



Prescribing Points

A NEWSLETTER FOR ALL HEALTH CARE PROFESSIONALS IN OXFORDSHIRE, WRITTEN BY THE MEDICINES MANAGEMENT TEAM, OXFORDSHIRE PCT, JUBILEE HOUSE, OXFORD BUSINESS PARK SOUTH, OXFORD, OX4 2LH.

Date of issue: June 2011

VOLUME No: 20.05 Written by Laura Tully, Sara Wilds & Louisa Griffiths

Inside this issue:

Concerns that tiotropium Respimat inhaler is associated with an increased risk of death

[A recent study published in the BMJ](#) reviewed the risk of mortality associated with long term use of tiotropium delivered using a mist inhaler for symptomatic improvement in COPD. The study analysed mortality data from five trials which included 6522 participants with COPD, of whom 3686 received tiotropium mist inhaler and 2836 a placebo.

The tiotropium mist inhaler was associated with a **significantly increased risk of death** (Relative risk 1.52, 95% CI 1.06-2.16, $p=0.02$). The increase in **risk** was observed with **both study doses** and remained present when the three year-long studies were analysed separately. It is **estimated** that for every **124 patients treated for a year** with the inhaler instead of placebo

it would be expected to observe **one additional death** (NNT 124, 95% CI 52 – 5682). The study did not include comparisons of mortality data from patients taking tiotropium using a Handihaler (dry powder inhaler). There is an ongoing trial being conducted comparing the two devices. There is currently indirect evidence to suggest that the Handihaler may be safer to use than the Respimat, however this evidence is not confirmed.

This analysis does have limitations mainly arising from the study data quality. This analysis did not have access to individual patient data to allow a cause specific mortality analysis or a time to event analysis. Additionally, the included studies varied in duration, drug dose used and the population studied.

Further studies should clarify the effects of long acting inhaled anticholinergics on cardiovascular events and mortality among vulnerable subgroups at the highest risk of systemic anticholinergic effects, such as those with pre-existing arrhythmias, cardiomegaly, or moderate to severe renal impairment who are typically excluded from trials.

<i>Concerns with tiotropium Respimat</i>	1
<i>Prednisolone 5mg</i>	1
<i>Pioglitazone</i>	2
<i>Anticholinergic effects in the over 65s</i>	3

So what?

Prescribers have been advised by the MHRA to inform patients about the possibility of this increased risk and to exercise caution when prescribing tiotropium mist inhaler, particularly in patients with possible underlying cardiac disease. If tiotropium treatment is considered appropriate the Handihaler formulation should be used first line.

Concessionary price increase allows all practices to consider switching prednisolone 5mg EC tabs to plain.

There is no good evidence that using enteric coated (EC) prednisolone reduces the risk of causing peptic ulcers (PU) compared with plain prednisolone, the potential advantage of EC preparations is speculative only and the cost is significantly higher than the plain tabs. All prescriptions for prednisolone 5mg tabs should therefore be written as plain rather than EC tabs.

The drive to switch prescriptions from EC prednisolone to the standard release version was held up in the early part of 2011 due to supply issues with the plain tabs. We are now advised that this is no longer presenting an issue, but the acquisition price has been reported to be higher than the tariff price on some occasions. NCSO (No Cheaper Stock Obtainable) status was awarded to allow for this within pharmacies, but it is not permissible for dispensing practices. This has been overcome, as for the month of June the Department of Health has granted a concessionary price increase for the plain prednisolone 5mg tablets of £4.46 (pack of 28 tablets). All prescriptions dispensed in the month of June will automatically be paid at this price rather than the stated tariff price and no further endorsement is necessary. This applies to pharmacies and dispensing practices alike and makes it possible to consider this switch for all patients.

The price increase should account for dispensing stock bought at higher than current tariff price, however it is still considerably lower than the tariff price for EC tablets and **therefore switching from EC to plain tabs still represents a**

So what?

All prescriptions for prednisolone 5mg should be prescribed as standard tablets and **not** EC. Practices should consider switching existing prescriptions from the EC version to plain tabs.

Pioglitazone and the Occurrence of Bladder Cancer

The European Medicines Agency (EMA) has published an [update](#) on their ongoing benefit-risk review of pioglitazone ▼-containing medicines and the occurrence of bladder cancer. The Committee for Medicinal Products for Human Use (CHMP) will finalise its review in July and make recommendations on the future use of these medicines then.

