LOTHIAN PRESCRIBING BULLETIN

Supporting prescribing excellence - informing colleagues in primary and secondary care

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In this issue …

Antidepressants in patients receiving tamoxifen

CYP2D6 genetic polymorphisms and concomitant use of potent CYP2D6 inhibitors may be associated with variability in clinical response in patients treated with tamoxifen for breast cancer.[1] The antidepressants fluoxetine and paroxetine, both selective serotonin re-uptake inhibitors (SSRIs), are known to inhibit CYP2D6, an enzyme which converts tamoxifen to one of its active metabolites, endoxifen.

There is, however, conflicting evidence as to whether concomitant use of certain SSRIs and tamoxifen produces any clinically significant outcome. A population based cohort study carried out in Canada showed that paroxetine was found to "*reduce or abolish the benefit of tamoxifen in women with breast cancer*".[2] However, a more recent observational study published in the Journal of Clinical Oncology in May 2010 found that "*there is insufficient evidence to withhold CYP2D6 inhibitors from patients during tamoxifen therapy*".[3]

In its recent review of the evidence, the MHRA stated that strong CYP2D6 inhibitors, which include paroxetine, fluoxetine, bupropion, quinidine and cinacalcet, should *not* be prescribed with tamoxifen.[1] The British National Formulary[4] also advises that fluoxetine and paroxetine should not be prescribed with tamoxifen.

Fluoxetine [a strong CYP2D6 inhibitor] and citalopram [a weak CYP2D6 inhibitor] are the first and second line treatments for newly diagnosed major depression in the Lothian Joint Formulary. Venlafaxine, a weak CYP2D6 inhibitor, may be recommended by oncologists in Lothian as the antidepressant of choice for managing hot flushes in patients on tamoxifen, although it is not included in the LJF.

Key messages:

- **Concomitant use of drugs that are potent inhibitors of the CYP2D6 enzyme should be avoided whenever possible in patients treated with tamoxifen for breast cancer[1]**
- **In Lothian, citalopram, the LJF second choice antidepressant for newly diagnosed depression, is a weak CYP2D6 inhibitor and therefore can be prescribed with tamoxifen.**

References

1. Drug Safety Update. Medicines and Healthcare products Regulatory Agency. November 2010. www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON099863
2. Kelly CM *et al*. Br Med J 2010;*340*:c693.
3. Dezentje VO *et al*. J Clin Oncol 2010;*28*:2423-29.
4. British National Formulary No.60. September 2010.

Thanks to Gerry Hughes, Pre-Reg Pharmacist, for contributing this article.

Gabapentin misuse

Lothian Substance Misuse Services wish to alert prescribers and pharmacists to the possibility of misuse of gabapentin capsules and tablets. Gabapentin is available as a generic product and as Neurontin® and is licensed for the treatment of partial seizures and for the treatment of neuropathic pain.[1]

Although evidence is currently scarce, anecdotal reports indicate that gabapentin misuse does occur. Recent intelligence received by the Lothian Controlled Drug Governance Team, and results from a survey involving the Lothian Pain Service, suggest that some substance misusers have been misusing gabapentin, and some take gabapentin with opiates for increased effects.

Case reports have also been published outwith the UK describing gabapentin misuse in patients with histories of substance misuse, either to deal with cravings or withdrawal symptoms, or as a substitute for substances such as cocaine.[2]

Some prescribers may think of gabapentin as a 'safer' pain relieving alternative to opioids, for substance misusers. It is important to be aware that gabapentin itself may be misused and may increase risk of misuse if used with other drugs including opioids.

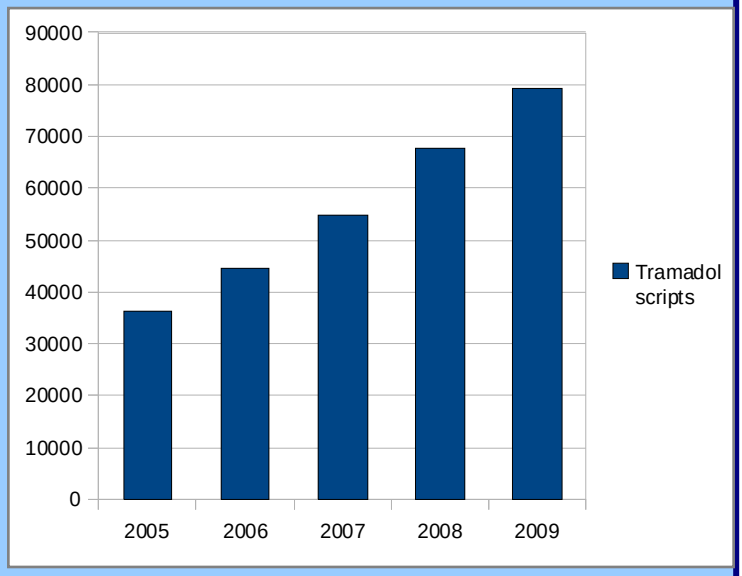
References

1. Summary of Product Characteristics, Neurontin®. www.medicines.org.uk
2. Webb J. British Columbia Drug & Poison Information Centre. 2008. http://dpic.org/article/professional/gabapentin-abuse [accessed 19/12/10]

Thanks to Amanda Hart, Pharmacist, for contributing this article.

