LOTHIAN PRESCRIBING BULLETIN

Supporting prescribing excellence - informing colleagues in primary and secondary care

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In this issue …

Inside: 3rd article on chronic pain: Opioids

Clinical trials - what's happening locally?

The purpose of a clinical trial is to establish the safety and efficacy of an Investigational Medicinal Product (IMP), study its pharmacokinetics and identify adverse reactions. There are around 200 clinical drug trials currently recruiting patients in NHS Lothian across primary and secondary care. These range from small, locally sponsored, single-centre studies to large multicentre, international, commercially sponsored studies.

Clinical trials are conducted in a series of phases.

- **Phase I:** the first experiment in humans, involving around 20 to 80 subjects
- **Phase II:** clinical investigation for treatment effects to establish efficacy and dose
- **Phase III:** full scale evaluation in a large number of patients; will always involve a comparison to a placebo or standard treatment, the results of which will produce bulk data for the marketing authorisation
- **Phase IV:** the post marketing surveillance period where information is gathered on the incidence of adverse effects.

Two trials currently running in Lothian are the AspECT study and the Myeloma XI study.

The aim of the AspECT trial is to investigate the benefits of acid suppression and/or aspirin in reducing the risk of oesophageal cancer development in those with Barrett's oesophagus. Currently over 100 patients are participating in this randomised study of aspirin and esomeprazole chemoprevention which is due for completion in 2018.

The Myeloma XI trial is a Phase III randomised trial comparing the biological therapies lenalidomide, bortezomib and carfilzomib with currently available treatments in patients with newly diagnosed myeloma. There are two treatment groups in this trial; intensive treatment and non-intensive treatment. The trial will recruit 4000 patients and is due for completion in 2018.

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Clinical trials are supported in all clinical specialities. Over the past 18 months there has been a significant increase in the number of trials in multiple sclerosis and rheumatology, partly due to specialist centres being located in Edinburgh.
Sixty percent of actively recruiting trials are in oncology / haematology. This number is high due to the current research focus on targeted therapy, vaccines and immunotherapy.

The pharmacy clinical trials team across the hospitals ensures compliance with relevant regulation and legislation, local and national guidelines and good clinical practice. Trial protocols specify the trial design, selection and withdrawal of subjects, drug treatment, storage and handling requirements for the IMP, assessment of safety and efficacy, quality control, ethical considerations and exit strategies. The Medicines and Healthcare products Regulatory Agency (MHRA) authorises and regulates clinical trials as described on the UK Government gov.uk website.

Useful resources:

1. For information regarding a specific clinical trial please search the UK Clinical Trials Gateway Database www.ukctg.nihr.ac.uk
2. To learn more about clinical trials please visit the NHS Education for Scotland website.

Thanks to Hazel Milligan and Ruaridh Buchan, Specialist Clinical Trial Pharmacists, Steven Allen and Elaine Agnew, Pre-registration Pharmacist Trainees, for contributing this article.

Opioids in chronic pain – do your patients know the risks?

Despite significant risks of harm and limited benefits, prescribing of strong opioids for chronic pain has risen dramatically over the last 10 years, such that it is now becoming a significant public health problem. Opioids often produce a significant early improvement in pain scores but, due to the development of tolerance and other adverse effects (endocrine and immune dysfunction, osteoporosis, increased fracture risk, etc.), only a limited number of patients with chronic non-cancer pain get overall benefit in the longer term.

It is important to carefully consider the risks of *any* drug treatment before prescribing, but especially so with strong opioids. Explain these risks to the patient and offer alternatives, including non-pharmacological therapies. Many patients choose to avoid starting opioids when aware of the risks and alternatives, even in the face of significant pain. Concise guidance is available from SIGN 136: management of chronic pain, Annex 4, pathway for using strong opioids.

Avoid prescribing strong opioids in patients with visceral pain, fibromyalgia and somatoform (functional, medically unexplained) pain. Avoid routine opioid use in neuropathic pain and only use with caution if a personal or family history of addiction (including alcohol misuse).

This is the third of a series of articles on chronic pain

If choosing to prescribe strong opioids, use modified release morphine as first choice and avoid immediate release preparations which may contribute to dose escalation. Avoid combining opioids unless on specialist advice. Prescribing should involve regular review, assessment of efficacy and adverse effects and an awareness of potential long term harms. It is recognised that tramadol is frequently used but it is not recommended in the LJF for chronic pain and should be treated with all the same cautions as morphine and other strong opioids.

