

## NEWSLETTER

Supporting the North Derbyshire Health Community

Volume 5: Issue 6

September 2006

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### PACEF update

The current Traffic Lights list can be accessed via your PCT website ([www.chesterfieldpct.nhs.uk](http://www.chesterfieldpct.nhs.uk), [www.highpeakanddalespct.nhs.uk](http://www.highpeakanddalespct.nhs.uk), or [www.northeasternderbyshirepct.nhs.uk](http://www.northeasternderbyshirepct.nhs.uk)) or 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>
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
Desloratidine	July 2006	BROWN
Levocetirizine	July 2006	BROWN
Pegaptanib injection	July 2006	RED
Rotigotine patch	July 2006	BROWN
Zaleplon	July 2006	BROWN
Zolpidem	July 2006	BROWN
Zopiclone	July 2006	BROWN
Formoterol cfc-free MDI (Atimos Modulite)	June 2006	GREEN
Letrozole	June 2006	AMBER
Acamprosate	April 2006	AMBER (moved from RED)
Ivabradine	April 2006	BROWN
Nebivolol	April 2006	BROWN
Revatio (sildenafil 20mg tablet for PAH)	April 2006	RED
Inhaled insulin (Exubera)	April 2006	RED

### Early detection of COPD

Patients with COPD typically present late, often with respiratory tract infections that have not previously been linked with COPD or with breathlessness misdiagnosed as asthma. Studies suggest that, among cigarette smokers older than 40 years, about 20% of those without a respiratory diagnosis and at least a quarter of

those with a diagnosis of asthma actually have COPD<sup>1</sup>. By the time most have COPD diagnosed, at least 50% of their lung function will have been lost.

Thus, a priority in primary care should be earlier detection and correct diagnosis. The use of a simple questionnaire may allow easier detection of patients who need spirometry<sup>1</sup>.

### Simple questionnaire for evaluating risk of COPD

Patient characteristic	Value	Score*
Age (years)?	40-49	0
	50-59	4
	60-69	8
	≥70	10
Smoking pack years? (one "pack year" is 20 cigarettes smoked/day for one year)	0-14	0
	15-24	2
	25-49	3
	≥50	7
Body mass index?	<25.4	5
	25.4-29.7	1
	>29.7	0
Cough affected by weather?	Yes	3
	No or no cough	0
Sputum production in absence of a cold?	Yes	3
	No	0
Sputum production first thing in the morning?	Yes	0
	No	3
Wheezes?	Sometimes or often	4
	Never	0
Has or used to have any allergies?	Yes	0
	No	3

\*Total scores of ≥ 17 suggest increased risk of COPD being present

1. BMJ 2006; 333: 188-90

### Shared decision making about medicines

Further to the article in the July edition, on the subject of wasted medicines and avoidable adverse events, it has long been suggested that developing concordant relationships with patients could reduce wastage. However, there are barriers to developing concordance.

At this summer's National Prescribing Centre conference, one of the workshops was on the subject of improving concordance and particularly of involving patients in shared decision-making about medicines. Dr Wendy Clyne of the Medicines Partnership Programme at NPC Plus suggests the following types of dialogue are useful for involving patients in decision-making.

#### Exploring patient expectations

- 'What do you want to get out of our appointment today?'
- 'What would you like to see happen here?'

#### Determining a patient's preference for their role in decision-making

- 'In the past, I've always taken the lead here in deciding what to do – but we could try something different. How would you feel if we both talked through the various options together?'
- 'I'd like to talk to you about how we're going to decide what to do here. I could just tell you what I think is best, we could talk through the various options together or I could give you the information and you decide the best way forward on your own.'
- 'Some people like to just be told what to do by their doctor/pharmacist/nurse while others like to be a bit more involved in decisions. How do you feel?'

### **Eliciting patient concerns**

- 'Do you have any concerns about this medication?'
- 'Is there anything in particular that worries you?'
- 'Have you had any bad experiences with this kind of thing in the past?'
- 'Could you tell me a bit more about that?'
- 'How do you find having [this condition] generally?'
- 'Can you tell me what a typical day is like for you with [this condition]?'
- 'What is the biggest challenge you face with your [condition] and its treatment?'
- 'I guess it's a case of weighing up the good and bad about taking the medicine. How does it all weigh up for you?'

### **Giving patients information**

- 'Is there anything else you would like to know about?'
- 'Can I give you some more information about that?'
- 'Would you like to know more?'
- 'Would you like to know how most people get on when they take this medicine?'
- 'Do you have any questions?'

