NHS Lincolnshire

Prescribing and Clinical Effectiveness Bulletin

Volume 3; Number 4 **April 2009**

What's new this month:

- **Methylnaltrexone bromide injection (Relistor) is approved for use subject to advice from a palliative care specialist (see page 3).**
- **Ethinylestradiol/etonogestrel vaginal ring (NuvaRing) is not approved for use due to concerns over cost-effectiveness (see page 3).**
- **Calcipotriol/betamethasone gel (Xamiol) is approved for use within the scalp psoriasis treatment pathway (see page 4).**
- **Tadalafil (Cialis Once-A-Day) is approved for use subject to NHS restrictions and previous exposure/response to on demand tadalafil and an intended frequency of intercourse of more than once a week (see page 5).**
- **Zoledronic acid intravenous infusion (Aclasta) has been approved for use under specialist supervision within the ULHT Osteoporosis Clinic (see page 6).**
- **NICE have updated their Technology Appraisal on the use of amantadine, oseltamivir and zanamivir for the treatment of influenza and have issued Clinical Guidelines on Chronic Kidney Disease and Medicines Adherence (see pages 8 to 12).**
- **The Medicines and Healthcare products Regulatory Agency (MHRA) have raised safety concerns relating to methylphenidate, atomoxetine, risperidone, exenatide and alendronic acid (see page 12).**
- **The National Patient Safety Agency have issued a Rapid Response Report raising concerns over the risk of using oral bowel cleansing solutions in inappropriate patients (see page 15).**

CONTENTS

Page 3	**New Drug Assessment: Methylnaltrexone bromide injection (Relistor)**
Page 3	**New Drug Assessment: Ethinylestradiol/ etonogestrel vaginal ring (NuvaRing)**
Page 4	**Rapid Assessment: Calcipotriol/ betamethasone gel (Xamiol)**
Page 5	**Rapid Assessment: Tadalafil 2.5mg and 5mg tablets (Cialis Once-A-Day)**
Page 6	**Review: Zoledronic acid intravenous infusion (Aclasta)**
Page 7	**New Trials in Brief**
Page 8	**NICE Technology Appraisal 168: *Amantadine, oseltamivir and zanamivir for the treatment of influenza* (February 2009)**
Page 9	**NICE Clinical Guideline 73: *Chronic kidney disease: Early identification and management of chronic kidney disease in adults in primary and secondary care* (September 2008)**
Page 11	**NICE Clinical Guideline 76: *Medicines adherence: Involving patients in decisions about prescribed medicines and supporting adherence* (January 2009)**
Page 12	**MHRA Safety Update: Methylphenidate; Atomoxetine; Antipsychotics in Dementia; Exenatide and pancreatitis; Bisphosphonates and stress fractures**
Page 15	**National Patient Safety Agency (NPSA) Rapid Response Report – Reducing Risk of Harm from Oral Bowel Cleansing Solutions (February 2009)**

This bulletin has been created specifically to convey details of decisions taken at the Prescribing and Clinical Effectiveness Forum (PACEF) to all stakeholders across the Lincolnshire Healthcare Community in both primary and secondary care. Steps will be taken to ensure the widest possible distribution across NHS Lincolnshire and within United Lincolnshire Hospitals Trust and Lincolnshire Partnership Trust. Both paper and electronic copies will be circulated initially with a view to evolving into complete electronic distribution as soon as we are confident that all key stakeholders can access E-mail. There are also plans to make all bulletins, guidelines, formularies, new product assessments, care pathways and other PACEF publications available through the NHS Lincolnshire website.

SUMMARY OF PACEF DECISIONS: MARCH 2009 UPDATE

Drug	Indication(s)	Traffic Light Status
Amantadine capsules (Lysovir)	Prophylaxis and treatment of influenza A	RED-RED
Calcipotriol and betamethasone gel (Xamiol)	Topical treatment for scalp psoriasis	GREEN subject to constraints in the ULHT *Dermatology Handbook*
Ethinylestradiol/ etonogestrel vaginal ring (NuvaRing)	Licensed as a form of contraception in women of fertile age	RED-RED
Methylnaltrexone bromide injection (Relistor)	Opioid induced constipation in patients receiving palliative care when response to usual laxative therapy is inadequate	AMBER. Should only be prescribed in primary care following advice from the medical team at St Barnabus Hospice. No shared care guideline is required.
Oseltamivir (Tamiflu) capsules	Treatment and post-exposure prophylaxis of influenza	GREEN subject to NICE restrictions; all prescriptions should be endorsed 'SLS'.
Tadalafil 2.5mg and 5mg tablets (Cialis Once-A-Day)	Licensed for once daily use in the treatment of erectile dysfunction (ED)	GREEN Subject to SLS restriction. Should only be used in those who have had previous exposure and response to on demand tadalifil and who have an intended frequency of intercourse of more than once a week.
Zanamivir (Relenza) dry powder for inhalation	Treatment and post-exposure prophylaxis of influenza	GREEN subject to NICE restrictions; all prescriptions should be endorsed 'SLS'.
Zoledronic acid intravenous infusion (Aclasta)	Once yearly IV infusion bisphosphonate licensed for the treatment of post menopausal osteoporosis	RED For use under specialist supervision within ULHT Osteoporosis Clinic only

RED-RED: This signifies that a product is **not recommended** for prescribing in **both** primary and secondary care. All new products are classified as RED-RED pending assessment by PACEF.
RED: This signifies that a product has been approved for use within ULHT and/or LPFT **only** and has **no role in primary care**.
AMBER: This signifies that a drug has been approved for use in primary care **subject to specialist initiation; a shared care guideline (SCG) may also be required**. The main purpose of the SCG will be to clearly define both specialist and GP responsibilities. Not all AMBER drugs that require SCGs are currently covered by formal documents; in the coming months PACEF will be working to rectify this.
GREEN: This signifies a product that is **approved for initiation in either primary or secondary care**. Specialist initiation and shared care guidelines are not considered necessary.