Chronic pain is a complicated biopsychosocial condition and strong opioids may often be used to 'numb' psychological pain. Any attempt to address problematic opioid use needs to recognise this and find alternative ways to manage unpleasant emotional experiences.

It is worth considering a practice-based review of all patients on regular strong opioids; this will be included as a local GMS medicines management audit option in 2015/16.

Key messages

- **For many patients with chronic non-cancer pain the risks of strong opioids outweigh the benefits.**
- **Consider referral to or advice from a pain specialist if opioid doses are escalating or not helping pain or if prescribing more than 180mg of morphine equivalent per day. Advice is available via lothianchronicpainservice@nhslothian.scot.nhs.uk or the new SCI Gateway 'Advice Only' service.**

Thanks to Dr John Hardman, RCGP Scotland representative on clinical guideline development group for SIGN 136: Management of Chronic Pain, and GP, Dalhousie Medical Practice, Bonnyrigg.

Drugs and driving

A new law on driving after taking certain drugs (including some medicines) came into force in March 2015 in **England and Wales only.** This new law will not be brought into force in Scotland for the foreseeable future. However, under existing legislation it is still an offence to drive if your ability is adversely affected. Patients should be advised that if they feel their illness or medication affects their driving they should not drive and discuss this with their doctor.
For full article please see the News section of the LJF website.

LJF amendments

The LJF amendments are now added to the News section of the LJF website.
Please click here to see amendments from January and March 2015.

Urinary incontinence: regular review for patient safety

Urinary incontinence is a common symptom that can affect all ages, with a wide range of severity and nature.[1] The most common forms are urge (overactivity of detrusor muscles which control the bladder) and stress (weakening or damaging of the pelvic floor muscles and the urethral sphincter) incontinence. Management can involve conservative, pharmacological or surgical approaches. Initially there should be a trial of lifestyle interventions and pelvic floor muscle training or bladder training as appropriate, before a medicine is started. Following on from this, pharmacotherapy can be considered.[1]

Lothian Joint Formulary 7.4.2 Recommendations

Urge incontinence

1st choice: oxybutynin hydrochloride or solifenacin

Antimuscarinic (anticholinergic) therapy should be reviewed after six months and if symptoms are well-controlled therapy may be reduced or discontinued as symptoms may not recur.
Oxybutynin use may be limited due to its side-effects, which are possibly reduced if started at low dose and gradually increased. Solifenacin may be used for patients unable to tolerate oxybutynin.

Stress incontinence in women

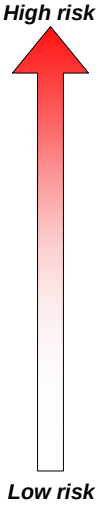
1st choice: pelvic floor muscle exercises
2nd choice: duloxetine on specialist advice + pelvic floor muscle exercises

Initiation of duloxetine should only be considered by a gynaecologist or urologist in secondary care. Patients should be reviewed after 12 weeks and, where there are no signs of improvement, treatment should be discontinued.

Antimuscarinic potency and patient safety

Patients on long term drug treatment should be reviewed annually (or every six months for patients over 75 years old) to assess the continued need.[1] Antimuscarinics are poorly tolerated in frail patients.[2] Elderly patients are at higher risk of adverse drug effects such as falls and impaired cognitive function. There is also the concern of increased mortality linked to the number and potency of antimuscarinic agents prescribed, therefore this burden needs to be considered during patient medication reviews. Continuation of these medicines should have a well defined indication.

A *modified Anticholinergic Risk Scale (mARS)* has been used to rank the anticholinergic potential of different medicines on a scale of 0-3; the higher the number the stronger the risk of adverse side-effects.[2,3] Examples are shown below.



3 very strong	amitriptyline chlorphenamine oxybutynin thioridazine
2 strong	cetirizine cimetidine dosulepin loperamide loratadine prochlorperazine pseudoephedrine solifenacin tiotropium tolterodine
1 moderate	lofepramine metoclopramide mirtazapine paroxetine quetiapine ranitidine selegiline

Key messages

- **Regular review and awareness of the antimuscarinic burden will increase patient safety.**
- **Review patients on long term treatment annually (and every six months in patients over 75 years old) to assess the need for continued use.**