### **Exploring the practicalities of medicine taking**

- 'How easy do you find it to take your medicines?'
- 'How do you remember when to take your medicines?' [Does the patient have a system for remembering?]
- 'In the course of a normal day, are you able to work in taking your medicines?'
- 'Who can help you with this?'

### **Eliciting a decision about medicine-taking**

- 'Are you ready to make a decision about where you want to go from here?'
- 'What have you decided to do about this?'
- 'On the basis of our discussion today, what decision do you want to make now about your medicines?'
- 'Where does this leave you?'

### **New studies of raloxifene**

#### **The RUTH trial (N Engl J Med 2006; 355:125-37)**

##### *Participants*

10,101 postmenopausal women (mean age 67.5 years) with CHD or multiple risk factors for CHD.

##### *Intervention*

Raloxifene 60mg or placebo daily for a median of 5.6 years.

Two primary endpoints: coronary events (CHD death, MI, or hospitalisation for ACS) and invasive breast cancer.

##### *Results*

- Raloxifene had no significant effect on the risk of primary coronary events; HR 0.95 (CI 0.84 to 1.07), p=0.40.
- Raloxifene reduced the risk of invasive breast cancer, primarily due to a reduced risk of oestrogen-receptor-positive invasive breast cancers; HR 0.56 (CI 0.38 to 0.83); p = 0.003 (NNT = 169).
- Raloxifene reduced the risk of clinical vertebral fractures; HR 0.65 (CI 0.47 to 0.89), p = 0.007 (NNT = 154).
- Raloxifene increased the risk of VTE; HR 1.44 (CI 1.06 to 1.95), p = 0.02 (NNH=156).
- Raloxifene was associated with an increased risk of fatal stroke; HR 1.49 (CI 1.00 to 2.24), p = 0.05 (NNH = 250).
- Raloxifene also significantly increased the risk of gallbladder disease (NNH = 91), hot flushes (NNH = 31), leg cramps (NNH = 33), and peripheral oedema (NNH = 43).

### Discussion

- Despite favourable changes in lipid levels, raloxifene did not significantly affect the risk of CHD.
- Raloxifene did reduce the risk of invasive breast cancer and vertebral fractures (but not non-vertebral fractures) but the NNTs are high. The lack of effect on non-vertebral fractures was also shown in the MORE study<sup>1</sup>.
- Raloxifene increased the risks of VTE and fatal stroke (this endpoint was just statistically significant) but the NNHs are high.
- The difference in the absolute rates of events that were decreased was similar to the difference in the absolute rates of events that were increased. As the accompanying editorial<sup>2</sup> says “for women represented by the RUTH cohort of women with or at increased risk of CHD, the moderate benefits of raloxifene for breast cancer prophylaxis do not seem to justify the risks”.

1. JAMA 1999; 282:637-45

2. N Engl J Med 2006; 355:190-2

### The STAR trial (JAMA 2006; 295:2727-41)

#### Participants

19,747 postmenopausal women of mean age 58.5 years with increased 5-year breast cancer risk (mean risk 4.03%).

#### Intervention

Oral tamoxifen 20mg/day or raloxifene 60mg/day over 5 years. The mean time of follow-up was 3.9 years and the mean duration of treatment was 3.1 and 3.2 years for tamoxifen and raloxifene respectively.

The main outcome measures were incidence of invasive breast cancer, non-invasive breast cancer, uterine cancer, bone fractures, and thromboembolic events.

#### Results

- There was no difference between the effect of tamoxifen and the effect of raloxifene on the incidence of invasive breast cancer; RR 1.02 (CI 0.82 to 1.28),  $p = 0.83$ .
- There were fewer non-invasive breast cancers in the tamoxifen group than in the raloxifene group, although this difference did not reach statistical significance; RR 1.40 (CI 0.98 to 2.00);  $p = 0.052$ .
- There was no significant difference in the rates for uterine cancer; RR 0.62 (CI 0.35 to 1.08),  $p = 0.07$ . Among those who did not have a diagnosis of uterine cancer, there was a significant difference in the incidence of uterine hyperplasia – raloxifene (14 cases) and tamoxifen (84 cases); RR 0.16 (CI 0.09 to 0.29). There also was a reduction in the number of hysterectomies performed during follow-up among women not diagnosed with endometrial cancer – raloxifene (111) and tamoxifen (244); RR 0.44 (CI 0.35 to 0.56).
- No differences were found for other invasive cancer sites, for ischaemic heart disease, for stroke, or for osteoporotic fractures.
- Thromboembolic events occurred less often in the raloxifene group; RR 0.70 (CI 0.54 to 0.91),  $p = 0.01$ . The NNH for tamoxifen is 238.
- Among those who were cataract-free at baseline, the incidence of cataracts and cataract surgery were statistically significantly less in the raloxifene group.
- In an accompanying paper looking at quality-of-life (QoL), no significant differences were found between the tamoxifen and raloxifene groups in patient-reported outcomes for physical health, mental health, and depression, although the tamoxifen group reported better sexual function<sup>1</sup>.

