

## NEWSLETTER

Supporting the Derbyshire Health Community

Volume 5: Issue 9

December 2006



*Merry Christmas to all our readers*

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### PACEF update

The current Traffic Lights list can be accessed via the PACEF intranet site  
[www.nodyis.nhs.uk/guidelines/pacef%20web.htm](http://www.nodyis.nhs.uk/guidelines/pacef%20web.htm).

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

<u>Drug</u>	<u>Date considered</u>	<u>Decision</u>
Varenicline	December 2006	BROWN
Dexibuprofen	November 2006	BROWN
Valganciclovir	November 2006	RED
Efalizumab	September 2006	RED
Rituximab	September 2006	RED
Clenil Modulite (beclometasone cfc-free MDI)	August 2006	GREEN Prescribe by brand name
Celluvisc eye drops	August 2006	GREEN
Natalizumab	August 2006	RED
Rimonabant	August 2006	BROWN

### Varenicline

Varenicline is an oral selective partial agonist of nicotinic receptors that is designed to block the rewards from, and reduce the craving for, cigarette smoking. It is now licensed as an aid to smoking cessation in adults.

Varenicline produces better quit rates than placebo. It has also been compared with bupropion and may have some advantage over bupropion but this was not consistently shown in all studies. Unfortunately, there are, as yet, no published data comparing varenicline with NRT. Varenicline is more expensive than NRT and bupropion. The trials involved intensive in-person and telephone counselling, which may not be available in the real world and quit rates in practice may therefore be lower.

Varenicline has been discussed at PACEF and the absence of a comparison with NRT makes it difficult to assess its place in therapy. For the time being, PACEF has classified varenicline as a BROWN drug. When the trial against NRT is published we will appraise this and reconsider the decision.

### **Choice of bisphosphonates**

Now that alendronate is available generically there is a big difference in the costs and a clear winner in the choice of which bisphosphonate to use when one is indicated.

	<b>Cost for 28 days</b>
Alendronate 70mg weekly (generic)	£7.31
Alendronate 10mg daily (generic)	£27.92
Fosamax Once Weekly	£22.80
Risedronate 35mg weekly	£20.30
Risedronate 5mg daily	£19.10

Surprisingly there is a considerable amount of branded Fosamax Once Weekly prescribing. If all alendronate 10mg daily, Fosamax Once Weekly and risedronate prescriptions were changed to generic alendronate 70mg weekly this would release about £250,000 p.a. in north Derbyshire. This was discussed at PACEF and it was agreed that alendronate 70mg weekly is the recommended bisphosphonate and that serious consideration should be given to switching.

**Key point:** generic alendronate 70mg weekly is the recommended bisphosphonate when one is indicated.

We can prescribe a bisphosphonate but will patients take them? Recent research suggests that most women quickly stop taking bisphosphonates<sup>1</sup>. The authors evaluated a very large managed care database to determine the use patterns of women who were newly diagnosed with osteoporosis and had been started on a bisphosphonate. The average age was 64 years and 85% had been placed on a weekly dosing regimen.

Women quickly stopped taking the drug therapy, with only 50% of the women taking it after 3 months, and only 1 in 5 still taking the drug after one year. These results are similar to those seen in other studies.

As the 'POEM Bottom Line' for this study says "since this short duration is unlikely to provide them with meaningful benefit, the money spent on BMD testing and the rest of the diagnostic work-up and follow-up, along with the cost of the initial drug therapy, is essentially wasted on 4 out of 5 women diagnosed with osteoporosis".

1. S Med J 2006; 99:570-5

### **Cognitive therapy superior to zopiclone for insomnia**

Cognitive behavioural therapy (CBT), consisting of one 50-minute session per week for 6 weeks, has been shown to be significantly more effective than zopiclone in the treatment of chronic insomnia in older adults<sup>1</sup>.