REPORTING INCIDENTS TO THE NATIONAL PATIENT SAFETY AGENCY (NPSA)
The NPSA are keen to encourage the anonymous reporting of patient safety errors and systems failures both from healthcare professionals and patients. The National Reporting and Learning System (NRLS) has been set up to facilitate this process. Healthcare professionals can either report patient safety incidents through their local risk management scheme or directly into the NRLS using the eForm on the NPSA website. Please access www.npsa.nhs.uk for more information. **All healthcare professionals are encouraged to report incidents, errors and systems failures; the aim is to help the NHS to learn from things that go wrong.**

NEW DRUG ASSESSMENT: METHYLNALTREXONE BROMIDE INJECTION (RELISTOR)

Methylnaltrexone is the first of a new class of drug known as peripherally acting mu-opioid receptor antagonists. It is licensed for the treatment of opioid induced constipation in adult patients who are receiving palliative care where response to usual laxative therapy has not been sufficient. Supporting evidence from two underpowered and short-term clinical trials against placebo shows that methylnaltrexone alleviates opioid–induced constipation without compromising analgesia. The drug appears to be well tolerated with the most common adverse effect being abdominal pain and flatulence, although there is no long term safety data. The manufacturer recommends that treatment should be restricted to patients with advanced disease and limited life expectancy and treatment should be for a limited period. The maximum length of treatment is not defined in the SPC, although trials were for four months and the EMEA recommends that the treatment period should not exceed three months. Methylnaltrexone is much more expensive than standard laxatives (about twenty five times the cost), however, the higher cost could be offset by prevented hospitalisations. The judicious use of methylnaltrexone may enable some patients to remain at home during the final stages of their illness.

PACEF Recommendation:
Methylnaltrexone bromide injection (Relistor) is designated AMBER. It should only be prescribed by a GP in response to specialist advice from the medical team at St Barnabus Hospice. There is no requirement for a shared care guideline.

NEW DRUG ASSESSMENT: ETHINYLESTRADIOL/ETONOGESTREL VAGINAL RING (NUVARING)

NuvaRing is a combined hormonal contraceptive vaginal ring containing ethinylestradiol (EE) and etonogestrel. Once inserted, the ring remains in place for three weeks releasing an average dose of 120mcg etonogestrel and 15mcg ethinylestradiol every 24 hours. Published trial evidence is limited to a number of studies investigating contraceptive efficacy and cycle control in comparison to a narrow range of commonly prescribed oral contraceptives (Microgynon 30 and Yasmin). There are no published trials comparing the ring with alternative forms of contraception, although a Cochrane review from 2003 utilized existing data to conclude that the contraceptive effectiveness of the vaginal ring was comparable to combined oral contraception and the combined hormonal contraceptive patch. Comparative trials looking at cycle control show NuvaRing is linked to a lower incidence of late withdrawal bleeds and the establishment of more regular bleeding patterns than the combined oral contraceptive. The adverse effect profile and the list of contraindications are similar to those normally associated with combined hormonal contraception. Specifically, the use of the ring has been linked to local reactions such

as vaginitis and increased vaginal discharge. NuvaRing has been available in the USA since 2002 and a number of European countries since 2003.

A cost comparison reveals that NuvaRing is considerably more expensive than combined oral contraception and even the combined hormonal contraceptive patch.

Drug	Dose	Cost(£)/3mths
NuvaRing (EE 15mcg, etonogestrel 120mcg)	**1 ring inserted for 3 weeks followed by ring free week.**	**£27.00**
Low strength (oral)		
Mercilon (EE 20mcg, desogestrol 150mcg)	1 tablet each day for 21 days followed by 7pill-free days.	£6.70
Low strength (transdermal)		
Evra (EE 20mcg, norelgestromin 150mcg)	1 patch each week for 3 weeks, followed by patch free week.	£16.26
Standard strength (oral)		
Microgynon 30/ Ovranette (EE 30mcg, levonorgesterol 150mcg)	1 tablet each day for 21 days followed by 7 pill-free days.	£2.99/£2.29
Yasmin (EE 30mcg, drospirenone 3mg)		£14.70

NuvaRing has a short shelf life of only 4 months at room temperature.

PACEF Recommendation:
PACEF were convinced of the contraceptive efficacy and tolerability of NuvaRing, but were concerned about the excessive cost in comparison to alternatives. As a result of these concerns over cost-effectiveness, NuvaRing is designated RED-RED. Where the oral route is unsuitable due to hormonal related vomiting or nausea/vomiting related to other medical conditions or treatment, the combined hormonal contraceptive patch (Evra) is recommended as an alternative.

RAPID ASSESSMENT: CALCIPOTRIOL/BETAMETHASONE GEL (XAMIOL)

Xamiol gel is a new gel formulation containing a combination of a vitamin D analogue (calcipotriol) and a corticosteroid (betamethasone); it is licensed for the treatment of scalp psoriasis. Evidence from clinical trials demonstrates its superior efficacy to formulations of the individual components; no comparative studies between Xamiol and a combination of calcipotriol and betamethasone prescribed as separate components currently exist. Treatment consists of 1 to 4 grams applied to affected areas of the scalp once daily for a recommended treatment period of 4 weeks.

