

NEWSLETTER

Supporting the Derbyshire Health Community

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Welcome to new readers

A warm welcome to all new readers of the PACE Newsletter. This has been produced for health professionals in north Derbyshire since 1995. Feedback suggests that it is a useful resource. Post-reorganisation it is now being provided Derbyshire-wide. If you have any comments/suggestions, my contact details are below. Past issues will hopefully soon be available from the Derbyshire County PCT website but in the meantime are available at www.ukmicentral.nhs.uk.

CEPPaC

Due to the reorganisation, PACEF (in the north) and PAG (in the south) have been dissolved. They have been replaced by a new countywide group, the Clinical Effectiveness, Prescribing, and Prioritisation Committee (CEPPaC). CEPPaC will be adopting a traffic light classification for prescribing responsibilities with five categories, which will be updated every month.

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 CEPPaC does not recommend for use (DARK Brown) or only in restricted circumstances (LIGHT Brown) due to lack of data on safety, effectiveness, or cost-effectiveness.

The most recent updates are in the table below:

Drug	Date considered	Decision
Grazax (grass pollen allergen extract)	April 2007	DARK BROWN
Lanthanum carbonate	April 2007	RED
Varenicline	April 2007	GREEN (second line use only)
Pregabalin	April 2007	LIGHT BROWN
Colief liquid	April 2007	LIGHT BROWN
Ranibizumab	April 2007	RED
Exforge (amlodipine + valsartan)	April 2007	DARK BROWN
Darifenacin	April 2007	LIGHT BROWN
Rotigotine patch	April 2007	LIGHT BROWN

Work is ongoing to amalgamate the current north and south lists.

Grazax

This is licensed for seasonal grass pollen-induced allergic rhinoconjunctivitis in adults with a positive skin prick test or IgE test to grass pollen. It is recommended only to be initiated by physicians with experience in the

treatment of allergic diseases. CEPPaC concluded that there was insufficient evidence with which to make a decision to commission this drug.

Varenicline

Previously PACEF and PAG had advised no prescribing of varenicline pending additional data. CEPPaC has now reviewed a new systematic review and meta-analysis of the effectiveness of smoking cessation therapies and also the Scottish Medicines Consortium review of varenicline. NRT still remains the first line treatment option but varenicline is now a second line option, along with bupropion on the advice of a smoking cessation adviser. This is limited to a 12-week course, as the evidence for a 24-week course was not considered to be sufficiently robust.

Pregabalin

CEPPaC approved pregabalin for limited use in pain relief for those instances where a patient responds to maximal doses of gabapentin but are unable to tolerate it.

Colief liquid

Colief is included in Part XV of the Drug Tariff (Borderline Substances) only for relief of symptoms associated with lactose intolerance, provided that lactose intolerance has been confirmed by appropriate testing. It cannot be prescribed for any other indications. The prescription needs to be endorsed 'ACBS'.

Rotigotine

Rotigotine patches are only appropriate for those patients who are intolerant of all other dopamine agonists.

Fracture risk - a class effect of glitazones?

Further to last month's article on rosiglitazone and fractures, it appears that this may be a class effect. Takeda, the makers of pioglitazone, have now also written to US healthcare professionals informing them of an increased risk of fractures in female patients taking pioglitazone compared with a comparator. The majority of fractures observed in female patients who received pioglitazone were in the distal upper limb (forearm, hand and wrist) or distal lower limb (foot, ankle, fibula and tibia).

Similar to the previous GSK letter, the Takeda letter advises that the risk of fractures should be considered in the care of female patients with type 2 diabetes who are currently being treated with pioglitazone, or when initiation of pioglitazone treatment is being considered.

This risk may be confined to women but the risk of heart failure with glitazones and the weight gain are not sexist (see December 2003 and November 2005 PACE Newsletters for more information).

Key point: glitazones may increase the risk of fractures in female patients
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Glucosamine prescribing

After trying, or in conjunction with paracetamol, a trial of glucosamine is a treatment option in patients suffering from osteoarthritis of the knee. There is RCT evidence that it is effective and its use may well mean that potentially toxic NSAIDs or coxibs need not be used. The dose is 1,500mg once daily. Onset of action may take 4 to 6 weeks.