Tramadol use increasing

Prescriptions for tramadol increased in Lothian by over 200% in just 4 years (2005 to 2009). The reason for this rise is not clear. Tramadol is not recommended in the Lothian Joint Formulary (LJF) as a first choice analgesic. Additionally, it commonly causes nausea and vomiting and although rare can cause seizures especially in patients on drugs which lower the seizure threshold, e.g. SSRI antidepressants. Modified release versions of tramadol are more expensive than the standard preparations and should not be prescribed. The LJF continues to recommend that tramadol should be reserved for patients in whom constipation poses a major threat (e.g. after bowel surgery) or who experience unacceptable sedation or respiratory depression with other opioids.



Reminder - safe use of methotrexate

Methotrexate, an anti-metabolite and immunosuppressant, is used in the treatment of cancer, rheumatoid arthritis, psoriasis and Crohn's disease. Serious adverse effects with methotrexate include blood dyscrasias and liver, kidney and lung damage.

Key messages:

- **Prescribe and dispense only the 2.5mg strength of methotrexate tablets**
- **Prescribe and dispense methotrexate *once a week***
- **Prescribe folic acid once weekly to prevent methotrexate-induced side effects.**

In 2004 the National Patient Safety Agency[1] highlighted the safety issues around prescribing and dispensing methotrexate. NHS Quality Improvement Scotland endorsed the NPSA report and asked Scottish Health Boards to implement the recommendations. From this the Lothian Area Drug and Therapeutics Committee produced a 'safe practice' checklist[2] and articles were included in this bulletin[2,3].

References

1. Improving compliance with oral methotrexate guidelines. Reissued guidance. The National Patient Safety Agency (NPSA). 1 June 2006. www.npsa.nhs.uk/patientsafety/alerts-and-directives/alerts/oral-methotrexate/
2. Lothian Prescribing Bulletin. Issue No. 15. July 2005. www.ljf.scot.nhs.uk/lpb/LPB15_Methotrexate.pdf
3. Lothian Prescribing Bulletin. Issue No. 30. January 2008. www.ljf.scot.nhs.uk/lpb/LPB30.pdf

Calcium supplements and cardiovascular risk

Various media have reported that calcium supplements can increase the risk of heart attacks and cardiovascular events. This is in response to a meta-analysis published in the British Medical Journal.[1]

This has resulted in queries from worried patients to GPs, the Lothian Osteoporosis Service and medicines information departments.

The trials included in this analysis did not generally include cardiovascular disease as a pre-defined primary endpoint and patients taking calcium and vitamin D were excluded. A previous study showed that calcium and vitamin D does not increase the risk of cardiovascular disease or stroke.[2]

Although this BMJ study raises concerns over calcium supplements (without vitamin D) being associated with a risk of increasing cardiovascular events, the current evidence overall is insufficient to affect practice.

Key messages:

- **Calcium and vitamin D supplements in combination with bisphosphonates remain the recommended treatment for patients with high risk of osteoporotic fractures**
- **Estimate your patient's calcium intake using the online calculator.[3] Those with adequate dietary intake may not require additional supplementation at all.**

References

1. Bolland MJ *et al*. Br Med J 2010;*341*:c3691.
2. Hsia J *et al*. Circulation 2007;*115*:846-54.
3. Online calcium intake calculator www.rheum.med.ed.ac.uk/calcium-calculator.php [accessed 20/12/10]

Overseas visitors requesting prescriptions for controlled drugs

There may be occasions when overseas visitors who are not ordinarily eligible for NHS treatment (i.e. not covered by Reciprocal Healthcare Arrangements) need a prescription for a Schedule 2 or 3 Controlled Drug.

The Scottish Government Primary Care Division confirmed to the Accountable Officers Network in February 2010 that 'GPs have the discretion to offer treatment to a temporary resident and to provide that treatment on the NHS. However, some GPs may opt to treat the patient on a private, fee-paying basis.'