Xamiol gel is expensive in comparison to alternative preparations:

Drug	Cost (£) per pack
Combination preps	
Xamiol gel (betamethasone/calcipotriol)	60g £36.50
Calcipotriol only preps	
Dovonex scalp solution	60ml £13.04, 120ml £26.07
Corticosteroid only preps	
Betnovate (betamethasone)	100ml 5.30
Betacap(betamethasone)	100ml £3.92
Bettamouse (betamethasone)	100g £9.75
Dermovate (clobetasol)	100ml £11.06
Synlar gel (fluocinolone)	30g £5.56 60g £10.02
Coal tar containing preps	

Cocois oint	40g £6.22 100g £11.69
Sebco oint	40g £4.54 100g £8.52
Alphosyl shampoo	250ml £3.43
Capsal shampoo	250ml £4.91
Polytar liquid	250ml £2.23

PACEF Recommendations

After a review of the existing evidence, PACEF are convinced that Xamiol gel has a role in those patients insufficiently responsive to steroidal scalp application monotherapy and as an alternative to a topical steroid plus coal tar ointment. As a result of this the scalp psoriasis treatment pathway in the ULH *Dermatology Handbook* is to be revised as follows:

Routine control/prevention: Coal tar shampoos (e.g. Polytar, Alphosyl) or antifungal shampoos (e.g. ketoconazole)

Shampoos should be used regularly to prevent or control mild disease. Most patients will respond to a tar containing shampoo, however a few will achieve better results with either ketoconazole or a salicyclic acid product.

Flares

When the condition flares, a steroidal preparation would normally be required for a few weeks. If there is also a thick scale present, this should be removed by using a tar ointment (e.g. Cocois, Sebco) for the first week. Where the patient does not respond to monotherapy with a steroidal scalp application, Xamiol gel can be considered as an alternative to a steroidal application plus coal tar ointment.

Within this context, Xamiol gel is designated GREEN.

RAPID ASSESSMENT: TADALAFIL 2.5MG AND 5MG TABLETS (CIALIS ONCE-A-DAY)

Oral tadalafil (Cialis) 10mg and 20mg has been available for several years for the treatment of erectile dysfunction (ED). It is one of a group of drugs known as the phosphodiesterase type-5 inhibitors; the other drugs in the group are sildenafil (Viagra) and vardenafil (Levitra). The 10mg and 20mg strengths of tadalafil are not recommended for continuous daily use; they are intended to be taken prior to anticipated sexual activity.

A daily dose version of tadalifil, known as Cialis Once-A-Day, is now available in 2.5mg and 5mg strengths. It is designed to be taken daily by men who have responded to the on-demand regimen and who may have intercourse more than once a week.

A cost comparison of all phosphodiesterase type-5 inhibitors currently available reveals the following:

	Dose	28 day cost
Tadalafil (Cialis Once-A-Day) 2.5mg or 5mg	**2.5mg to 5mg once daily**	**£54.99**
Tadalafil (Cialis) 10mg or 20mg	10mg or 20mg once weekly	£24.99
Tadalafil (Cialis) 10mg or 20mg	10mg or 20mg twice weekly	£49.97
Sildenafil (Viagra) 25mg	25mg once or twice weekly	£16.59 to £33.19
Sildenafil (Viagra) 50mg	50mg once or twice weekly	£21.27 to £42.54
Sildenafil (Viagra) 100mg	100mg once or twice weekly	£23.50 to £46.99
Vardenafil (Levitra) 5mg	5mg once or twice weekly	£16.58 to £33.19
Vardenafil (Levitra) 10mg	10mg once or twice weekly	£22.24 to £44.47
Vardenafil (Levitra) 20mg	20mg once or twice weekly	£23.50 to £46.99

From the cost comparison we can conclude that once daily tadalafil only becomes equivalent in cost to as required tadalafil where usage is higher than one dose of tadalafil per week. Both sildenafil (Viagra) and vardenafil (Levitra) are currently lower in price than tadalafil at once weekly doses, but are not currently available in once daily formulations.

The Department of Health have issued the following advice:

- One treatment a week will be appropriate for most patients being treated for ED.
- If the GP, in exercising his clinical judgement, considers that more than one treatment a week is appropriate, he should prescribe that amount on the NHS. In exercising this judgement, GPs may consider Cialis Once-A-Day suitable for a small number of patients.

PACEF Recommendation:
Prescribers are reminded that phosphodiesterase type-5 inhibitors (sildenafil, tadalafil and vardenafil) should only be prescribed on the NHS to treat ED in men who: (1) have diabetes, multiple sclerosis, Parkinson's disease, poliomyelitis, prostate cancer, severe pelvic injury, single gene neurological disease, spina bifida or spinal cord surgery; (2) are receiving dialysis for renal failure; (3) have had radical pelvic surgery, prostatectomy (including transurethral resection of the prostate) or kidney transplant. Additional arrangements are in place to treat those suffering severe distress as a result of impotence, although the *BNF* specifies that prescribing should be from specialist centres only. All prescriptions should be marked 'SLS'. In terms of recommended quantities, one treatment a week is considered appropriate for most patients, although a GP may prescribe more at his/her discretion. Within this context, tadalafil (Cialis Once-A-Day) is designated GREEN subject to previous exposure and response to on demand tadalafil and an intended frequency of intercourse of more than once a week. Regular review is recommended. A more detailed review of the evidence base for daily tadalafil compared to on-demand tadalafil is in progress.