Some glucosamine products are blacklisted so it can be prescribed generically as glucosamine sulphate or the following brands can be prescribed on NHS FP10 prescription:

	Approximate cost of 28 days treatment
Valupak® glucosamine 1500mg daily	£2.12
Natrahealth® glucosamine 1500mg daily	£2.13
Lifespan® glucosamine 1500mg daily	£2.58

Use of one of these products would maintain continuity of supply.

A recent report from the North West Medicines Information Centre has looked at the adverse effects of glucosamine. This is their summary:

- Glucosamine supplements are widely used for the relief of pain and symptoms associated with osteoarthritis. They appear to be well tolerated, with a reported frequency of adverse effects similar to that with placebo.
- Mild gastrointestinal disturbance is the most common adverse effect. Other adverse effects include headache, drowsiness, insomnia and skin reactions.
- Although glucosamine should not precipitate allergic reactions in patients sensitive to shellfish, as the non-synthetic preparations are derived from the shell and not the flesh of shellfish, some sources recommend cautious use or avoidance of these products in patients at risk.
- Glucosamine does not appear to adversely affect plasma blood glucose in patients without diabetes. However, data relating to its effects in patients with diabetes are lacking. It may be wise for patients with diabetes to monitor their blood glucose levels more closely if they start to take glucosamine or change the product taken.
- Glucosamine should be used with caution in patients with renal impairment or those taking nephrotoxic medication.

Seven reports suggesting an interaction between glucosamine and warfarin were highlighted by the MHRA in 2006. The WHO Adverse Drug Reaction database contains 20 reports of possible interaction between warfarin and glucosamine (including the UK ones). Nineteen reports are of increased warfarin effect. The mechanism of the interaction is unclear. The MHRA recommends that patients on warfarin should not take glucosamine. There is a theoretical risk that glucosamine may interact with doxorubicin, etoposide and teniposide. Because of the potential clinical significance of this interaction, concomitant administration of glucosamine should be avoided.

Another RCT of glucosamine sulphate 1500mg daily for the treatment of symptoms in knee OA has recently been published¹. Comparators were paracetamol as well as placebo. The majority of participants were women with a mean age of 64 (Beatles' song springs to mind!). This was a 6-month study and responders were defined as those with a high degree of pain improvement on the WOMAC pain subscale. There were more responders to glucosamine (39.6%) than to paracetamol (33.3%) and placebo (21.2%) { $p=0.004$ and $p=0.047$, respectively, versus placebo}. This gives an NNT of 5 for glucosamine (remarkably similar to previous RCTs) and 8 for paracetamol compared to placebo. Glucosamine was well tolerated, and did not differ from placebo in terms of frequency of adverse events or abnormal findings of laboratory evaluations, including glucose serum levels.

1. Arthritis and Rheumatism 2007; 56: 555-67

SSRIs and the risk of fracture

A recent epidemiological study suggests that use of SSRIs is associated with an increased risk of fragility fracture¹. The authors of the study note that both fractures and depression are common in older people. SSRIs are commonly used for the treatment of depression, and the authors therefore aimed to determine whether SSRI use was associated with an increased fracture risk. They carried out a prospective cohort study in people aged 50 and over, living in the community, and followed them for five years. Fragility fracture was defined as proven fractures associated with minimal trauma; risk of fracture was calculated for reported SSRI use controlling for relevant confounding factors.

There were 5,008 people in the study cohort, and daily SSRI use was reported by 137 of these. After adjustment for potential confounders, daily SSRI use was associated with substantially increased risk of incident clinical fragility fracture (hazard rate, 2.1; 95% CI 1.3-3.4). Daily SSRI use was also associated with increased odds of falling (odds ratio, 2.2; 95% CI, 1.4-3.5), lower bone mineral density at the hip, and a trend toward lower bone mineral density at the spine. These effects were dose dependent and were similar for those who reported taking SSRIs at baseline and at 5 years follow up. Based on their analysis, the authors conclude that daily use of SSRIs is associated with an increased risk of fragility fractures. Given the frequency of both depression and osteoporosis in this age group, they suggest that the association may be a significant public health issue.