While the review is ongoing the CHMP is not recommending any changes to the use of pioglitazone-containing medicines. However, prescribers should be aware of this safety concern about bladder cancer, in addition to several other safety concerns with this drug (see below). Pioglitazone remains a [black triangle drug](#) and any suspected adverse reactions should be reported through the [Yellow Card](#) system.

Healthcare professionals should continue to follow NICE guidance on type 2 diabetes, which places pioglitazone generally as a third-line hypoglycaemic option for patients following metformin and a sulfonylurea. [A previous NPC Rapid Review](#) discusses its place in therapy following the withdrawal of rosiglitazone.

What is the background to this?

The risk of bladder cancer in association with pioglitazone has been under close review by the CHMP since 2000, and the manufacturer is conducting several cohort studies to investigate this concern. The three interim study reports have so far not confirmed a clear association between the use of pioglitazone and the occurrence of bladder cancer, but there is a signal of a potential increased risk in those with longest exposure and highest cumulative dose. The current review of pioglitazone-containing medicines was initiated in March 2011, following clinically relevant signals of the possibility of such an increased risk from spontaneous reports and various trial data.

The CHMP has discussed the French cohort study, which prompted the [French Medicines Agency decision](#) to suspend the use of pioglitazone-containing medicines in France earlier this month. They felt this study strengthened the signal of a small increased risk of bladder cancer, but that it had several methodological limitations, which could weaken its findings. It was subsequently [reported that Germany had also suspended pioglitazone](#).

Overall, the Committee agreed that there were still numerous issues to be resolved before it could make recommendations on the future use of pioglitazone-containing medicines. They have referred the issue to the Scientific Advisory Group on Diabetes/Endocrinology to discuss in early July 2011. Following which, the CHMP will give its final opinion on the benefits and risks of these medicines.

Pioglitazone remains an option but prescribers should be aware that this drug is not without safety issues. These were discussed in some detail in previous [MeReC Rapid Reviews No. 2199](#) and [3909](#).

Briefly, there is consistent evidence that pioglitazone can cause weight gain and fluid retention, and lead to new or worsening heart failure. This is not a rare occurrence, and it can be serious and sometimes fatal. Pioglitazone is [contraindicated](#) in patients with heart failure or a history of heart failure. With regard to ischaemic heart disease, the majority of published studies do not suggest that there is an increased risk of ischaemic heart disease with pioglitazone, like there is with rosiglitazone. However, as head-to-head comparisons from prospective RCTs comparing the cardiovascular safety of rosiglitazone and pioglitazone are not available, we should still be cautious with pioglitazone use.

NICE [advises](#) that pioglitazone should not be commenced or continued in people with a higher risk of fracture, because it may increase this risk further. And recently, a meta-analysis has suggested that glitazones could be associated with an increased risk of [pneumonia or lower respiratory tract infection](#).

As the recently published [MeReC Bulletin on type 2 diabetes](#) discusses in some detail, the preferred hypoglycaemic drugs recommended by NICE are metformin, a sulfonylurea and human NPH insulin. These interventions have been shown in randomised controlled trials to help patients live longer or better lives. Newer hypoglycaemic drugs, such as pioglitazone, may have a role in some individuals. However, as the withdrawal of rosiglitazone, and mounting safety concerns over pioglitazone, illustrate, their long term safety is not established, and robust evidence that they help patients live longer or better is not yet available.

So What?

Pioglitazone remains an option but prescribers should be aware that this drug is not without safety issues. NICE guidance on type 2 diabetes places pioglitazone generally as a third-line hypoglycaemic option for patients following metformin and a sulfonylurea. But progression to triple blood glucose lowering therapy should not be automatic, and clinicians should discuss adherence and the risks and benefits of this approach with individual patients.

Risk of drugs with anticholinergic effects in the over 65s

A side effect of many commonly used drugs appears to increase the risks of both cognitive impairment and death in older people, according to new research led by the University of East Anglia.

As part of the Medical Research Council's Cognitive Function and Ageing Studies (CFAS) project, the study is the first systematic investigation into the long term health impacts of 'anticholinergic activity' – a known potential side effect of many prescription and over the counter drugs which affects the brain by blocking a key neurotransmitter called acetylcholine. The findings are published today by the Journal of the American Geriatrics Society.