REVIEW: ZOLEDRONIC ACID INTRAVENOUS INFUSION (ACLASTA)

PACEF evaluated zoledronic acid intravenous infusion (Aclasta) in January 2008 and concluded that there was insufficient evidence to support its use in the treatment of postmenopausal osteoporosis. Specifically, concerns were identified around clinical effectiveness, cost effectiveness and safety in comparison to other bisphosphonates. As a result of this, the product was designated RED/RED. Since the recent publication of NICE Technology Appraisals 160 and 161 on the primary and secondary prevention of osteoporotic fragility fractures in postmenopausal osteoporosis (October 2008), PACEF have undertaken to review all key osteoporosis treatments not covered by NICE guidance.

Since the publication of our earlier review of zoledronic acid infusion, the following publications have appeared:

Scottish Medicines Consortium (SMC) Zoledronic Acid 5mg solution for infusion (Aclasta) (February 2008)

The SMC approved zoledronic acid infusion for restricted use within NHS Scotland, for the treatment of osteoporosis in post-menopausal women at increased risk of

fracture. Use must be restricted to those women who are unsuitable for or intolerant to oral treatment options; treatment should be under specialist supervision only. The administration of a bisphosphonate infusion is an invasive procedure which can cause transient flu like symptoms. The only other bisphosphonate that can be administered as an infusion is ibandronate (Bonviva) which has to be administered once every three months. Annual zoledronic acid infusion has the advantage of a reduction in administration frequency and the risks associated with this.

Medicines and Healthcare products Regulatory Agency (MHRA), *Drug Safety update* (July 2008): Bisphosphonates and atrial fibrillation

Recent concerns on the increased risk of atrial fibrillation (AF) associated with bisphosphonate have resulted in a Europe wide review of clinical data. The conclusions of this review were recently highlighted to healthcare professionals through the MHRA *Drug Safety Update.* The risk of AF associated with bisphosphonate treatment seems to be low and the balance of risks and benefits for bisphosphonates remains favourable. To date, clinical trial results suggest an increased risk of AF with zoledronic acid, pamidronic acid and possibly alendronic acid. The product information for zoledronic acid and pamidronic acid has been updated to alert prescribers to the risk of AF; the risk of AF with alendronic acid is being kept under close review.

***Drug and Therapeutics Bulletin* (DTB) Vol 46 No 12 (December 2008): 'Annual zoledronic acid for osteoporosis', Vol 46; No 12; 93-96.**

The *DTB* reviewed the use of zoledronic acid IV infusion for the treatment of postmenopausal osteoporosis and concluded that the drug provides an option for patients unable to tolerate oral treatments for osteoporosis. There is evidence that zoledronic acid reduces the likelihood of vertebral or hip fractures in post menopausal women, and also reduces the chance of a subsequent fracture in men or women with a recent hip fracture. Due to the lack of comparative data with other treatments, it is not known whether zoledronic acid is more of less likely to prevent fractures than alternative therapies; it is also difficult to assess comparative tolerability due to the absence of comparative evidence. The *DTB* also highlights the risk of AF in association with zoledronic acid and recommends further investigation.

PACEF Recommendation:
Following a review of these recent publications, zoledronic acid IV infusion (Aclasta) is re-classified as RED. The drug can only be used within the ULHT Osteoporosis Clinic under specialist supervision.

NEW TRIALS IN BRIEF: FEBRUARY AND MARCH 2009

Fish oils and cardiac mortality: *BMJ* 2008; 337:a2931

A recent systematic review of 12 randomised controlled trials (RCTs) (n = 32,779) compared patients taking fish oils to controls in a range of heterogeneous populations, including primary prevention, post MI and percutaneous coronary intervention. There was no statistically significant reduction in the risk of sudden cardiac death or all cause mortality, but there was a significant reduction in death from cardiac causes. The absolute risk reduction was 0.53%; the Number Needed to Treat (NNT) was 189. The funnel plot of results suggests publication bias. **PACEF are keeping the existing RED-RED status of Omacor under review.**

The use of NSAIDs in patients with heart failure: *Arch Intern Med* 2009; 169(2): 141-9

An observational study investigating the risk of death, re-admission for heart failure or admission for MI associated with NSAID use among 107,092 Danish patients who survived their first admission for heart failure. Both diclofenac and celecoxib were associated with a higher risk of death, re-admission for heart failure and admission for MI. At doses less than 1200mg/day ibuprofen did not increase the risk of death, but all doses of ibuprofen increased the risk of readmission for heart failure and admission for MI. Naproxen at daily doses greater than 500mg increased the risk of death; it was also associated with an increased risk of re-admission for heart failure at all doses. Surprisingly, daily doses of naproxen of 500mg or less were associated with an increased risk of admission for MI; at higher doses the increased risk was not statistically significant. **Prescribers are reminded of existing PACEF advice on the use of NSAIDs:**

PACEF Recommendations:
Oral NSAIDs and Cox-2 inhibitors are third line options that should only be used when absolutely necessary; the lowest effective dose for the shortest duration should be used. In terms of product selection, low dose ibuprofen (e.g. 1200mg per day) has the lowest GI risk of standard NSAIDs. Low dose ibuprofen and naproxen (1000mg per day) have a lower thrombotic risk than other NSAIDs and coxibs; epidemiological data does not suggest an increased risk of myocardial infarction (MI) with either agent. Diclofenac 150mg per day has a thrombotic risk similar to coxibs (i.e. 3 additional events per 1000 users per year). Coxibs have a reduced GI risk relative to most NSAIDs, but are associated with a small increased thrombotic risk similar to diclofenac. Coxibs are contra-indicated in cardiovascular disease. A meta analysis of case controlled studies has also shown an increased thrombotic risk with meloxicam.