The investigators identified 46 adults with a mean age 61 years who met DSM-IV criteria for chronic insomnia. Eligible patients were randomised (concealed allocation assignment) to 1 of 3 treatment groups: (1) CBT, including an individual 50-minute treatment session once a week for 6 weeks, focusing on sleep hygiene education, sleep restriction, stimulus control, cognitive therapy, and progressive relaxation techniques; (2) zopiclone therapy, 7.5 mg nightly; or (3) placebo. Individuals assessing outcomes were blinded to treatment group assignment. Follow-up occurred for 98% and 83% of subjects at 6 weeks and 6 months, respectively.

Using intention-to-treat analysis, total wake time while attempting to sleep was significantly reduced in the CBT group (52%) at 6 weeks compared with 4% and 16% in the zopiclone and placebo groups. At 6 months, total wake time, sleep efficiency, and slow-wave sleep were all significantly better in the CBT group than in the other 2 groups. The percentage of patients who reached a predetermined clinically significant level of sleep efficiency of at least 85% at 6 months was significantly higher in the CBT group than in the zopiclone group (78% vs 40%; NNT = 2.5; 95% CI, 1.5-14). Self-adherence to treatment remained similar in both the CBT and zopiclone group, but was significantly lower in the placebo group. Daytime sleepiness was not specifically assessed.

1. JAMA 2006; 295:2851-58

## Sedative hypnotics in older people

Hypnotics are much less often prescribed today than they were a few years ago. This is because more is now known about their risks and benefits.

Many people say they have problems with “poor sleep” but most often they are actually getting enough, but perhaps not at the right times. As we get older our bodies need less rest and may only need a few hours sleep a night. Any sleep taken during the day, like an afternoon nap, reduces what the body needs at night. For example, someone needing 5 hours sleep, that takes a 2-hour nap after lunch, will only sleep 3 hours at night. If they go to bed at 11pm, they will be awake again at 2am. This is often quite normal and not “poor sleep”.

Another common explanation for sleep problems is caffeine. People who drink caffeine past about 6pm may well find it disrupts their sleep, either by keeping them awake, or because it makes them need to urinate in the night. Pain is another common reason why people wake up in the night.

Having realistic expectations of how much sleep your body needs is important. Reducing caffeine intake, particularly in the evenings, may also solve any problems. If pain is the problem, using a suitable painkiller should help.

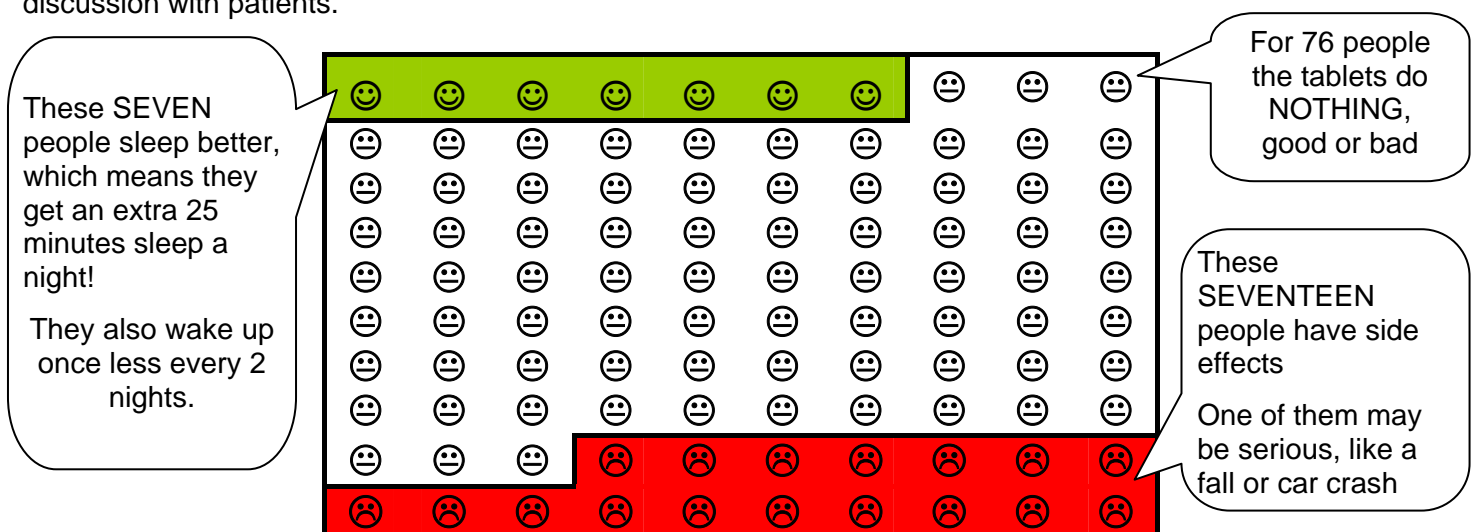
Despite this some people still have sleep problems and often ask for sleeping tablets to help. A meta-analysis gives us a pretty clear picture of the risk and benefits of hypnotics in older people<sup>1</sup>.