The authors suggest that SSRIs may increase fracture risk because of their effect on bone physiology and on the risk of falling. Functional serotonin receptors and transporters have been localised to bone, while the administration of SSRIs decreases bone mass and strength in growing mice.

The National Library for Health's review of this study concludes: "The authors' conclusions appear to be supported by the findings of this reasonably well-conducted study. There were only 137 participants who were daily users of SSRIs, so the population was relatively small. The outcomes measured and confounding variables assessed appear to have been appropriate; however, the use of interviews to ascertain the use of SSRIs, the incidence of fractures and the presence of confounding variables may affect the reliability of the data. The authors did not report the actual number of fractures occurring in each of the groups, which would have been useful information to assess the impact of a two-fold increase in fractures; from a graph showing fracture-free survival it appears that approximately 12% (16) daily users of SSRIs and 6% non-users suffered a fracture within five years. Participants were assessed for use of SSRIs at baseline and at year five, therefore, participants who used SSRIs daily in the period between assessments would have been missed. In addition, the duration of SSRI use was unknown. The authors state that further studies that include controlled prospective trials are needed to confirm their findings, which appears appropriate."

Epidemiological studies cannot prove cause and effect, only show a possible association. A single, small study like this one is not sufficient to change practice

1. Arch Intern med 2007; 167:188-94

PPIs and the risk of hip fracture

Significant hypochlorhydria as a result of proton pump inhibitor (PPI) therapy may cause calcium malabsorption, resulting in a higher risk of bone fractures. A recent study analysed data obtained from the United Kingdom General Practice Research Database relating to prescription use and subsequent diagnoses and hospitalizations for hip fracture¹. Cases consisted of individuals older than 50 years of age with first occurrence of hip fracture at least 1 year after the beginning of their standard follow-up period. Up to 10 controls were selected for each case matching for multiple variables, including sex, year of birth, and duration of follow-up. The exposure of interest was the effect of cumulative duration of PPI therapy for up to 4 years.

The authors performed a statistical analysis of the data to control for other potential confounders, including body mass index, smoking history, alcoholism, impaired mobility, atherosclerotic vascular disease, peptic ulcer disease, renal failure, among others. There were 13,556 hip fracture cases and 135,386 controls. PPI use for more than 1 year was associated with a significantly increased risk of hip fracture, adjusted Odds Ratio 1.44 (95% CI 1.30-1.59); NNH/person-years = 1266; (944-1856). The associated risk was further increased among patients taking higher doses of PPI and with increasing duration of use. Histamine 2 receptor antagonist therapy (e.g. ranitidine, cimetidine) did not significantly increase hip fracture risk, AOR 1.21 (0.67 to 2.22); p=0.46. The highest risk was in long-term users of high-dose PPI therapy, AOR 2.65 (1.80 to 3.90); p<0.001.

The InfoPOEM bottom line is: "Long-term use (greater than one year) of PPIs is associated with an increased risk of hip fracture in adults over age 50 years. Risk is also higher among individuals taking higher doses of PPIs and increases with duration of use. Appropriate use, dose, and duration of therapy should be carefully assessed on an individual basis".

This is a larger study than the SSRI one above. The association is statistically significant but the effect size is not huge, which is not to say it should be ignored. For somebody without other risk factors for hip fracture, two times a low risk is still a low risk. In frail elderly people it might be a different matter. There are other interventions to lower risk, from providing grab rails and removing trip hazards to using calcium and vitamin D supplementation (at least 800iu vitamin D per day). But of course the standard advice for symptom control to use the lowest effective dose for the shortest possible time (intermittently if appropriate) holds as true as ever.

Key point: long-term PPI therapy, particularly at high doses, may be associated with an increased risk of hip fracture. Consider the baseline risk.