Prescribers should consider low dose ibuprofen first line whenever an NSAID is indicated. Naproxen represents a suitable second line alternative, although GI risk is higher. Diclofenac is not an appropriate first line choice due to an increased thrombotic risk on a scale comparable to the risk of coxibs; particular caution should be exercised in those with cardiovascular disease. Similar concerns exist around meloxicam. Prescribing of NSAIDs of higher GI risk (e.g. piroxicam) should be kept to a minimum.

NICE TECHNOLOGY APPRAISAL 168: *AMANTADINE, OSELTAMIVIR AND ZANAMIVIR FOR THE TREATMENT OF INFLUENZA* (FEBRUARY 2009)

The key recommendations are as follows:

- Oseltamivir and zanamivir are recommended, within their marketing authorisations, for the **treatment of influenza in adults and children** if all of the following apply: (1) National surveillance schemes have indicated that influenza virus A or B is circulating; (2) The person is in an 'at risk' group; (3) The person presents with an influenza-like illness and is able to begin treatment within 48 hours of the onset of symptoms (or within 36 hours for zanamivir treatment in children).
- During localised outbreaks of influenza-like illness (outside periods when influenza virus is confirmed by the HPA as circulating in the community), oseltamivir and zanamivir may be used for the treatment of influenza in 'at-risk' people living in long-term residential or nursing homes. There should be a high level of certainty that influenza is the causative agent (usually based on virological evidence of infection with influenza in the initial case).
- Amantadine is not recommended for the treatment of influenza.

PACEF Recommedations:
Both oseltamivir and zanamivir are designated GREEN subject to NICE restrictions. Both drugs are included in the Selected List Scheme (SLS) and are only approved for use within the NHS as designated by NICE. All prescriptions should be endorsed 'SLS'. Oseltamivir (Tamiflu) is currently the agent of lowest acquisition cost. Amantadine remains RED-RED for the treatment of influenza.

NICE CLINICAL GUIDELINE 73: *CHRONIC KIDNEY DISEASE* (SEPTEMBER 2008)

Chronic Kidney Disease (CKD) describes abnormal kidney function and/or structure. It is common, frequently unrecognized and often exists in conjunction with other conditions (e.g. CVD and diabetes). CKD is asymptomatic, but detectable. Because of the lack of specific symptoms, people with CKD often remain undiagnosed or are diagnosed late when CKD has already reached an advanced stage. Treatment can prevent or delay progression, reduce or prevent complications and reduce the risk of CVD.

CKD is classified into 5 stages:

Stage	GFR (ml/min/1.73m^2)	Description
1	$\geq$ 90	Normal or increased GFR, with other evidence of kidney damage
2	60-89	Slight decrease in GFR, with other evidence of kidney damage
3A	45-59	Moderate decrease in GFR, with or without other evidence of kidney damage
3B	30-44	Moderate decrease in GFR, with or without other evidence of kidney damage
4	15-29	Severe decrease in GFR, with or without other evidence of kidney damage
5	< 15	Established renal failure

The key NICE recommendations are as follows:

- **Offer testing for CKD to people with any of the following risk factors:** diabetes, hypertension, CVD (e.g. ischaemic heart disease, chronic heart failure, peripheral vascular disease and cerebral vascular disease), structural renal tract disease, renal calculi, prostatic hypertrophy, multisystem diseases with potential kidney involvement (e.g. systemic lupus erythematosus), family history of stage 5 CKD or hereditary kidney disease, opportunistic detection of haematuria or proteinuria.
- **Proteinuria should be identified and detected using urine albumin:creatinine ratio (ACR)** as it has a greater sensitivity than protein:creatinine ratio (PCR) for low levels of proteinuria.
- **People with CKD in the following groups should normally be referred for specialist assessment**: (1) stage 4 and 5 CKD (with or without diabetes); (2) higher levels of proteinuria (ACR 70mg/mmol or more) unless known to be due to diabetes and already properly treated; (3) proteinuria (ACR 30mg/mmol or more or urinary protein excretion 0.5g/24h or more) together with haematuria; (4) rapidly declining estimate of GFR (eGFR) (more than 5ml/min/1.73m^2 in 1 year or more than 10ml /min/1.73m^2 in 5 years); (5) hypertension poorly controlled despite the use at least four antihypertensive

drugs at therapeutic doses; (6) people with or suspected of having rare or genetic causes of CKD; and (7) suspected renal artery stenosis.