Twenty-four RCTs of pharmacological treatment (benzodiazepines and Z-drugs) for insomnia for at least 5 consecutive nights in people aged 60 or over with insomnia and otherwise free of psychiatric or psychological disorders were included. Total sleep time increased (mean 25.2 minutes,  $p < 0.001$ ), and the number of nighttime awakenings decreased (0.63,  $p < 0.001$ ) with hypnotic use compared with placebo. However adverse events were more common with hypnotics than with placebo. Adverse cognitive events were 4.78 times more common ( $p < 0.01$ ), adverse psychomotor events were 2.61 times more common ( $p > 0.05$ ), and reports of daytime fatigue were 3.82 times more common ( $p < 0.001$ ).

The NNT for improved sleep quality was 13 and the NNH for any adverse event was 6. This ratio indicates that an adverse event is twice as likely as enhanced quality of sleep.

The authors conclude that improvements in sleep are statistically significant, but the magnitude of effect is small. The increased risk of adverse events is statistically significant and potentially clinically relevant in older people at risk of falls and cognitive impairment. In people over 60, the benefits of these drugs may not justify the increased risk, particularly if the patient has additional risk factors for cognitive or psychomotor adverse events.

One of my NPC colleagues, Magnus Hird, has presented the results of this study as a visual aid to facilitate discussion with patients.



1. BMJ 2005; 331:1169-73

**Bronchiolitis in children**

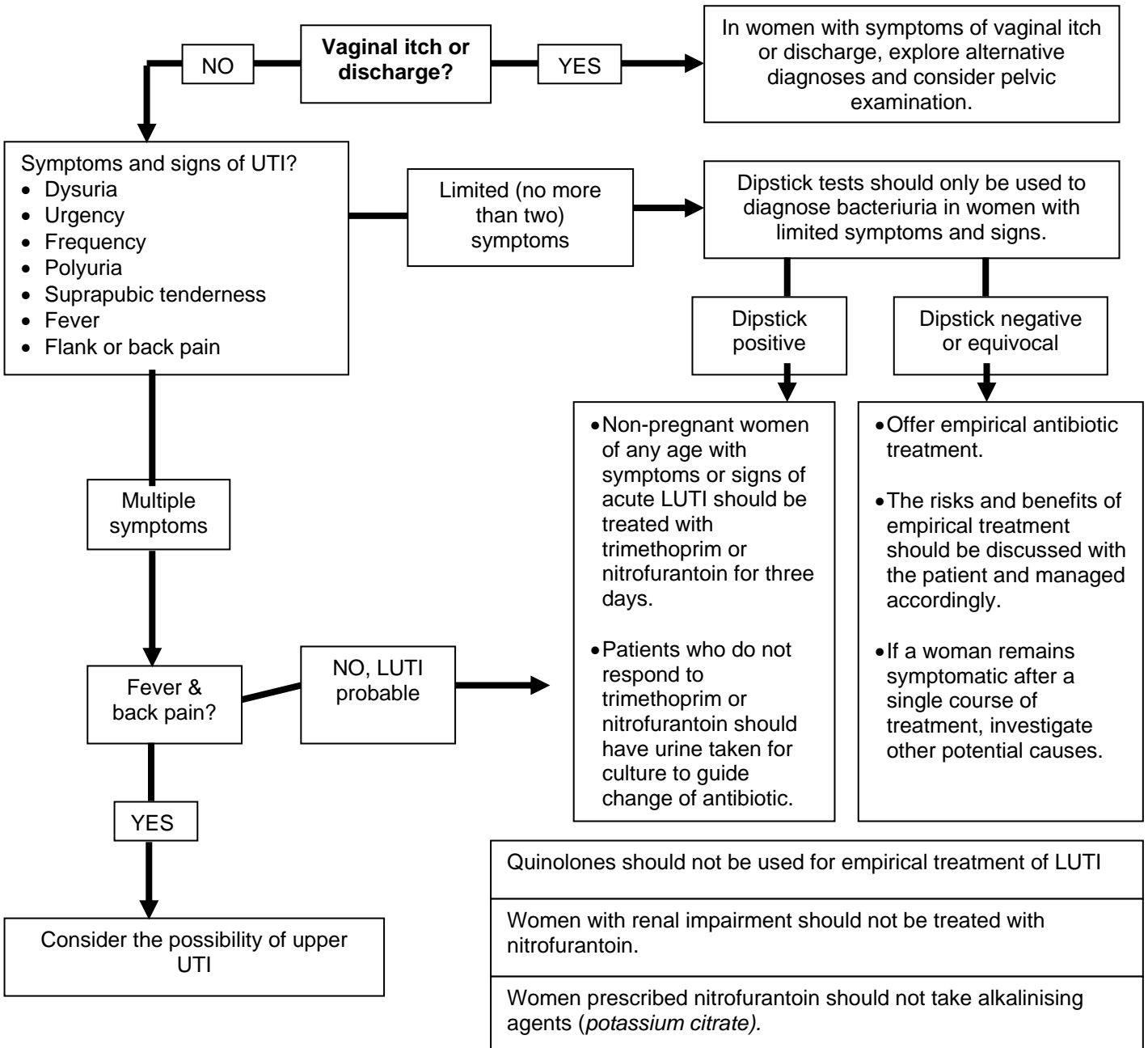
SIGN have produced a guideline for managing bronchiolitis in children (available at [www.sign.ac.uk](http://www.sign.ac.uk)). It says that the following treatments are **not** recommended for infants with acute bronchiolitis:

- Nebulised ribavirin
- Antibiotic therapy
- Inhaled beta 2 agonist bronchodilators
- Nebulised ipratropium
- Nebulised epinephrine [adrenaline]
- Inhaled corticosteroids
- Oral systemic corticosteroids
- Chest physiotherapy using vibration and percussion

They found insufficient evidence on which to base a recommendation for montelukast. No studies were identified on the effectiveness of steam, nasal decongestion, homeopathic remedies or any complementary therapies.

**Management of suspected UTI**

SIGN have also produced a guideline on the management of suspected bacterial UTI in adults. This is their algorithm for the management of suspected lower UTI in non-pregnant women:



### **Antibiotics for acute otitis media**

Evidence from systematic reviews suggests that antibiotics provide only marginal benefit in AOM, at the expense of adverse drug reactions. Prescribing antibiotics is known to encourage clinic visits for subsequent episodes, intensify pressure on clinicians to prescribe, and promote antibiotic resistance. As AOM resolves spontaneously in most children, these factors have resulted in guidelines recommending not prescribing antibiotics on the first visit but to treat the child with adequate pain relief and start watchful waiting and consider a delayed prescription.

A recent meta-analysis of individual patient data from RCTs of the effects of antibiotics in children aged from 6 months to 12 years with AOM aimed to identify subgroups who would and would not benefit more than others from treatment with antibiotics<sup>1</sup>. The primary outcome was defined as an extended course of AOM, consisting of pain, fever, or both at 3-7 days.

Children with otorrhoea (discharge from the ear) seemed to benefit most from treatment with antibiotics, irrespective of other characteristics. The NNT was 3. The effects of antibiotic treatment were not significantly modified by age or bilateral disease alone, but in children younger than 2 years of age with bilateral AOM there was significant benefit with a NNT of 4.

The authors concluded that antibiotics seem to be most beneficial in children younger than 2 years of age with bilateral AOM, and in children with both AOM and otorrhoea. They recommend that for most other children with mild disease an observational policy seems justified.

