occur for every 21 women (NNH=21).

The accompanying editorial² advises 'Until further evidence of their net benefit is available, the appropriate role for these drugs is unclear.'

1. CMAJ 2009; 180:32-39
2. CMAJ 2009; 180:16-17

Risks of PPI use

Another study adds to the evidence base that PPIs may increase the risk of osteoporosis-related fractures¹. This case-control study found that use of PPIs increased the risk of hip fracture after 5 or more years of continuous exposure. The risk of any osteoporotic fracture was increased after at least 7 years of continuous exposure to PPIs. The calculated odds ratios for exposure to PPIs were similar to those for other established osteoporotic fracture risk factors, such as smoking, low BMI and excessive alcohol intake.

The authors conclude 'Because evidence also suggests that use of proton pump inhibitors may be associated with an increased risk of enteric infections such as *clostridium difficile* and community acquired pneumonia, clinicians must be increasingly vigilant in ensuring that proton pump inhibitors are used sparingly and only when absolutely indicated'.

The accompanying editorial² points out that three large, well-designed studies now report an association between the use of PPIs and fractures and that this association appears to be both dose- and duration-dependant.

A recent cohort study³ suggests that PPI use is associated with a small but significant increased risk of hospitalisation for pneumonia. The 16% increase in risk equates to 4 extra hospitalisations each year for every 1000 people prescribed a PPI. As the authors point out, while the increased risk is small, the prevalent use of PPIs means that many people could be affected.

The accompanying editorial⁴ (titled 'Risks of proton pump inhibitors: what every doctor should know') advises 'it is prudent and best practice to warn patients about the potential serious (albeit rare) side effects of PPIs, to prescribe the lowest possible dose of PPI (when indicated) for as short a time as possible, and to consider alternative management options if these are available'.

1. CMAJ 2008; 179:319-26
2. CMAJ 2008; 179:306-7
3. MJA 2009; 190:114-16
4. MJA 2009; 190:109-11

Risks of NSAID use in heart failure

A recent, very large observational study¹ (population of Denmark) has found that people with heart failure who took NSAIDs, particularly at higher doses, were at substantially greater risk of death or hospitalisation for heart failure or MI, than non-users. Users of coxibs or diclofenac were at highest risk.

The number of patients needed to be treated to cause one additional death (NNH) per year were:

Rofecoxib	9 (8 to 11)
Celecoxib	14 (11 to 19)
Diclofenac	11 (9 to 13)
Ibuprofen	53 (36 to 100)
Naproxen	51 (22 to 158)
Other NSAIDs	43 (29 to 78)

Low doses of ibuprofen ($\leq 1200\text{mg/day}$) and naproxen ($\leq 500\text{mg/day}$) were not associated with increased mortality risk, although high doses of both were associated with an increased risk of death.

The NPC recommend the following action²:

“Prescribers should consider the cardiovascular risk of NSAIDs and use them only when **essential** in people with heart failure. Patients with heart failure who are prescribed NSAIDs, particularly diclofenac or coxibs, should have their NSAID medication reviewed. If an NSAID is essential, the first choice drug is ibuprofen at 1200mg/day or less. Naproxen is probably next choice, although the risks with this drug are greater.”

1. Arch Intern Med 2009; 169:141-9
2. www.npci.org.uk/blog/?p=291

Drug induced *Clostridium difficile* infection

Clostridium difficile is often present in the lower gastrointestinal tract, but can proliferate, produce cytotoxins and cause profuse watery diarrhoea. Several risk factors have been identified for *C.difficile* infection. These include age over 65 years, exposure to certain antibiotics – particularly long courses and possibly the use of acid-suppressing medications such as proton pump inhibitors.

Prudent use of antibiotics is an essential component of controlling *C.difficile* infection. An effective antimicrobial control programme should include avoiding broad spectrum antibiotics, only prescribing antibiotics when necessary, and then for as short a duration as practicable.

The Regional Drug and Therapeutics Centre at the Wolfson Unit, Newcastle upon Tyne, have produced a useful leaflet on drug-induced *C.difficile* infection (CDI)¹.

Several risk factors have been identified for CDI. Patients over the age of 65 years are particularly at risk and the occurrence of CDI in this age group is increasing. Patients who are suffering from severe underlying diseases, e.g. cancer, and those who are immunocompromised, are also particularly susceptible. Other factors that may increase the risk of CDI include close contact with other patients e.g. in care homes, recent gastrointestinal procedures and the presence of nasogastric tubes.

Antibiotic use is the most significant and frequently reported predisposing risk factor for CDI in hospital and community settings.