### Discussion

- There was no difference in the primary endpoint of invasive breast cancer rates for tamoxifen or raloxifene.
- Raloxifene was associated with slightly fewer thromboembolic events and fewer hysterectomies, cataracts, and cataract surgery. A lower rate of non-invasive breast cancer with tamoxifen did not quite reach statistical significance.
- The STAR symptom and QoL data showed a similarity between the two treatments in physical and mental health. The QoL and adverse effect burden would seem to be comparable<sup>2</sup>.

- Raloxifene is not currently licensed for breast cancer prevention. If it gains a licence will it be cost-effective? Tamoxifen 20mg/day costs £35.63 per year compared to £222.39 for raloxifene.

1. JAMA 2006; 295: 2742-51
2. JAMA 2006; 295: 2784-6

### **Anticholinergics or beta-agonists in COPD?**

NICE clinical guideline 12 on the management of COPD recommends the use of a short-acting bronchodilator (beta-agonist or anticholinergic) as first-line pharmacological therapy to manage symptoms. If a patient is still symptomatic after trying both types of short-acting bronchodilator together, then a long-acting bronchodilator (beta-agonist or anticholinergic) is recommended. NICE does not say which type of bronchodilator should be tried first, giving the impression that they are equivalent.

The objective of a recent meta-analysis was to compare the effects of beta-agonists and anticholinergics on exacerbations requiring withdrawal from the trial, severe exacerbations requiring hospitalisation, and respiratory deaths in patients with COPD<sup>1</sup>.

#### **Method**

- The authors searched MEDLINE, EMBASE, and Cochrane databases to identify RCTs on beta-agonist or anticholinergic use in patients with COPD, published between 1966 and December 2005. Trials were not excluded on the basis of language. The search was augmented by scanning relevant files from the FDA website and references of identified reviews.
- Trials were included if they were RCTs of beta-agonists or anticholinergics compared with placebo or each other, were of at least 3 months duration and reported at least one COPD exacerbation requiring withdrawal from the trial or hospitalisation, or any respiratory death.
- Two reviewers assessed the methodological quality of each trial according to randomisation procedure, allocation concealment, blinding, reporting of dropouts and withdrawals, and intention-to-treat analysis.
- COPD exacerbations were those that required withdrawal from the study or hospitalisation. Severe exacerbations were those requiring hospitalisation. A respiratory death was defined as a death thought to be due to a lower respiratory tract event. Attempts were made to contact the investigators to obtain additional information concerning exacerbations and death.
- Results are reported separately for placebo-controlled trials of anticholinergics and beta-agonists, and for trials comparing beta-agonists to anticholinergics.
- This meta-analysis was not sponsored by the pharmaceutical industry.

#### **Results**

- Of 88 potentially relevant trials, 22 met the inclusion criteria. This gave a total of 15,276 participants followed for 25,460 patient years. Mean trial duration was 20 months (range 3 to 60), with a mean study size of 694 participants (62 to 3,923). The mean (SD) age of participants at baseline was 59.9 (7.7) years in the anticholinergic group, 63.5 (1.0) in the beta-agonist group and 59.6 (7.4) in the placebo group. Concomitant corticosteroids were used in 58.3% of the anticholinergic group, 56.5% of the beta-agonist group and 57.4% of the placebo group.
- Seven trials compared inhaled anticholinergics with placebo (4 used tiotropium). Anticholinergics reduced the risk of a COPD exacerbation requesting withdrawal by 40%, RR 0.60 (CI 0.48 to 0.75) and a severe exacerbation requiring hospitalisation by 33%, RR 0.67 (CI 0.53 to 0.86). The absolute risk reduction for severe exacerbations was approximately 4 cases per 100 patient-years of treatment compared with placebo, with a NNT of 25.
- Five trials reported respiratory deaths, four of which used tiotropium. There were 2 reported deaths out of 4,036 participants in the anticholinergic group and 12 respiratory deaths out of 3,845 participants in the placebo group, with a reduction in risk of 73%, RR 0.27 (CI 0.09 to 0.81). The absolute risk reduction for respiratory deaths with anticholinergics was 0.36% per year (NNT of 278).
- There were 13 trials that compared beta-agonists use with placebo and all but one used a LABA. The risk of withdrawal from the trial for COPD exacerbation was reduced by 19%, RR 0.81 (CI 0.68 to 0.95), without any significant effect on hospitalisation, RR 1.08 (CI 0.61 to 1.95).
- Four trials reported respiratory deaths and all used LABAs. Beta-agonist use was associated with a significant increase in respiratory deaths, RR 2.47 (CI 1.12 to 5.45), compared with placebo. There were 21 deaths out of 1,320 participants in the beta agonist group (1.59%) and 8 deaths out of 1,084