- **In people with CKD aim to keep the BP below 140/90.**
- **In people with CKD and diabetes and also in people with an ACR 70mg/mmol or more aim to keep the BP below 130/80.**
- Encourage people with CKD to take exercise, achieve a healthy weight and stop smoking.
- Offer Angiotensin-converting enzyme inhibitors (ACEIs)/ angiotensin-II receptor blockers (ARBs) to people with diabetes and ACR more than 2.5mg/mmol (men) or more than 3.5mg/mmol (women) irrespective of the presence of hypertension or CKD stage.
- Offer ACEIs/ARBs to non-diabetic people with CKD and hypertension and ACR 30mg/mmol or more.
- Offer ACEIs/ARBs to non-diabetic people with CKD and hypertension and ACR 70mg/mmol or more) irrespective of the presence of hypertension or CKD stage.
- When using ACEIs/ARBs start treatment with an ACEI and move to an ARB if the ACEI is not tolerated. Use the maximum tolerated therapeutic dose before adding a second line agent.
- Before starting ACEI/ARB therapy in people with CKD, measure serum potassium concentrations and estimate GFR. Repeat these measurements between 1 and 2 weeks after starting ACEI/ARB therapy and after each dose increase. ACEI/ARB therapy should not normally be started if the pre-treatment serum potassium concentration is significantly above the reference range (i.e. more than 5.0mmol/l)
- Offer non-diabetic people with CKD and hypertension and ACR less than 30mg/mmol a choice of antihypertensive treatment according to NICE guidance on hypertension to prevent or ameliorate progression of CKD.
- Monitor GFR in people prescribed drugs known to be nephrotoxic (e.g. ciclosporin, tacrolimus and and lithium). Check GFR at least annually in people receiving long-term systemic NSAID treatment.
- In people with CKD the chronic use of NSAIDs may be associated with progression; acute use is associated with a reversible fall in GFR. Exercise caution when treating people with CKD over a prolonged period of time.
- The use of statin therapy for primary prevention of CVD in people with CKD should not differ from its use in people without CKD. Offer statins to people with CKD for the secondary prevention of CVD irrespective of baseline lipid values.
- Offer antiplatelet drugs to people with CKD for the secondary prevention of CVD. CKD is not a contra-indication to the use of low-dose aspirin, although there is an increased risk of minor bleeding in people with CKD given multiple antiplatelet drugs.
- There is insufficient evidence to recommend the routine use of drugs to lower uric acid in people with CKD who have asymptomatic hyperuricaemia.
- Offer bisphosphonates if indicated for the prevention and treatment of osteoporosis. When vitamin D supplementation is indicated in people with CKD offer cholecalciferol or ergocalciferol to people with stage 1, 2, 3A or 3B; 1-alpha-hydroxycholecalciferol (alfacalcidol) or 1,25-dihydroxycholecalciferol (calcitriol) should be offered to people with stage 4 or 5 CKD.

NICE CLINICAL GUIDELINE 76: *MEDICINES ADHERENCE* (JANUARY 2009)

Between a third and a half of medicines prescribed for long-term conditions (LTCs) are not used as recommended; this compromises patient care and represents an economic loss to society. Non-adherence usually results from a failure of the prescriber to fully agree the prescription with the patient on initiation and a failure to monitor and support the patient once the medicine has been dispensed. There are two types of non-adherence: (1) intentional (the patient actively decides not to follow treatment recommendations) and (2) unintentional (the patient wants to follow treatment recommendations but has practical problems).

The key NICE recommendations are as follows:

- All patients should be offered the opportunity to be involved in making decisions about their prescribed medicines.
- Consider the best way of making information understandable and accessible to the patient (e.g. pictures, symbols, large print, different languages etc). Physical or learning difficulties, sight or hearing problems, difficulties with reading or speaking English can all create barriers to communication in the consultation.
- Encourage patients to ask about their condition and treatment. Clearly explain the disease or condition and how the proposed medicine will help. Openly discuss the pros and cons of proposed treatments. Clarify what the patient hopes the treatment will achieve.
- Increasing patient involvement may mean that the patient decides not to take or stop taking a medicine. If, in the healthcare professional's view, this could have an adverse effect, the information provided to the patient on risks and benefits and the patient's decision should be recorded.
- Accept that the patient has the right to decide not to take a medicine, even if you do not agree with the decision, as long as the patient has the capacity to make an informed decision and has been provided with the information needed to make such a decision.
- Recognise that non-adherence is common and that most patients are non-adherent sometimes. Adherence should be routinely assessed as part of prescribing, dispensing and review of medicines. Consider using records of prescription re-ordering, pharmacy patient medication records and return of unused medicines to identify potential non-adherence and patients needing additional support.
- Review the patient's knowledge, understanding and concerns about their medicines at each review, especially in those receiving multiple medicines for long-term conditions.
- Encourage patients, families and carers to keep an up-to-date list of all medicines the patient is currently taking including names and dosages of both prescription and non-prescription medicines, herbal and nutritional supplements.
- Patients may have concerns about or wish to discuss: (1) adverse effects; (2) risk of dependence; (3) what will happen if they do not take their medicine as prescribed; (4) availability of non-pharmacological alternatives; (5) how to reduce or stop one of their current medications; (6) how to fit their medicines into their daily routine; (7) how to make a choice between medicines if they believe they are taking too many etc.
- Patients may wish to minimise the number of medicines they take.
- Patients should be offered information about a medicine before it is prescribed. Do not assume that the patient information leaflet provided with

each dispensed medicine will meet the needs of all patients. Address any concerns patients may have after reading the PIL provided.