Table 1: Relative risk of antibiotics and their association with CDI
High risk antibiotics for CDI
Second-generation cephalosporins e.g. cefaclor, cefuroxime Third-generation cephalosporins e.g. cefixime, cefotaxime, ceftazidime, ceftriaxone Clindamycin Quinolones e.g. ciprofloxacin, levofloxacin, ofloxacin, norfloxacin
Intermediate risk antibiotics for CDI
Macrolides e.g. erythromycin, clarithromycin Aminopenicillins* e.g. co-amoxiclav, amoxicillin, ampicillin *risk increases with prolonged courses
Low risk antibiotics for CDI
Trimethoprim Tetracyclines e.g. tetracycline, oxytetracycline, doxycycline Benzylpenicillin/Phenoxymethylpenicillin Aminoglycosides e.g. gentamicin Vancomycin Piperacillin with tazobactam

Practice Point – components of an effective antimicrobial control programme include

- Only prescribe antibiotics when necessary, e.g. avoidance of use for sore throat, coughs and colds etc.
- Prescribe short durations of antibiotics including single-dose prophylaxis.
- Avoid broad spectrum antibiotics. Use narrow spectrum agents when clinically appropriate and according to sensitivity testing.
- Consult local guidance.

Diarrhoea is a common adverse reaction which has been reported with most drugs (see table 2). Antimicrobials account for 25% of drug induced diarrhoea, although most cases are benign. Alternative diagnoses for diarrhoea are important; therefore the timing of when the medicine was first taken and when diarrhoea first appears is important.

Acarbose	Laxatives
Antimicrobials	Leflunamide
Biguanides	Magnesium preparations (e.g. antacids)
Bile salts	Metoclopramide
Colchicine	Misoprostol
Cytotoxics	NSAIDs (e.g. aspirin, ibuprofen)
Dipyridamole	Olsalazine
Gold preparations	Orlistat
Iron salts	Proton pump inhibitors

1. www.nyrdtc.nhs.uk/docs/smu/RDTC_SMU_04.pdf

Prescribing off-label or unlicensed medicines

There are clinical situations when the use of unlicensed medicines or use of medicines outside the terms of the licence (i.e. 'off-label') may be judged by the prescriber to be in the best interest of the patient on the basis of available evidence. Such practice is particularly common in certain areas of medicine: for instance, in paediatrics where difficulties in the development of age-appropriate formulations means that many medicines used in children are used off-label or are unlicensed.

Healthcare professionals may regard it necessary to prescribe or advise on the use of an unlicensed medicine (i.e., through the so-called 'specials' regime when no licensed suitable alternative is available, or when a medicine is prepared in a pharmacy by, or under the supervision of, a pharmacist), or the use of a licensed medicine outside the terms defined by the licence (e.g., outside defined indications, doses, routes of administration, or contrary to listed warnings).

The responsibility that falls on healthcare professionals when prescribing an unlicensed medicine or a medicine off-label may be greater than when prescribing a licensed medicine within the terms of its licence. Prescribers should pay particular attention to the risks associated with using unlicensed medicines or using a licensed medicine off-label. These risks may include: adverse reactions; product quality; or discrepant product information or labelling (e.g., absence of information for some unlicensed medicines, information in a foreign language for unlicensed imports, and potential confusion for patients or carers when the Patient Information Leaflet is inconsistent with a medicine's off-label use).

Advice for prescribers from the MHRA/CHM¹:

Consider...

- Before prescribing an unlicensed medicine, be satisfied that an alternative, licensed medicine would not meet the patient's needs
- Before prescribing a medicine off-label, be satisfied that such use would better serve the patient's needs than an appropriately licensed alternative.
- Before prescribing an unlicensed medicine or using a medicine off-label:
 - Be satisfied that there is a sufficient evidence base and/or experience of using the medicine to show its safety and efficacy

- Take responsibility for prescribing the medicine and for overseeing the patient's care, including monitoring and follow-up
- Record the medicine prescribed and, where common practice is not being followed, the reasons for prescribing this medicine; you may wish to record that you have discussed the issue with the patient

Communicate: best practice is that...

- You give patients, or those authorising treatment on their behalf, sufficient information about the proposed treatment, including known serious or common adverse reactions, to enable them to make an informed decision
- Where current practice supports the use of a medicine outside the terms of its licence, it may not be necessary to draw attention to the licence when seeking consent. However, it is good practice to give as much information as patients or carers require or which they may see as relevant.
- You explain the reasons for prescribing a medicine off-label or prescribing an unlicensed medicine where there is little evidence to support its use, or where the use of a medicine is innovative.

Report suspected adverse reactions...

- Healthcare professionals have a responsibility to help monitor the safety of medicines in clinical use through submission of suspected adverse drug reactions to the MHRA and CHM via the Yellow Card Scheme (see www.yellowcard.gov.uk). Such reporting is equally important for unlicensed medicines or those used off-label as for those that are licensed.

1. Drug Safety Update, volume 2, issue 9, April 2009

Dipyridamole for stroke prevention

NICE TAG 90 (May 2005) states that the combination of MR dipyridamole and aspirin is recommended for people who have had an ischaemic stroke or a TIA for a period of 2 years from the most recent event. Thereafter, or if MR dipyridamole is not tolerated, preventative therapy should revert to standard care (including long-term treatment with low-dose aspirin).