1. Lancet 2006; 368:1429-35

### **Management strategies for acute infective conjunctivitis**

Evidence is lacking on the effectiveness of prescribing topical antibiotics for conjunctivitis in primary care. A Cochrane review showed a marginal benefit from such treatment<sup>1</sup>. A recent study compared three strategies for acute infective conjunctivitis in general practice<sup>2</sup>.

The investigators enrolled 307 adults and children (aged 1 year or more) seen in 30 general practices in southern England who presented with uncomplicated acute infective conjunctivitis. The patients were randomly assigned, using concealed allocation, to receive immediate antibiotic treatment with chloramphenicol eye drops, delayed antibiotic treatment (prescription to be collected after 3 days), or no treatment (control group). Antibiotics were used by 99% of the immediate group, 53% of the delayed group, and 30% of the control group.

Prescribing strategies did not affect the severity of symptoms but duration of moderate symptoms was less with antibiotics: no antibiotics 4.8 days; immediate antibiotics 3.3 days, delayed antibiotics 3.9 days. By day 8 there was no significant difference between the groups. The immediate antibiotic group were more likely than controls to believe that antibiotics were effective (OR 2.4, NNT 5) and more likely to state their intention to reattend for eye infections (OR 3.2, NNT 4). The delayed antibiotic group was not significantly different from the controls for these outcomes. About half the patients were cultured for the presence of bacteria and significant bacterial growth was found in 50%. However, no significant difference was found in outcome measures between those with and without bacterial growth.

The authors concluded that delayed prescribing of antibiotics is probably the most appropriate strategy for managing acute conjunctivitis in primary care. It reduces antibiotic use, shows no evidence of medicalisation, provides similar duration and severity of symptoms to immediate prescribing, and reduces reattendance for eye infections.

1. BJGP 2005; 55:962-4
2. BMJ 2006; 333:321-4

### **Thiazides and raised blood glucose levels**

In the PACE newsletter of March 2006, I discussed whether raised blood glucose levels that can occur with thiazides are of any significance. At the time there was no evidence to suggest that thiazide-induced increases in blood glucose had any adverse outcome. The BHS/NICE update hypertension guideline acknowledged this – “it is not clear that an elevated blood glucose developing as a consequence of drug

treatment has the same long-term health impact as in other circumstances”. Indeed, evidence is mounting that thiazide-induced diabetes may be completely benign.

A recently reported analysis of data from the ALLHAT study compared the effect of first-line thiazide, CCB or ACEI on fasting glucose (FG) levels and determined the cardiovascular and renal disease risks associated with elevated FG levels and incident diabetes mellitus (DM)<sup>1</sup>. Mean FG levels increased during follow-up in all three treatment groups but was greatest with chlortalidone. At year 2 the increase was 0.47 mmol/L for chlortalidone, 0.31 mmol/L for amlodipine, and 0.19 mmol/L for lisinopril. Overall the risk of FG level ever being higher than 6.9 mmol/L was 2.9% higher for chlortalidone than amlodipine and 4.5% higher than lisinopril. However, there was no significant association of FG level change with subsequent CHD, stroke, CV disease, total mortality, or end-stage renal disease.

The authors conclude that fasting glucose levels increase in older adults with hypertension regardless of treatment type. For those taking chlortalidone vs other medications, the risk of developing FG levels higher than 6.9 mmol/L is moderately greater, but there is no conclusive or consistent evidence that this diuretic – associated increase in DM risk increases the risk of clinical events. They comment that diuretics lead to elevated glucose levels by mechanisms different from those associated with DM.

The accompanying editorial agrees that thiazide-induced DM is a different and benign disease entity compared with either de novo DM or that which develops in the context of other antihypertensives<sup>2</sup>. It concludes “viewed through the humbling and wide-angle lens of outcome research, thiazides become the cornerstone on which blood pressure-lowering treatment should be built”.

1. Arch Intern Med 2006; 166:2191-2201

2. Arch Intern Med 2006; 166:2174-6

### **The newborn and 6-8 week infant physical examination**

The UK National Screening Committee has launched the NIPE toolbox: a web-based searchable database for everyone involved in the physical examination of the newborn and 6-8 week infants. This is the first time information about CDs, websites, journal articles, books, and simulators has been brought together. The toolbox contains information on the four main screening components of the physical examination: hearts, eyes, hips, testes, and the overall physical examination together with materials that address general professional and policy related issues.