- Inpatients should be provided with the same information as patients initiated on a new medicine within another setting.
- Typically information provided to patients should include: (1) what the medicine is; (2) how the medicine is likely to benefit their condition; (3) details of side effects and what to do if they occur; (4) how to take the medicine; (5) what to do if a dose is missed; (6) whether treatment will be short-term or ongoing; (7) how to get a further supply etc.
- If a patient is not taking their medicines, determine whether this is intentional (due to beliefs or concerns about their medicines) or unintentional (due to practical problems).
- Interventions to improve adherence include: suggesting that the patient records their medicine taking and monitors their condition; simplifying the dosage regimen; using a multi-compartment medicines system. If side effects are a problem consider adjusting the dose or switching to another medicine. If prescription charges are a problem consider alternative options to reduce costs (e.g. pre-payment certificate).
- Healthcare professionals involved in prescribing, dispensing or reviewing medicines should ensure that there are robust processes for communicating with other healthcare professionals involved in the patient's care.
- On transfer between services (e.g. between hospitals and care homes or on discharge form hospital) patients and healthcare providers should receive a written report including: (1) the patient's diagnosis; (2) a list of medicines the patient should be taking; (3) identification of new medicines started; (4) identification of any medicines that were stopped and why; (5) information on which medicines should be continued after transfer from that service and for how long; (6) any known adverse reactions or allergies; (7) any potential difficulties with adherence and any actions taken (e.g. multi-compartment medicines system).

PACEF Recommendations:

Where this is not happening at present, prescribers are encouraged to review medicines adherence as part of regular medication review; dispensing practices should incorporate adherence review into dispensary review of medicines (DRUMs). Community pharmacists are encouraged to build adherence review into their Medicines Use Reviews (MURs); an updated and expanded MUR pack is in development and will be circulated later in the year. Some work will be undertaken at the interface between primary and secondary care to ensure that discharge information provided on transfer between services includes all of the details specified above. The results of a recent waste audit published in *PACE Bulletin* Vol 2, No 7 (May 2008) provide a valuable insight into typical patterns of pharmaceutical waste and links to poor adherence.

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY (MHRA) SAFETY UPDATE: MARCH 2009

Methylphenidate – updated guidance on safe and effective use in ADHD

Methylphenidate is licensed for the treatment of attention-deficit/ hyperactivity disorder (ADHD) under specialist supervision and is also used unlicensed for the treatment of narcolepsy. NICE CG 72 on Attention Deficit Hyperactivity Disorder recommends that methylphenidate should be considered as one of the first line drug

treatments in school age children and young people with severe ADHD and severe impairment. The European Medicines Agency (EMEA) has completed a review of the benefits and risks of methylphenidate after recent concerns about its cardiovascular, cerebrovascular and psychiatric safety and has issued the following advice:

Contraindications

Methylphenidate should not be used in patients with:

- A diagnosis or history of mental illness, including depressive and psychotic disorders.
- A diagnosis or history of severe and episodic bipolar disorder that is not well controlled.
- A pre-existing cerebrovascular disorder (e.g. cerebral aneurysm). Advice needs to be obtained from cardiac specialists before use in individuals with pre-existing cardiovascular disorders such as severe hypotension, heart failure or congenital heart disease.

A full list of contraindications appears in *Drug Safety Update*, Vol 2, No 8 (March 2009).

Pre-treatment screening

Before prescribing the following checks should take place:

- Assessment of patient's cardiovascular status including blood pressure and heart rate.
- A complete medical history should be obtained including details of past and current medication, psychiatric disorders, family history of sudden cardiac death or unexplained death and accurate pre-treatment height and weight on a growth chart.
- Patients should receive further specialist cardiac evaluation if medical history suggests a risk or presence of cardiac disease.

Ongoing monitoring

- Blood pressure and pulse should be recorded on a centile chart at every dose adjustment and at least every six months.
- Height, weight and appetite should be recorded at least every 6 months on a growth chart.
- Methylphenidate can cause or worsen some psychiatric disorders such as depression, suicidal thoughts, hostility, anxiety, agitation, psychosis and mania. Development of new or worsening of pre-existing symptoms should be monitored at every dose adjustment and then at least every 6 months, and at every visit.
- Prescribers should look out for signs of misuse or abuse of medication including patients supplying medication to others for whom it has not been prescribed.
- Patients who develop symptoms such as palpitations, chest pain on exertion, unexplained syncope, dyspnoea or other symptoms suggestive of heart disease during methylphenidate treatment should undergo prompt specialist evaluation.

PACEF Recommendation:

The Shared Care Guideline for the treatment of ADHD with methylphenidate and other drugs is currently under review; the new version will incorporate MHRA recommendations and will be available later in the year.

Atomoxetine –risk of psychotic or manic symptoms

Atomoxetine is a selective noradrenaline reuptake inhibitor licensed for the treatment of ADHD. The MHRA have continued to receive reports of possible nervous system and psychiatric adverse effects and have recommended that product information is updated to reflect these reports. They have issued the following advice to healthcare professionals:

- At normal doses atomoxetine can be associated with treatment- emergent psychotic or manic symptoms (e.g. hallucinations, delusional thinking, mania or agitation in children and adolescents without a history of psychotic illness or mania).
- If such symptoms occur during atomoxetine treatment, there may be a causal link and consideration should be given to discontinuation of treatment.
- It remains possible that atomoxetine might exacerbate pre-existing psychotic or manic symptoms.

PACEF Recommendation:
Atomoxetine will also be considered as part of the ongoing review of ADHD shared care.

Antipsychotics: use in elderly people with dementia

There is a clear risk of stroke and a small increased risk of death when antipsychotics (typical or atypical) are used in elderly people with dementia. Risperidone is the only antipsychotic licensed for the treatment of dementia related behavioural disturbances; it is licensed for short-term use (up to 6 weeks) in the treatment of persistent aggression in Alzheimer's dementia. For this new indication, risperidone has been given 'black triangle' status. Healthcare professionals are asked to report via the yellow card system all suspected side effects to risperidone that occur when it is used to treat elderly people with dementia. A careful assessment of risks and benefits is recommended. Prescribers should consider the risk of a cerebrovascular event in patients with a previous history of stroke or transient ischaemic attack or in those with risk factors for cerebrovascular disease including hypertension, diabetes, smoking or AF.