In Derbyshire, as a result of the publication of the ESPRIT study¹, which showed continued benefit for the combination for at least 5 years, the advice is to prescribe aspirin 50-75mg daily and dipyridamole MR 200mg twice daily for as long as is tolerated and then aspirin alone.

This recommendation has been supported by a meta-analysis comparing dipyridamole plus aspirin (D+A) versus aspirin alone (ASA) in secondary prevention after TIA or stroke². The trial-adjusted hazard ratio (HR) for the composite event of vascular death, non-fatal MI and non-fatal stroke was 0.82 (CI 0.72 to 0.92). D+A were also more effective than ASA in preventing recurrent stroke; HR 0.78 (0.68 to 0.90).

The authors concluded that the combination of aspirin and dipyridamole is more effective than aspirin alone in patients with TIA or ischaemic stroke of presumed arterial origin in the secondary prevention of stroke and other vascular events. This superiority was found in all sub-groups and was independent of baseline risk. The advantage starts early on and remains present over time.

The combination of aspirin with clopidogrel is not recommended as the MATCH trial³ showed no benefit in reducing the risk of ischaemic events after stroke or TIA but an increase in life-threatening bleeding (NNH=50).

The PROFESS study has compared aspirin + dipyridamole MR with clopidogrel for recurrent stroke⁴. The primary outcome was first recurrence of stroke. After a mean of 2.5 years recurrent stroke occurred in 9.0% receiving the combination and 8.8% receiving clopidogrel (HR 1.01 [CI 0.92 to 1.11]). The authors concluded "There is no evidence that either of the two treatments was superior to the other in the prevention of recurrent stroke".

1. Lancet 2006; 367:1665-73
 2. J Neurol Neurosurg Psychiatry 2008; 79:1218-23
 3. Lancet 2004; 364:331-7
 4. N Engl J Med 2008; 359:1238-51

Z-drugs and road traffic accidents

A study in Norway¹ found that people prescribed zopiclone or zolpidem had double the risk of road traffic accidents compared with people who weren't prescribed hypnotics, similar to the increased risk seen with nitrazepam.

Absolute rates of traffic accidents associated with hypnotic prescription were between about 5 and 9 accidents per exposed 1000 person-years in groups treated with hypnotics compared with about 2 per 1000 person-years in the group not exposed to hypnotics.

The NPC recommends the following action²:

“Prescribers should follow NICE guidance for the use of Z-drugs in the management of insomnia. After non-drug therapies have been explored, hypnotics should be used in the lowest dose possible for no more than 4 weeks in the case of benzodiazepines and between 2 and 4 weeks with Z-drugs. Prescribers should be aware that clinical evidence to differentiate Z-drugs from benzodiazepines is weak, and in practice there appears to be little to choose between them in terms of efficacy, side-effects (including next-day effects) and dependency. Patients should be advised that there is around a doubling of the relative risk of road traffic accidents associated with taking a Z-drug, and they need to be very cautious about driving the day after taking any hypnotic.”

1. Sleep Med 2008; 9:818-22
2. www.npci.org.uk/blog/?p=249

Antiepileptics: adverse effects on bone

The antiepileptic drugs carbamazepine, phenytoin, primidone, and phenobarbital are known to cause osteomalacia, and the product information for healthcare professionals for these drugs contains information about this risk. Osteoporosis is also a recognised side-effect of carbamazepine.

A recent review of data from published preclinical studies, epidemiological studies, and UK Yellow Card data found that long-term treatment with carbamazepine, phenytoin, and primidone, and in addition long-term treatment with sodium valproate, is associated with decreased bone mineral density that results in an increased risk of developing osteopenia, osteoporosis, and fractures in the following at-risk patients:

- those who are immobilised for long periods
- those who have inadequate sun exposure
- those with inadequate dietary calcium intake

There is limited understanding of the effects of antiepileptics on bone. Some evidence suggests that antiepileptics (including phenytoin, phenobarbital, carbamazepine, and primidone) induce the cytochrome P450 enzyme system, which results in increased clearance of vitamin D, leading to secondary hyperparathyroidism, increased bone turnover, and reduced bone density. The mechanism by which sodium valproate, a non-enzyme-inducing drug, causes decreased bone mineral density is unclear.

At present there are insufficient data to support an association between decreased bone mineral density, osteopenia, osteoporosis, and osteomalacia and other antiepileptic drugs.

Advice for healthcare professionals from the MHRA/CHM¹:

- The available data suggest that phenytoin, carbamazepine, primidone, and sodium valproate are associated with decreased bone mineral density, which may lead to osteopenia, osteoporosis, and increased fractures in at-risk patients
- Phenytoin, carbamazepine, phenobarbital, and primidone are associated with an increased risk of osteomalacia
- Vitamin D supplementation should be considered for at-risk patients who receive long-term treatment with primidone, phenytoin, carbamazepine, phenobarbital, or sodium valproate.

1. Drug Safety Update, volume 2, issue 9, April 2009