The toolbox can be navigated by searching each aspect of the examination and there is a ‘Search’ facility to enter the name of an author, title or specific topic and go straight to the most relevant items. The information about resources in the toolbox can be printed and the user can select specific resources to create, store or generate their personal reference list.

To access the digital toolbox go to: [www.nipetoolbox.screening.nhs.uk](http://www.nipetoolbox.screening.nhs.uk)

### **Prescribing of modified-release morphine preparations and fentanyl patches**

The Royal Pharmaceutical Society of Great Britain’s Practice Committee has issued a statement that it **does not recommend** routine brand name prescribing of modified-release morphine preparations and fentanyl patches. The Practice Committee agreed some good practice points:

- Pharmacist should take steps to prevent unintentional changes of the brand supplied to patients. If the brand of strong modified-release morphine preparations needs to be changed then the pharmacist should ensure that the patient and the patient’s carers understand and accept the need for change.
- Pharmacists should adhere to local prescribing policies on the use of long-acting modified-release morphine preparations.
- There are important differences between matrix patches and reservoir patches. Reservoir patches of fentanyl should **never** be cut to deliver a smaller dose because this disrupts the controlled-release mechanism. The practice of cutting fentanyl matrix patches falls outside the product licence and pharmacists should be aware that the summary of product characteristics for a brand of matrix patch states, “Durogesic DTrans patches should not be cut. No data are available on cut or divided patches”.

### **More on eGFR and CKD**

A recently published study from Norway compared strategies for detecting patients with CKD and examined the occurrence of end stage renal disease or CV death in these patients over 8 years<sup>1</sup>. 65,604 people (70.6% of all adults aged  $\geq 20$  in the county) were involved in the study.

The prevalence of CKD stage 3-5 (eGFR  $<60$ ) was 4.7%. This means that we would need to screen 20.6 people to identify one case of CKD. Restriction of screening to those with hypertension, diabetes, or age  $>55$  would identify 93.2% of patients with CKD, with a number needed to screen of 8.7.

During the 8-year follow-up only 38 of the 3069 people with CKD (1.24%) progressed to end stage renal disease, and the risk was especially low in people without diabetes or hypertension, women, and those aged  $\geq 70$  or with a eGFR of 45-59 at screening. In contrast, there was a high CV mortality: 3.5, 7.4, and 10.1 deaths per 100 person years among people with an eGFR of 45-59, 30-44, and  $<30$ , respectively. In those with an eGFR  $<30$  the incidence of end stage renal disease was 2.6 compared with CV mortality of 10.1 per 100 person years.

The authors comment that comprehensive cost-effectiveness studies are needed to show whether screening is justified or not and the optimal screening interval also remains to be found. They note that reliance on one creatinine measurement might lead to misclassification.

The accompanying editorial<sup>2</sup> comments that the purpose of screening is to identify people who should be treated differently and identifying people with a low GFR may lead to harm from labeling. It adds that many people in the community (especially elderly people) with low GFR have disease that does not progress, which further limits the potential benefit of screening. The author recommends that case finding should continue in patients who have risks for or evidence of kidney disease, who are taking drugs that affect kidney function, or whose comorbidities make knowledge of kidney function important.

A letter in the BMJ points out that in the data from the modification of diet in renal disease study that were used to generate the eGFR equations, samples were taken from predominantly fasting subjects<sup>3</sup>. In clinical practice, however, samples for serum creatine concentration and eGFR are generally used in situations where the patient's recent dietary intake is not considered.

The authors investigated the impact of meals on creatine concentration and eGFR by having blood samples taken before and after normal helpings of meat-containing meals supplied by the hospital canteen. Median eGFR fell from 84.0 preprandially to 59.5 1-2 hours after eating ( $p<0.0001$ ) and 64.0 3-4 hours after eating ( $p<0.0001$ ). This led to apparent changes in staging of CKD. They conclude that the risk of misdiagnosis or incorrect staging of CKD is high after a meal containing cooked meat. They recommend that serum creatine measurement should be carried out when a patient has fasted or specifically avoided a cooked meat meal on the day of blood sampling.