References

1. Urinary incontinence: The management of urinary incontinence in women. NICE Guideline 171. National Institute for Health and Care Excellence. September 2013. www.nice.org.uk/guidance/CG171 *[Accessed 20.04.15]*
2. Polypharmacy Guidance for the safe and effective use of multiple medicines to manage long term conditions. DL (2015) 004. The Scottish Government. 15 April 2015. www.sehd.scot.nhs.uk/publications/DC20150415polypharmacy.pdf *[Accessed 22.04.15]*
3. Sumukadas D *et al.* Temporal trends in anticholinergic medication prescription in older people: repeated cross-sectional analysis of population prescribing data. Age and Ageing 2014;*43*:515- 21. http://ageing.oxfordjournals.org/content/43/4/515.full *[Accessed 20.04.15]*

Thanks to Courtney Armstrong and Cathriona Gavin, Pre-registration Pharmacist Trainees, for contributing this article.

Lactose-free medicines are not usually necessary in adults

Lactose is widely used in pharmaceuticals. Ingestion of lactose by lactose intolerant/lactase deficient patients can lead to gastrointestinal symptoms. Symptoms vary according to the quantity of lactose ingested, the patient's ability to digest lactose and the amount and type of colonic flora. Patients with lactose intolerance may request lactose-free formulations of their medicines, however **most individuals do not need a severely restricted or lactose-free diet.**[1]

Most individuals with presumed lactose intolerance or malabsorption can tolerate 12g to 15g of lactose[2] (240 to 300mL milk). The dose of lactose in most pharmaceuticals is usually < 2g per day.[1] Therefore in most lactose intolerant adults, lactose-free medicines are not necessary. Some severely lactose intolerant individuals may develop gastrointestinal symptoms with lactose doses as low as 100mg to 200mg.[1] The amount of lactose used may vary by manufacturer, product, formulation and strength.

Liquid preparations of *most* medicines are lactose-free and may provide an alternative option. The Summaries of Product Characteristics (SPCs) will inform whether lactose is included as an excipient; for most branded and many generic UK medicines this can be checked at www.medicines.org.uk. Further to this, the lactose content of medicines can be determined by consulting the relevant manufacturer of the product.

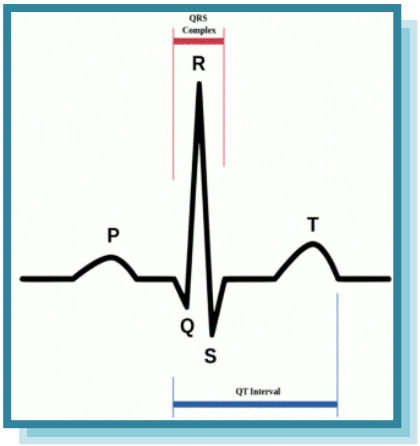
Note this article does not apply to individuals with lactose allergy, galactosemia or children.

References

1. Q&A 131.6 What factors need to be considered when prescribing for lactose intolerant adults? Prepared by UK Medicines Information UKMi pharmacists for NHS healthcare professionals. 15 August 2013 (partial revision 2 October 2013 and 25 February 2014).
2. Shaukat A *et al.* Systematic Review: Effective Management Strategies for Lactose Intolerance. Ann Intern Med. 2010;*152*:797-803. http://annals.org/article.aspx?articleid=745835 *[Accessed 20.04.15]*

New local guidance on drug-induced prolonged QT interval

Guidance on the measurement, risk factors, prescribing and monitoring for *'Drug Induced QT Interval Prolongation'* has been produced. It was approved in November 2014 by the University Hospital Division Drug and Therapeutics Committee and the Cancer Therapeutics Advisory Committee, and is now available on the NHS Lothian intranet:
NHSLothian > Healthcare > A-Z > Cardiac Services > **Cardiology guidelines**
or
NHSLothian > Healthcare > A-Z > Respiratory > **Respiratory Guidelines**



The guidance:

- ✓ stratifies drugs that are known to prolong QT interval into known risk, possible risk and conditional risk. Some commonly prescribed examples of drugs that have a known risk are clarithromycin, haloperidol, methadone and citalopram.
- ✓ includes information on prescribing and monitoring of these drugs.
- ✓ provides details of the patient risk factors that increase the risk of prolonged QT interval.
- ✓ includes a helpful reminder on how to measure the QT interval on an ECG and a decision pathway for prescribing and/or cardiology advice.

Supplement: Recent SMC and Lothian Formulary Committee Recommendations

The supplements can be accessed via the LJF website www.ljf.scot.nhs.uk in 'Prescribing Bulletins'.

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