Exenatide (Byetta): risk of acute pancreatitis

Concerns around the association of pancreatitis and exenatide were first raised in the May 2008 edition of the *Drug Safety Update* and reported in *PACE Bulletin* Vol 2 No 10. In the UK up to February 2009, a total of 6 reports of pancreatitis and three of acute pancreatitis had been received by the MHRA: world wide there have been 396 reported cases, including 9 reports of necrotising or haemorrhagic pancreatitis, two of which were fatal. Reports of renal impairment including renal failure have also been received.

MHRA advice to healthcare professionals is as follows:

- There have been reports of necrotising and haemorrhagic pancreatitis with exenatide, some of which were fatal.
- If pancreatitis is suspected, treatment with exenatide should be suspended immediately; if pancreatitis is diagnosed, exenatide should be permanently discontinued.
- Diagnosed pancreatitis with an unexpectedly prolonged course, haemodynamic instability, fever, failure of medical therapy, or presence of fluid collections on CT suggest possible necrosis.

- Exenatide is not recommended for use in patients with end-stage renal disease or severe renal impairment (creatinine clearance <30ml/min)

PACEF Recommendation:
Prescribers are reminded that exenatide should only be used within NICE recommendations. It is an option at Step Three of the treatment of type 2 diabetes mellitus in patients with a BMI >35kg/m^2 and specific psychological, biochemical or physical problems arising from high body weight and inadequate blood glucose control ($HbA_{1c} \geq 7.5\%$) with conventional oral agents after a trial of metformin and sulfonylurea and where high cost medication would otherwise be started, such as a glitazone or insulin. Treatment should be continued only if a beneficial response occurs and is maintained. This is defined as at least a 1.0 percentage point reduction in HbA_{1c} in 6 months and weight loss in excess of 5% at 1 year. Exenatide is currently designated GREEN, but remains under review.

Bisphosphonates: atypical stress fractures

Recent reports received by the MHRA suggest that long term use of alendronic acid may be associated with an increased risk of atypical stress fractures (also known as insufficiency fractures) of the proximal femoral shaft. Following a European wide review of bisphosphonates, the MHRA has issued the following advice to healthcare professionals:

- Atypical stress fractures have been reported in patients treated long-term with alendronic acid; the time of onset is between 18months and 10 years.
- Fractures occur after minimal or no trauma and some patients experience thigh pain for weeks or months before diagnosis of a fracture. Fractures are frequently bilateral; the contralateral femur should be examined for all patients presenting with a femoral shaft fracture. These fractures are also associated with poor healing rates.
- Alendronic acid should be discontinued in all patients presenting with atypical stress fractures; affected patients should receive no further treatment with bisphosphonates unless benefits of treatment outweigh risks.
- The product information for alendronic acid is to be updated to include a warning on atypical stress fractures.
- There is limited data for other bisphosphonates, but there is a possibility that other agents may be associated with similar risks. The risk of atypical stress fractures with all bisphosphonates will be kept under close review and further information will be issued when available.

PACEF Recommendation:
Recently published NICE TAs on the primary and secondary prevention of osteoporotic fragility fractures in postmenopausal osteoporosis recommend generic weekly alendronic acid 70mg first line. Prescribers are advised to continue to prescribe generic alendronate as advocated by NICE. PACEF will keep this under review as more information emerges.

NATIONAL PATIENT SAFETY AGENCY (NPSA) RAPID RESPONSE REPORT – REDUCING RISK OF HARM FROM ORAL BOWEL CLEANSING SOLUTIONS (RRR012) (FEBRUARY 2009)

Death and harm from electrolyte abnormalities, dehydration and serious gastro-intestinal problems have been reported following the inappropriate use of oral bowel cleansing preparations prior to surgery and /or investigative procedures.

Patient groups identified as particularly at risk are frail and debilitated elderly patients, children and those contraindicated from receiving these treatments.

The NPSA recommend that:

- A clinical assessment is undertaken by the clinician authorising the surgery or investigative procedure (including GPs using the direct access route) to ensure that there is no contraindication (e.g. diverticulitis) or risk (e.g. concurrent medication such as diuretics) from the use of a bowel cleansing solution.
- Use of a bowel cleansing solution is authorised by the clinician at the same time as the surgery or investigative procedure. (This may be done by using the same form).
- A clinician requesting the surgery or procedure and authorising the use of a bowel cleansing solution is responsible for ensuring that an explanation on the safe use of the product is provided to the patient or carer.
- A safe system exists that involves an authorised clinical professional in the supply of the medicine and written information (including named contact) for each patient.

PACEF Recommendation:
Whilst the majority of incidents reported to the NPSA occurred within secondary care (94%), there is some prescribing of oral bowel cleansing solutions in Lincolnshire primary care, particularly sodium picosulfate (Picolax). All prescribers of oral bowel cleansing solutions are urged to undertake the clinical assessment as advocated by the NPSA to minimize this risk.

Acknowlegements

Many thanks to Cathy Johnson, Interface Lead Pharmacist and Gill Kaylor, Prescribing Adviser for their contributions to this edition of the *PACE Bulletin*.

Stephen Gibson,
Head of Prescribing and Medicines Management,
NHS Lincolnshire

steve.gibson@lpct.nhs.uk