1. JAMA 2006; 296:2947-53

Antenatal and postnatal mental health

NICE has issued clinical guideline No. 45 on this subject. The quick reference guide is available at <http://guidance.nice.org.uk/CG45/quickrefguide/pdf/English>

These are the key priorities for implementation:

Prediction and detection

- At a woman's first contact with services in both the antenatal and the postnatal periods, healthcare professionals (including midwives, obstetricians, health visitors and GPs) should ask questions about:
 - past or present severe mental illness including schizophrenia, bipolar disorder, psychosis in the postnatal period and severe depression
 - previous treatment by a psychiatrist/specialist mental health team including inpatient care
 - a family history of perinatal mental illnessOther specific predictors, such as poor relationships with her partner, should not be used for the routine prediction of the development of a mental disorder.
- At a woman's first contact with primary care, at her booking visit and postnatally (usually at 4 to 6 weeks and 3 to 4 months), healthcare professionals (including midwives, obstetricians, health visitors and GPs) should ask two questions to identify possible depression.
 - During the past month, have you often been bothered by feeling down, depressed or hopeless?
 - During the past month, have you often been bothered by having little interest or pleasure in doing things?A third question should be considered if the woman answers 'yes' to both of the initial questions.
 - Is this something you feel you need or want help with?

Psychological treatments

- Women requiring psychological treatment should be seen for treatment normally within 1 month of initial assessment, and no longer than 3 months afterwards. This is because of the lower threshold for access to psychological therapies during pregnancy and the postnatal period arising from the changing risk-benefit ratio for psychotropic medication at this time.

Explaining risks

- Before treatment decisions are made, healthcare professionals should discuss with the woman the absolute and relative risks associated with treating and not treating the mental disorder during pregnancy and the postnatal period. They should:
 - acknowledge the uncertainty surrounding the risks
 - explain the background risk of fetal malformations for pregnant women without a mental disorder
 - describe risks using natural frequencies rather than percentages (for example, 1 in 10 rather than 10%) and common denominators (for example, 1 in 100 and 25 in 100, rather than 1 in 100 and 1 in 4)
 - if possible use decision aids in a variety of verbal and visual formats that focus on an individualised view of the risks
 - provide written material to explain the risks (preferably individualised) and, if possible, audio-taped records of the consultation.

Management of depression

- When choosing an antidepressant for pregnant or breastfeeding women, prescribers should, while bearing in mind that the safety of these drugs is not well understood, take into account that:
 - tricyclic antidepressants, such as amitriptyline, imipramine and nortriptyline, have lower known risks during pregnancy than other antidepressants
 - most tricyclic antidepressants have a higher fatal toxicity index than selective serotonin reuptake inhibitors (SSRIs)
 - fluoxetine is the SSRI with the lowest known risk during pregnancy
 - imipramine, nortriptyline and sertraline are present in breast milk at relatively low levels
 - citalopram and fluoxetine are present in breast milk at relatively high levels
 - SSRIs taken after 20 weeks' gestation may be associated with an increased risk of persistent pulmonary hypertension in the neonate
 - Paroxetine taken in the first trimester may be associated with fetal heart defects
 - Venlafaxine may be associated with increased risk of high blood pressure at high doses, higher toxicity in overdose than SSRIs and some tricyclic antidepressants, and increased difficulty in withdrawal
 - All antidepressants carry the risk of withdrawal or toxicity in neonates; in most cases the effects are mild and self-limiting.

- For a woman who develops mild or moderate depression during pregnancy or the postnatal period, the following should be considered:
 - self-help strategies (guided self-help, computerised cognitive behavioural therapy or exercise)
 - non-directive counselling delivered at home (listening visits)
 - brief cognitive behavioural therapy or interpersonal psychotherapy.

The guideline gives the following specific advice on **psychotropic medication**.

Antipsychotics

Risks to consider

- Raised prolactin levels with some antipsychotics (amisulpride, risperidone, sulpiride)
- Gestational diabetes and weight gain with olanzapine
- Agranulocytosis in the fetus (theoretical) and breastfed infant with clozapine
- Extrapyramidal symptoms in the neonate especially with depot medication (these are usually self-limiting)

Actions to take

- Advise women taking antipsychotics who are planning a pregnancy that raised prolactin levels reduce the chances of conception. If levels are raised, consider an alternative drug
- If prescribing olanzapine to a pregnant woman, consider risk factors for gestational diabetes and weight gain, including family history, existing weight and ethnicity
- Do not routinely prescribe:
 - clozapine to women who are pregnant or breastfeeding; for those taking it, consider switching to another drug and monitor carefully
 - depot antipsychotics to pregnant women
 - anticholinergic drugs for extrapyramidal side effects of antipsychotics, except for short-term use; instead, adjust dose and timing of the antipsychotic or switch to another drug to avoid side effects

