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Supporting prescribing excellence - informing colleagues in primary and secondary care

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In this issue ...

Venlafaxine: Recent Advice from the CSM

In December 2004 the Committee on Safety of Medicines (CSM) released the findings of its Expert Working Group on the safety of selective serotonin reuptake inhibitor (SSRIs) and related antidepressant drugs[1]. This coincided with the publication by the National Institute for Clinical Excellence (NICE) of its guidelines on the management of depressive illness in primary and secondary care[2]. Both bodies recommended restrictions on the prescription of venlafaxine (Efexor®).

The CSM has now warned about venlafaxine's liability to be associated with discontinuation symptoms, cardiotoxicity and toxicity in overdose.

In a letter to health professionals[3], the CSM have advised that "*Efexor® should not be used in patients with heart disease (e.g. cardiac failure, coronary artery disease, ECG abnormalities including pre-existing QT prolongation), patients with electrolyte imbalance or in patients who are hypertensive. Patients currently doing well on treatment with venlafaxine can continue to the end of their course*".

The CSM also advised that "*treatment with venlafaxine should only be initiated by specialist mental health practitioners, including GPs with a special interest, and that there be should be arrangements in place for continuing supervision of the patient*".

Although increasingly popular with prescribers, venlafaxine is neither a first nor second choice drug in the Lothian Joint Formulary (LJF). The first choice for a new episode of depression is fluoxetine and the first choice for recurring depression is a previously successful antidepressant. Venlafaxine has been increasingly prescribed in Lothian, presumably because it was thought to have the multiple therapeutic actions of tricyclic antidepressants, but with fewer risks.

Venlafaxine may be an option in the treatment of major depression where an SSRI has proved ineffective and a second choice treatment has proved either ineffective or intolerable.

Key messages:

- **The CSM has recently issued a warning about venlafaxine's toxicity.**
- **Consider reviewing all patients on venlafaxine.**
- **The LJF first choice treatment for newly diagnosed depression is fluoxetine.**
- **The LJF first choice treatment for a recurrence of depression is a previously successful antidepressant.**

References

1. Report of the CSM Expert Working Group on the Safety of Selective Serotonin Reuptake Inhibitor Antidepressants. 6 December 2004. www.mhra.gov.uk/news/2004/SSRIfinal.pdf
2. Depression: Management of Depression in Primary and Secondary Care. NICE Clinical Guideline 23. www.nice.org.uk/pdf/CG023NICEguideline.pdf
3. Scottish Executive Health Department Urgent Message. Safety of Selective Serotonin Reuptake Inhibitor Antidepressants. 6 December 2004. www.mhra.gov.uk/news/2004/SSRI_Letter_061204.pdf

COX-2 Inhibitors ('the coxibs') - the story so far…

The coxibs (COX-2 inhibitors) were developed in an effort to produce an anti-inflammatory agent with the efficacy of the standard (non-selective) NSAIDs, but with reduced gastrointestinal toxicity.

Although launched with significant publicity, a number of independent sources including the Drug and Therapeutics Bulletin (DTB) and the Lothian Formulary Committee concluded that the evidence available suggested little advantage over conventional NSAIDs in terms of GI bleeding or perforation of gastric or duodenal ulcers[1]. In view of concerns over the cost effectiveness of these drugs the Lothian COX-2 Guidelines were produced.

In September 2004, new evidence of cardiovascular risk with rofecoxib[2,3,4] resulted in Merck Sharp and Dohme withdrawing the drug worldwide. Other coxibs may also have unexpected risks.

- The US Food and Drug Administration recently released a statement noting the adverse effects of celecoxib revealed in the Adenoma Prevention with Celecoxib (APC) trial *"Patients in the clinical trial taking 400mg of celecoxib twice daily had 3.4 times greater risk of cardiovascular events compared to placebo".*
- Pfizer recently released new safety information relating to parecoxib and valdecoxib. Two studies evaluating the use of parecoxib/valdecoxib for the treatment of pain following coronary artery bypass graft (CABG) showed a higher rate of serious cardiovascular thromboembolic events in the treatment arm compared to placebo. Pfizer have now stated that these two drugs are *contra-indicated* following CABG surgery.
- Pfizer have also recently reported serious skin reactions (some fatal) with valdecoxib.