participants in the placebo group (0.74%). This calculates as a crude NNT of 117. The authors added trials without respiratory deaths to the analysis, thus adding to the denominator, and calculated the absolute increase with beta-agonists to be 0.76% per year (NNH of 131).

- Seven trials directly compared beta-agonists with anticholinergics. Compared with anticholinergics, beta-agonists resulted in increased rates of exacerbations requiring withdrawal, RR 2.02 (CI 1.39 to 2.93) as well as severe exacerbations requiring hospitalisation, RR 1.95 (CI 1.06 to 3.59). Only 2 trials reported on respiratory deaths with a non-significant trend towards increased respiratory mortality with beta-agonist use, RR 6.91 (CI 0.85 to 55.97, p=0.07).
- Four trials compared anticholinergics alone to combination treatment. Use of anticholinergic alone was not associated with a significant difference in severe exacerbations, RR 0.83 (CI 0.25 to 3.83) or deaths, RR 0.35 (CI 0.04 to 3.3), compared with combination treatment.

### **Discussion/implications**

- The authors conclude that anticholinergics should be the bronchodilator of choice in patients with COPD.
- Compared with placebo, anticholinergics reduced severe exacerbations and respiratory deaths, whereas LABAs (as only one trial used a short-acting beta-agonist) did not reduce severe exacerbations and may even have worsened disease control, as there was a 2-fold increase in respiratory deaths.
- Although the number of deaths is small and no p-values are quoted, the confidence intervals for the RR are clear of 1, showing that it is a statistically significant difference.
- The addition of a LABA to an anticholinergic did not seem to improve clinical outcomes.
- The results of this meta-analysis, taken together with the Cochrane review<sup>2</sup> and the CCOHTA technology assessment<sup>3</sup>, suggest that **in COPD anticholinergics probably work better and are safer than LABAs, and should be tried first.**

1. J Gen Intern Med 2006; 21: online early doi:10.1111/j.1525-1497.2006.00507.x

2. Barr RG et al. The Cochrane Database of Systematic Reviews 2005, Issue2

3. Shukla VK et al. CCOHTA Technology Report Issue 65, March 2006

### **Black cohosh and menopausal hot flushes**

Further to the article in last month's newsletter highlighting the possibility of a connection between black cohosh and liver toxicity, a recent trial suggests that black cohosh does not actually relieve menopausal hot flushes<sup>1</sup>.

132 menopausal women, selected because their breast cancer history or breast cancer risk meant they were unable to take HRT, took part in a double blind, randomised, placebo-controlled crossover trial of a standardised preparation of black cohosh. Their mean age was 56 years. The women took black cohosh or placebo for 4 weeks, and then crossed over for another 4 weeks without a washout period.

During the first phase of the trial, black cohosh did not reduce the women's total hot flush scores compared with placebo (mean reduction 20% for black cohosh and 27% for placebo). Nor did it have any impact on frequency of hot flushes, quality of life, satisfaction with treatment, or scores on the Green climacteric scale. Both groups got moderately better during the first 2 weeks of treatment (whichever it was) and that improvement was sustained until the end of the trial.

**So, in this population of menopausal women, black cohosh did not work any better than placebo. For now, the weight of evidence does not support the routine use of black cohosh in these women<sup>1</sup>.**

1. BMJ 2006; 333: bmjupdates<sup>+</sup> (19/8)

### **Spacers versus nebulisers for beta-agonist treatment of acute asthma**

Metered dose inhalers with a spacer have for sometime now been promoted as being equally effective as using a nebuliser for administering inhaled beta-agonists to relieve bronchospasm in acute asthma. A recent Cochrane review has addressed whether this is in fact true<sup>1</sup>.