Lithium

Risks to consider

- Fetal heart defects (risk raised from 8 in 1000 to around 60 in 1000)
- Ebstein's anomaly (risk raised from 1 in 20,000 to 10 in 20,000)
- High levels in breast milk

Actions to take

- Do not routinely prescribe, particularly in the first trimester of pregnancy or during breastfeeding
- Advise a woman who is taking lithium and is planning a pregnancy, and who is well and not at high risk of relapse, to stop the drug
- If a woman taking lithium becomes pregnant:
 - if the pregnancy is confirmed in the first trimester, and the woman is well and not at high risk of relapse, stop the drug gradually over 4 weeks; explain that this may not remove the risk of cardiac defects in the fetus
 - if she is not well or is at high risk of relapse, consider:
 - ❖ switching gradually to an antipsychotic, or
 - ❖ stopping lithium and restarting it in the second trimester if the woman is not planning to breastfeed and her symptoms have responded better to lithium than to other drugs in the past, or
 - ❖ continuing with lithium if she is at high risk of relapse
- If a woman continues taking lithium during pregnancy:
 - check serum levels every 4 weeks, then weekly from the 36th week, and less than 24 hours after childbirth
 - adjust the dose to keep serum levels towards the lower end of the therapeutic range
 - make sure she maintains adequate fluid intake
- Woman taking lithium should deliver in hospital and be monitored during labour by the obstetric team. Monitoring should include fluid balance, because of the risk of dehydration and lithium toxicity (in prolonged labour, it may be appropriate to check serum lithium levels).

Antidepressants

Risks to consider

- Lowest known risks during pregnancy: tricyclic antidepressants (TCAs) such as amitriptyline, imipramine, nortriptyline; but most are more likely to cause death if taken in overdose than selective serotonin reuptake inhibitors (SSRIs).
- Lowest known risk with an SSRI during pregnancy: fluoxetine
- Fetal heart defects with paroxetine taken in the first trimester
- Persistent pulmonary hypertension in the neonate with SSRIs taken after 20 weeks' gestation
- High blood pressure with venlafaxine at high doses, together with higher toxicity in overdose than SSRIs and some TCAs and increased difficulty in withdrawal
- Withdrawal or toxicity in the neonate with all antidepressants (in most cases the effects are mild and self-limiting)
- Lower than other antidepressants in breast milk: imipramine, nortriptyline and sertraline
- Higher levels in breast milk: citalopram and fluoxetine

Actions to take

Advise a woman taking paroxetine who is planning pregnancy or has an unplanned pregnancy to stop the drug.

Benzodiazepines

Risks to consider

- Cleft palate and other fetal malformations
- Floppy baby syndrome in the neonate

Actions to take

- Do not routinely prescribe to pregnant women, except for the short-term treatment of extreme anxiety and agitation
- Consider gradually stopping in pregnant women

Carbamazepine and lamotrigine

Risks to consider

- Carbamazepine: neural tube defects (risk raised from 6 in 10,000 to around 20 to 50 in 10,000 and other major fetal malformations including gastrointestinal tract problems and cardiac abnormalities).
- Lamotrigine: oral cleft (risk estimated at nearly 9 in 1000), and dermatological problems (notably Stevens-Johnson syndrome) in the infant if taken while breastfeeding.

Actions to take

- Advise a woman taking these drugs who is planning a pregnancy or has an unplanned pregnancy to stop them. Consider an alternative (such as an antipsychotic) if appropriate.
- Do not routinely prescribe:
 - carbamazepine and lamotrigine for pregnant women
 - lamotrigine for women who are breastfeeding

Valproate

Risks to consider

- Neural tube defects (spina bifida and anencephaly; risk raised from around 6 in 10,000 to 100-200 in 10,000).
- Effects on the child's intellectual development.
- Polycystic ovary syndrome in women younger than 18 years.