1. BMJ 2006; 333:1047-50
2. BMJ 2006; 333:1030-31
3. BMJ 2006; 333:1072

### **More on HPV vaccines**

Further to the advice in last month's newsletter, we have received a letter from Sir Muir Gray, Programme Director of the UK National Screening Committee, advising against the use of HPV vaccine at the present time. He says "The situation is that DH, HPA, and NHS Cancer Screening Programmes are working together on this issue. No policy decision has been made, and there is much work to be done before we are able to make any recommendations."

He adds that as no advice has yet been issued on the appropriate use of HPV vaccine, they strongly advise health staff not to be drawn into discussions with vaccine manufacturers' sales and marketing staff. If you have queries about this issue they should be directed to Sue Cohen, Consultant in Public Health, here at Scarsdale.

**Key point:** PACEF strongly advises that there should be no prescribing of HPV vaccine, on the NHS or privately, until we have a national directive.

## **Management of urinary incontinence in women**

NICE has issued clinical guideline no. 40 on urinary incontinence. These are some of the key points. The full guideline is available at [www.nice.org.uk/page.aspx?o=CG40](http://www.nice.org.uk/page.aspx?o=CG40)

### ***Assessment and investigation***

- At the initial clinical assessment, the woman's urinary incontinence (UI) should be categorised as stress UI, mixed UI, or urge UI/overactive bladder syndrome (OAB). Initial treatment should be started on this basis. In mixed UI, treatment should be directed towards the predominant symptom.
- Bladder diaries should be used in the initial assessment of women with UI or OAB. Women should be encouraged to complete a minimum of 3 days of the diary covering variations in their usual activities, such as both working and leisure days.

### ***Conservative management***

- A trial of supervised pelvic floor muscle training of at least 3 months' duration should be offered as first-line treatment in women with stress or mixed UI.
- Bladder training lasting for a minimum of 6 weeks should be offered as first-line treatment to women with urge or mixed UI.
- Pelvic floor muscle training should be offered to women in their first pregnancy as a preventive strategy for UI.

### ***Drug therapy***

- There is no evidence of a clinically important difference in efficacy between antimuscarinic drugs. However, immediate-release non-proprietary oxybutynin is the most cost effective of the available options.
- Immediate-release non-proprietary oxybutynin should be offered to women with OAB or mixed UI as first-line drug treatment if bladder training has been ineffective. If immediate release oxybutynin is not well tolerated one of the other antimuscarinic options should be considered as alternatives. Women should be counselled about the adverse effects of antimuscarinic drugs.
- Propiverine should be considered as an option to treat frequency of urination in women with OAB, but is not recommended for the treatment of UI.
- Flavoxate, propantheline and imipramine should not be used for the treatment of UI or OAB in women.
- Duloxetine is not recommended as a first-line treatment for women with predominant stress UI. It should not routinely be used as a second-line treatment for women with stress UI, although it may be offered as second-line therapy if women prefer pharmacological to surgical treatment or are not suitable for surgical treatment. If duloxetine is prescribed, women should be counseled about its adverse effects.

The most frequently prescribed antimuscarinic in north Derbyshire is tolterodine but this is one of the most expensive options. This has been discussed at PACEF and it was agreed that immediate-release non-proprietary oxybutynin 2.5-5mg tds is the first-line antimuscarinic. Second line is modified-release oxybutynin 5-10mg daily, third-line is trospium 20mg bd, and fourth-line (if one is needed) is darifenacin 7.5-15mg daily.

## **Miracle hiccup cure**

If overindulgence this festive season leads to hiccups, what can you do to stop them? According to a letter in the BMJ<sup>1</sup> there are three surefire ways:

- Plugging both ears tightly, pushing both right and left tragus, and drinking an entire glass of water through a straw without pause, without releasing the pressure over the ears
- Digital rectal massage
- Intercourse to orgasm.

Mmmm, I wonder which would be my favourite?

Have a good one!

1. BMJ 2006; 333: 1222