If a GP determines that such a prescription is needed the only mechanism for this to be prescribed privately is by way of a PPCD1 pad and only 24 GPs across NHS Lothian hold such pads.

Patients cannot be given prescriptions for dispensing at a hospital pharmacy and treatment cannot be supplied from a private hospital unless the patient is under the care of that establishment.

The Controlled Drugs Governance Team (CDGT) is aware of an increase in requests from United States of America visitors requesting oxycodone, with various reasons being cited for having insufficient supplies to cover the duration of their visit. If you are faced with a request for a Schedule 2 or 3 Controlled Drug we would suggest in the interests of public safety that, in addition to all normal checks made, the doctor/prescriber may wish to also consider the following:

- ✓ Confirm the identity of the visitor via a passport, valid driving licence or other form of photographic ID
- ✓ Request proof of dates of travel
- ✓ Inform the CDGT if you are concerned in any way regarding the request.

Thanks to Judie Gillies, Lead Pharmacist, Controlled Drugs Governance Team, for contributing this article.

Herbal medicines and side effects

A public health campaign will be running in community pharmacies across Scotland from the 3rd January to 13th February 2011 to raise awareness of the concerns over the use of herbal medicines by patients. Yellow Card Centre Scotland, in collaboration with the MHRA and the Scottish Government Pharmaceutical Division, will be promoting awareness of herbal safety issues and reporting of potential side effects/drug interactions via the Patient Yellow Card. Herbal medicines have the potential to interact with prescription and over-the-counter medicines. Health Professionals should be aware of this and any suspicions relating to interactions of herbal preparations with patients' other medicines, or side effects should be reported via the Yellow Card.

Surveys have shown that most people do not tell their doctor that they are taking a herbal medicine, especially elderly patients. Doctors may not specifically ask, and so would have no reason to suspect that ill health was linked to consumption of a herbal medicine. Patients are much less likely to report to their doctor the suspected side effect of a medicine if they believe it may be linked to a herbal medicine.
The use of herbal medicines by older patients is increasing, and typically more than one herbal preparation is being taken, often concomitantly with prescription medicines.

Quality assurance - cause for concern

Many herbal medicines are still unlicensed and are purchased from outlets other than pharmacies, including Ayurvedic and Traditional Chinese Medicines (TCM) or via the internet. There is an international trade in poor quality, unregulated and unlicensed herbal preparations. Some of these have been found to contain banned pharmaceutical ingredients or heavy metals (arsenic, mercuric sulphide or red mercuric oxide), which are poisonous. Products may also contain harmful herbs that are not permitted in the UK, and you should be aware that unlicensed herbal medicines manufactured outside the UK may not be subject to any form of effective regulation. As a result contamination during the manufacturing process is possible (e.g. pesticides, mycotoxins or microbials). Indeed, some products actually contain pharmaceutical substances or analogues that are licensed as medicines (e.g. corticosteroids, sildenafil, antidiabetic agents).

By April 2011 all manufactured herbal medicines in the UK will be required to have either a traditional herbal registration or a product licence. However, this will not prevent patients from obtaining unlicensed preparations via the internet.

What side effects are reported?

The MHRA currently receives about 70 suspected adverse drug reaction reports relating to herbal medicines each year.[1] This is believed to represent only a small proportion of cases.

Some examples include:

- Delay in effective treatment for serious conditions (e.g. TCM practitioner advertising that herbal medicine will obviate need for coronary artery bypass graft)
- Interference with vital treatment (e.g. Ayurvedic clinic advising patient to discontinue antipsychotic medication and take alternative Ayurvedic remedies)
- Exploitation of vulnerable groups such as children and the seriously ill (e.g. parents wanting baby/child to have 'natural' cream for eczema, unaware that the products supplied actually contain undeclared steroids; patients with cancer have been prescribed large quantities of TCM)
- Overloading patient with multiple medications (e.g. adolescent boy with acne on over 100 TCM tablets a day for several months; patient hospitalised with serious unexplained abdominal pain)
- Unexpected rare but serious liver toxicity of plants with Kava Kava and Black Cohosh leading to liver transplants in some cases
- Interactions with other medicines (e.g. St John's Wort can interact with many prescribed medicines including contraceptive pill and immunosuppressant medicines).

Reference

1. Public Health Risk with Herbal Medicines: An Overview. Policy Division. Medicines and Healthcare products Regulatory Agency. July 2008. www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON023163&RevisionSelectionMethod=Latest (accessed 19/12/10).

Correspondence address:
Medicines Management Team (MMT)
Pentland House
47 Robb's Loan
Edinburgh
EH14 1TY **Tel: 0131-537-8510**

Email: prescribing@nhslothian.scot.nhs.uk