Medicines with some degree of anticholinergic effect are wide-ranging and many are frequently taken by older people. The groups with the greatest impact include: anti-depressants such as Amitriptyline, Imipramine and Clomipramine; tranquilisers such as Chlorpromazine and Trifluoperazine; bladder medication such as Oxybutynin; and antihistamines such as Chlorphenamine. Other drugs with an anticholinergic effect include: Atenolol, Furosemide and Nifedipine for heart problems; painkillers such as Codeine and Dextropropoxyphene; the asthma treatment Beclometasone; the epilepsy treatment Carbamazepine; and Timolol eyedrops which are used for glaucoma.

The large cohort study was launched as part of the drive to find ways of reducing risk factors for dementia which affects 820,000 people in the UK. The UEA researchers worked in collaboration with colleagues at University of Cambridge, Indiana University and National Health Service clinicians. The project was funded by the [Medical Research Council](#) (MRC) and the US [National Institute on Aging](#).

More than 13,000 men and women aged 65 and over from across the UK were included in the two-year study. Around half were found to use a medication with potential anticholinergic properties.

In the study, each drug taken by the participants was given a ranking based on the strength of its anticholinergic activity, or AntiCholinergic Burden (ACB) - 0 for no effect, 1 for mild effect, 2 for moderate effect and 3 for severe effect.

The key findings were:

- Twenty per cent of participants taking drugs with a total ACB of four or more had died by the end of the two-year study, compared with only seven per cent of those taking no anticholinergic drugs - the first time a link between anticholinergics and mortality has been shown.
- For every additional ACB point scored, the odds of dying increased by 26 per cent.
- Participants taking drugs with a combined ACB of five or more scored more than four per cent lower in a cognitive function test than those taking no anticholinergic medications – confirming evidence from previous smaller studies of a link between anticholinergics and cognitive impairment.
- The increased risks from anticholinergic drugs were shown to be cumulative, based on the number of anticholinergic drugs taken and the strength of each drug's anticholinergic effect.
- Those who were older, of lower social class, and with a greater number of health conditions tended to take the most anticholinergic drugs.

Lead author Dr Chris Fox, clinical senior lecturer at Norwich Medical School, University of East Anglia, said: "This is the first large scale study into the long-term impact of medicines which block acetylcholine - a common brain neurotransmitter - on humans, and our results show a potentially serious effect on mortality. Clinicians should conduct regular reviews of the medication taken by their older patients, both prescribed and over the counter, and wherever possible avoid prescribing multiple drugs with anticholinergic effects.

"Further research must now be undertaken to understand possible reasons for this link and, in particular, whether and how the anticholinergic drugs might cause the increased mortality."

The list of drugs rated in the study are included in the table overleaf.

So What?

Prescribers should be aware of this study and consider the anticholinergic effects of drugs in the over 65s, particularly where patients are taking multiple drugs with anticholinergic effects or presenting with cognitive impairment .

Risk of drugs with anticholinergic effects in the over 65s - list of drugs rated in the study:

ACB Score 1 (mild)	ACB Score 2 (moderate)	ACB Score 3 (severe)
Alimemazine	Amantadine	Amitriptyline
Alprazolam	Belladonna alkaloids	Amoxapine
Alverine	Carbamazepine	Atropine
Atenolol	Cyclobenzaprine	Benztropine
Beclometasone dipropionate	Cyproheptadine	Chlorpheniramine
Bupropion hydrochloride	Loxapine	Chlorpromazine
Captopril	Meperidine	Clemastine
Chlorthalidone	Methotrimeprazine	Clomipramine
Cimetidine hydrochloride	Molindone	Clozapine
Clorazepate	Oxcarbazepine	Darifenacin
Codeine	Pethidine hydrochloride	Desipramine
Colchicine	Pimozide	Dicyclomine
Dextropropoxyphene		Diphenhydramine
Diazepam		Doxepin
Digoxin		Flavoxate
Dipyridamole		Hydroxyzine
Disopyramide phosphate		Hyoscyamine
Fentanyl		Imipramine
Fluvoxamine		Meclizine
Furosemide		Nortriptyline
Haloperidol		Orphenadrine
Hydralazine		Oxybutynin
Hydrocortisone		Paroxetine
Isosorbide preparations		Perphenazine
Loperamide		Procyclidine
Metoprolol		Promazine
Morphine		Promethazine
Nifedipine		Propentheline
Prednisone/Prednisolone		Pyrilamine
Quinidine		Scopolamine
Ranitidine		Thioridazine (withdrawn)
Theophylline		Tolterodine
Timolol maleate		Trifluoperazine
Trazodone		Trihexyphenidyl
Triamterene		Trimipramine
Warfarin		