Where does that leave us?

In January 2005, the DTB reviewed coxibs again[5] and the accompanying press release stated: *"There's little convincing evidence to suggest that coxibs offer useful advantages over traditional NSAIDs in most situations. And with mounting evidence that coxibs may cause severe cardiovascular problems, it's hard to justify using these treatments in preference to the older drugs"*.

The Lothian COX-2 Guidelines are currently under review.

Key messages:

- ***All* selective COX-2 inhibitors are now contra-indicated in patients with established ischaemic heart disease, cerebrovascular disease and congestive heart failure (NYHA II-IV).**
- **The lowest effective dose of COX-2 inhibitor should be used for the shortest duration necessary.**
- **For patients with significant risk factors (hypertension, hyperlipidaemia, diabetes mellitus, smoking) or peripheral vascular disease, the balance of risks should be carefully considered before prescribing a COX-2 inhibitor.**
- **A clear GI safety advantage has not been established when COX-2 inhibitors are combined with aspirin.**
- **Where an NSAID is required and the patient is at high risk of upper GI side effects, use a conventional NSAID with a proton pump inhibitor.**

References

1. Are rofecoxib and celecoxib safer NSAIDs? Drug & Therapeutics Bull. 2000; *38:81*-6.
2. Bombardier C *et al*. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. N Engl J Med 2000; *343*:1520-28.
3. Whelton A *et al*. Effects of celecoxib and rofecoxib on blood pressure and edema [sic] in patients ≥ 65 years of age with systemic hypertension and osteoarthritis. M J Cardiol 2002; *90*:959-63.
4. Solomon DH *et al*. Relationship between selective cyclooxygenase-2 inhibitors and acute myocardial infarction in older adults. Circulation 2004; *109*:2068-73.
5. Taking stock of coxibs. Drug & Therapeutics Bull. 2005; *43:1*-6.

Stop Press …

Further information has recently been published on the use of COX-2 inhibitors, please see the following publications for details:

- European Medicines Agency (EMEA) Public Statement on valdecoxib and parecoxib sodium. 15 December 2004. www.emea.eu.int/pdfs/human/press/pus/2048020en.pdf
- Committee on Safety of Medicines (CSM) Advice on the use of celecoxib and other selective COX-2 inhibitors in the light of concerns about cardiovascular safety. 20 December 2004. www.mhra.gov.uk/news/2004/celecoxibhealthlink201204doc.pdf
- Maxwell SRJ, Webb DJ. COX-2 selective inhibitors - important lessons learned. Lancet. 2005; *365*:449-451.
- Taking stock of coxibs. Drug & Therapeutics Bull. 2005; *43*:1-6.
- Scottish Executive Health Department. Immediate Message. 17 February 2005. www.mhra.gov.uk

Mesalazine - no generics please

Mesalazine (5-aminosalicylic acid) is indicated in the management of inflammatory bowel disease (IBD) for the treatment of mild to moderate ulcerative colitis and maintenance of remission[1,2].

The LJF recommends that modified release (m/r) mesalazine should be prescribed as a *specified proprietary preparation*.
First choice = Pentasa® 500mg *slow release* tablets; Second choice = Asacol® MR 400 mg *enteric-coated* tablets. Since mesalazine is a topically acting drug, it must be available at the site of inflammation in order to achieve effect and is therefore available as a m/r preparation. The BNF notes that the delivery characteristics of mesalazine preparations may vary and these preparations should not be considered interchangeable.

A recent audit in North East Edinburgh confirmed that some patients are still being prescribed generic mesalazine[3].

Key messages:

- **Oral mesalazine is the LJF drug of choice for the maintenance of remission in patients with inflammatory bowel disease.**
- **Specify the brand name when prescribing m/r mesalazine.**

References
1. BNF no. 48. www.bnf.org
2. Maintenance drugs for inflammatory bowel disease. Drug & Therapeutics Bull. 2001; *39*(12):91-95.
3. Mesalazine audit. Magee D, MacBride-Stewart S. December 2004.

Thanks to Dr Jim Cowan, GP, South Central Edinburgh, Sean MacBride-Stewart, Primary Care Pharmacist, North East Edinburgh and Debbie Magee and Marjory Neill, Pre-registration Pharmacist Trainees, LUHD for contributing to this article.