They searched for randomised trials in adults and children (from 2 years of age) with asthma, where spacer beta-agonist delivery was compared with wet nebulisation. They found 25 suitable trials from emergency room and community settings.

Method of delivery of beta-agonist did not appear to affect hospital admission rates. In adults, the relative risk of admission for spacer versus nebuliser was 0.97 (CI 0.63 to 1.49). The relative risk for children was 0.65 (CI 0.40 to 1.06). This was very close to statistically significantly showing the spacer to be better. In children, length of stay in the emergency department was significantly shorter when the spacer was used, with a mean difference of -0.47 hours. Length of stay in the emergency department for adults was similar for the two delivery methods.

**The authors concluded that metered-dose inhalers with spacer produced outcomes that were at least equivalent to nebuliser delivery and spacers may have some advantages compared to nebulisers for children with acute asthma.**

1. Cates CJ et al. *The Cochrane Database of Systematic Reviews* 2006, Issue 2

### **Clostridium difficile policy**

There has been an increased incidence of *C.difficile* infection in North Derbyshire recently. As a result a *C.difficile* policy has been produced by the Primary Care Infection Control Team and agreed by the PCTs. The full document is available on the PACEF intranet site but some of the key points are included here.

*C.difficile* is an anaerobic, spore forming, gram-positive bacterium that is found in the large intestine. It is a common cause of antibiotic associated diarrhoea, causing illness when the balance of the normal gut flora is disturbed by the frequent use of certain antibiotics, e.g. cephalosporins. It accounts for 15-25% of antibiotic associated diarrhoea.

*C.difficile* infection can be debilitating, prolongs hospital stays and complications of the infection can be fatal. *C.difficile* has the potential to cause large outbreaks in healthcare settings if not managed appropriately, i.e. via standard precautions and isolation.

### ***Risk Factors***

Risk factors for *C. difficile* infections include the following:

- Elderly (over 65 years)
- Long length of stay in healthcare settings
- Recent use of antibiotics especially broad spectrum e.g. cephalosporins, which are harmful to normal gut flora
- Recent surgery, especially gastro-intestinal surgery
- Serious underlying disease/illness
- Immunocompromising conditions
- Prolonged use of proton pump inhibitors
- Poor cleaning or infection control practise

Possible cases of *C.difficile* infection can be identified where there are symptoms of diarrhoea occurring whilst patients are on antibiotics or shortly after a course of antibiotics (this may be up to 12 weeks later).

Where there is a suspicion of *C.difficile* infection a review of current antibiotic treatment should be made. Where a patient is on a proton pump inhibitor this should also be reviewed. Where possible these drugs should be discontinued as they may be contributing to the *C.difficile* infection.

Antibiotics should be used to treat the infection when the diarrhoea does not settle after 48 hours or is moderate to severe in nature. The antibiotic of choice is metronidazole for 7-10 days. Patients may receive two courses, if diarrhoea persists the microbiologist should be consulted, who may recommend the use of vancomycin.

Oral administration of these antibiotics is more effective than other routes.

Opioids should be avoided as they may prolong or worsen symptoms.

## Differentiating between urge and stress incontinence

A simple 3-item questionnaire can identify incontinence as being either stress or urge predominant in 3 out of 4 women<sup>1</sup>. The written questionnaire is self-administered by the patient and takes approximately 30 seconds to complete.

### The 3 Incontinence Questions (3IQ)

1. During the last 3 months, have you leaked urine (even a small amount)?

Yes

No



2. During the last 3 months, did you leak urine:  
(Tick all that apply)

a. When you were performing some physical activity, such as coughing, sneezing, lifting, or exercise?

b. When you had the urge or the feeling that you needed to empty your bladder, but you could not get to the toilet fast enough?

c. Without physical activity and without a sense of urgency?

3. During the last 3 months, did you leak urine *most often*:  
(Tick only one)

a. When you were performing some physical activity, such as coughing, sneezing, lifting, or exercise?

b. When you had the urge or the feeling that you needed to empty your bladder, but you could not get to the toilet fast enough?

c. Without physical activity and without a sense of urgency?

d. About equally as often with physical activity as with a sense of urgency?

Definitions of type of urinary incontinence are based on responses to question 3:

Response to Question 3	Type of Incontinence
a. Most often with physical activity	Stress only or stress predominant
b. Most often with the urge to empty the bladder	Urge only or urge predominant
c. Without physical activity or sense of urgency	Other cause only or other cause predominant
d. About equally with physical activity and sense of urgency	Mixed

1. Ann Intern Med 2006; 144: 715-23