Actions to take

- Do not routinely prescribe to women of child-bearing potential. If there is no effective alternative, explain risks during pregnancy and importance of using adequate contraception.
- Do not prescribe to women younger than 18 years (increased risk of unplanned pregnancy in this group).
- If a woman taking valproate is planning a pregnancy or pregnant, advise her to stop the drug. In the treatment of bipolar disorder consider, if appropriate, an alternative drug (usually an antipsychotic).
- If there is no alternative to valproate, limit doses to a maximum of 1 gram per day, in divided doses and in the slow-release form, with 5 mg per day folic acid.

Common warfarin drug interactions^{1,2}

The drugs in this list are more usually associated with loss of INR control in patients already established on warfarin. This list is not exhaustive - refer to the British National Formulary (BNF) for further information. If any of the drugs below are to be started in these patients then the use of alternatives in the same therapeutic class may be considered. If this is not possible then the patient's INR should be monitored as detailed below. Those drugs highlighted in **bold** may cause significant interactions and should be used with caution.

- Drugs marked * are liver enzyme inhibitors and increase the INR. They act very quickly (can be within 24 hours) and if the drug is withdrawn the effect disappears quickly depending on the drug half-life. The INR should if possible be monitored within 72 hours of starting the interacting drug and on withdrawal.
- Drugs marked \$ are liver enzyme inducers and decrease the INR. They act more slowly (up to a week) with peak effect at 2-3 weeks and can persist for up to 4 weeks after stopping depending on drug half-life. The INR will need checking after 1 week of concurrent therapy.
- Drugs with neither, have other mechanisms that affect the INR.

N.B. If a patient on warfarin is started on ANY other new medication a repeat INR after 1 week would be a sensible precaution.

Drugs that increase the INR and increase risk of bleed	
Gastrointestinal	cimetidine* , omeprazole* , esomeprazole*
Cardiovascular	amiodarone* (liver enzyme inhibition is slow and may persist long after withdrawal requiring weekly monitoring over 4 weeks), fibrates , propafenone* , propranolol, statins – no clinically relevant interaction will normally be seen however it is prudent to check INR in the weeks after initiation and at any dose change.
CNS	dextropropoxyphene* (in co-proxamol), fluvoxamine* , paracetamol (prolonged use at high dose), SSRIs* , tramadol
Anti-infectives (anti-infectives in general MAY cause raised INRs)	azole antifungals* (esp. miconazole including oral gel and vaginal), macrolides* (can be serious but unpredictable), metronidazole* , quinolones* (can be serious but unpredictable), tetracyclines , influenza vaccine
Endocrine	anabolic steroids (and danazol) , high dose corticosteroids , glucagon (high dose 50mg+ over 2 days) , flutamide , levothyroxine , propylthiouracil
NSAIDs N.B. ALL NSAIDs can increase the risk of bleeds and should be avoided if possible	IBUPROFEN at lowest effective dose (+/- PPI) is probably safest if an NSAID is required. Avoid glucosamine
Antiplatelets – increased bleed risk	Aspirin , clopidogrel , dipyridamole – only use if benefit outweighs risk of bleed
Miscellaneous	alcohol (acute), allopurinol*, disulfiram , fluorouracil , interferon, sulfinpyrazone , tamoxifen , zafirlukast*
Herbal preparations etc	boldo, carnitine, cranberry juice* , danshen, dong quai, fenugreek, fish oils, garlic, ginko biloba, glucosamine , lycium*, mango, melilot, papain, PC-SPES, quilinggao, sweet woodruff, tonka

Drugs that decrease the INR	
Miscellaneous	Alcohol\$ (chronic) , azathioprine , barbiturates\$, bosentan\$, carbamazepine\$, griseofulvin\$, mercaptopurine , nevirapine\$, OCP/HRT , raloxifene , rifampicin\$ (most potent inducer) , trazadone
Herbal preparation etc	avocado, co-enzyme Q10, green tea, natto, St Johns wort\$ (avoid)
Binding agents	colestyramine, sucralfate
Warfarin antagonist	vitamin K

Drugs that increase or decrease the INR	
Miscellaneous	Ginseng, phenytoin , quinidine

1. BNF edition 52, September 2006
2. Stockley's Drug Interactions, 6th edition. Pharmaceutical Press 2003

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