Notice to withdraw co-proxamol

On the recent advice of the Committee on Safety of Medicines (CSM), co-proxamol is to be withdrawn over the next 6 to 12 months[1]. This advice followed a review which determined that the efficacy of co-proxamol is poorly established and the risk of toxicity in overdose, both accidental and deliberate, is unacceptable. The advice noted that there is no robust evidence that efficacy of this combination product is superior to full strength paracetamol alone in either acute or chronic use. Patients currently receiving this drug should be switched to alternative pain management regimes at their next routine medication review.

Lothian Joint Formulary Advice on General Management of Pain (4.7 Analgesics)
(see www.ljf.scot.nhs.uk)

Step 1: (mild pain)	ibuprofen and/or paracetamol		
Step 2: (mild to moderate pain)	1st choice	-	co-codamol 8/500* tablets and/or NSAID
	2nd choice	-	co-codamol 30/500* tablets and/or NSAID

* Note that alternative formulations or strengths to co-codamol 8/500 and 30/500 tablets are significantly more expensive, e.g. co-codamol 12.8/500 tablets.

Key messages:

- **Co-proxamol is to be withdrawn from use over the next 6 to 12 months.**
- **Consider reviewing all patients currently on co-proxamol.**
- **Many patients may achieve adequate pain control with paracetamol.**
- **If a patient requires a combination analgesic the LJF 1st choice for mild to moderate pain is co-codamol.**

Reference
1. Scottish Executive Health Department. Immediate Message. 31 January 2005.
www.mhra.gov.uk/news/january/co-proxamol_healthprofessional.pdf

Fruit juice and drug interactions

Grapefruit Juice

Small quantities of grapefruit juice (250mL) can interact with certain drugs when taken simultaneously. The Committee on Safety of Medicines (CSM) recently issued advice about the interaction between grapefruit juice and simvastatin[1]. Patients taking simvastatin are advised to avoid grapefruit juice altogether as this could increase the risk of dose-related side effects, including rhabdomyolysis. Patients taking atorvastatin should also avoid drinking large quantities of grapefruit juice.

Significant interactions may also occur between grapefruit juice and a range of drugs, for example: buspirone, ciclosporin, efavirenz, sildenafil, sirolimus, tacrolimus, tadalafil, vardenafil and calcium-channel blockers (see BNF for full details).

The main interaction arises from psoralen, which is present in grapefruit juice. Psoralen inhibits the metabolism of certain drugs by enzyme CYP3A4, a subfamily of cytochrome P450.

Grapefruit segments, extract of unprocessed grapefruit and oranges from Seville may also cause drug interactions. Sweet oranges and their juices do not appear to have a similar effect. Tangelos, which are a hybrid of grapefruit, may also interfere with drug metabolism. Other citrus fruits such as lemons, limes and tangerines are thought to be safe.

Cranberry Juice and Warfarin

Cranberry juice contains flavonoids (antioxidants) which inhibit the activity of the cytochrome P450 enzyme that breaks down warfarin. The CSM have received 12 reports of suspected interactions involving warfarin and cranberry juice[1]. They have reviewed the evidence and have issued new advice. In summary this states that:

- Patients taking warfarin should avoid drinking cranberry juice, unless the health benefits outweigh any risks.
- For patients on warfarin taking cranberry juice regularly consider increased medical supervision and INR monitoring.
- It is unknown if other cranberry products such as capsules or concentrates have a similar reaction, therefore similar caution should be observed.

Key message:

Ensure that patients are aware of potential drug interactions with certain fruit juices.

Reference

1. Current Problems in Pharmacovigilance. Vol.30. October 2004.
http://medicines.mhra.gov.uk/ourwork/monitorsafequalmed/currentproblems/currentproblems_oct04.pdf

Thanks to Lubna Kerr, Prescribing Support Pharmacist, South Central Edinburgh for contributing to this article.

Guidance for the use of clopidogrel in Lothian

A copy of guidance for the use of clopidogrel in Lothian is enclosed with this issue of the Lothian Prescribing Bulletin. This represents a consensus view of cardiovascular clinicians in Lothian, and has been approved by the Lothian Formulary Committee.

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