APPROPRIATE USE OF NSAIDs

The safety and efficacy of COX-2 inhibitors and other NSAIDs is under intense scrutiny and review. In 2005, a local multi-disciplinary group reviewed clinical trial evidence and CSM advice to devise a guideline (available on our website) to clarify where traditional NSAIDs and COX-2 inhibitors should be used and where protection with a PPI is required. The advice is summarised below. For a full review of current evidence, please see PostScript Extra *Number 7, May 2006 on our website. This educational bulletin is produced largely for use by pharmacists and provides a useful summary of the issues for all health professionals.*

On 24 October 2006, the MHRA published new advice relating to NSAIDs used in high doses and for long-term treatment. They note that recent research into NSAIDs has shown that:

• Overall, the risks of heart attack and stroke are very small.

• It is likely that all NSAIDs carry some risk, but available evidence suggests that the risks may vary between medicines.

• Available evidence does not point to an increased risk for low dose ibuprofen (≤1200mg).

All NSAIDs including COX-2 inhibitors

• All NSAIDs, including COX-2 inhibitors, should be avoided, wherever possible, in patients at high-risk of gastrointestinal or cardiovascular complications.

• Paracetamol, given in full doses, should be tried first.

• The lowest effective dose of NSAID or COX-2 inhibitor should be prescribed for the shortest time necessary for control of symptoms.

• The need for long-term treatment should be reviewed periodically.

• Prescribing should be based on the safety profiles of individual NSAIDs or COX-2 inhibitors and on individual patient risk profiles (eg gastrointestinal and cardiovascular).

• Prescribers should not switch between NSAIDs without careful consideration of the overall safety profile of the products, a patient's individual risk factors, and patient preference.

• Concomitant aspirin (and possibly other antiplatelets) greatly increase the gastrointestinal risks of NSAIDs and severely reduce any gastrointestinal safety advantages of COX-2 inhibitors. Aspirin should only be co-prescribed if absolutely necessary.

New information on non-selective NSAIDs

• Non-selective NSAIDs may be associated with a small increased risk of thrombotic events (such as heart attack or stroke) when used at high doses and for long-term treatment.

• Evidence for diclofenac (particularly at the 150mg dose) suggests that this drug may have a small thrombotic risk, similar to that of licensed doses of etoricoxib, and possibly other COX-2 inhibitors.

• For ibuprofen, at high doses (eg 2400mg daily) there may be a small thrombotic risk but overall, at low doses (eg ≤1200mg), epidemiological data do not suggest increased risk.

• Naproxen is associated with a lower thrombotic risk than COX-2 inhibitors and, overall, epidemiological data do not suggest an increased risk of myocardial infarction; however, some increase in risk cannot be excluded on the basis of available evidence.

COX-2 inhibitors

• COX-2 inhibitors are no more effective than conventional NSAIDs. There are few situations, if any, in which a COX-2 inhibitor is unequivocally indicated.

• Patients with established IHD (including moderate to severe heart failure), peripheral arterial disease or cerebrovascular disease should be switched to alternative treatment. Gastro-protective agents (omeprazole or lansoprazole capsules) should be considered for patients switched to a conventional NSAID.

• Exercise caution with patients who have risk factors for heart disease, eg hypertension, hyperlipidaemia, diabetes and smoking.

• Patients with uncontrolled hypertension taking etoricoxib should be switched to alternative treatment.

• Hypersensitivity reactions and rare but serious, and sometimes fatal, skin reactions can occur with all COX-2 inhibitors. These mostly occur in the first month. Patients with a history of drug allergies may be at greater risk.

Any updates to this guideline in light of the new advice will be communicated in a future edition.

Clopidogrel prescribing guideline

The updated *Glasgow antiplatelet guidelines* were published in December 2004 and are available on the ADTC website. These clarify the roles of aspirin and clopidogrel in the prevention of thrombotic events. The guideline is intended to restrict clopidogrel to conditions where it has a proven benefit over aspirin, since the cost is more than 30 times greater. It has recently been agreed that Clyde will adopt the Glasgow guidelines.

Prescribing support pharmacists in primary care undertook evaluation of 878 patient reviews in 16 Glasgow GP practices between September 2005 and April 2006. They found that:

• 77% of patients were started on clopidogrel prior to the introduction of guidelines.

• 24% of patients had clopidogrel treatment initiated in primary care; 76% were started in secondary care.

• 66% of primary care starts and 74% of secondary care starts were deemed inappropriate according to the guidelines.

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PostScRipt

from the
NHSGGC Area Drug & Therapeutics Committee
Issue 36 November 2006

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Website
http://www.glasgowformulary.scot.nhs.uk

Alphabetical list of most recent ADTC decisions

For full details of SMC advice, visit **www.scottishmedicines.org** For previous ADTC decisions, visit **www.glasgowformulary.scot.nhs.uk**

Drug	Indication under consideration (There may be other licensed indications)	Glasgow decision	
Bimatoprost/timolol (Ganfort®)	Reduction of intra-ocular pressure in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers or prostaglandin analogues and for whom this combination offers an appropriate choice.	*Formulary* Acknowledge new formulation. Restricted to initiation by specialists.	√
Carglumic acid (Carbaglu®)	Hyperammonaemia due to N-acetylglutamate synthase deficiency.	*Formulary* Restricted to use by experts providing the supraregional specialist service for this disease	√
Choriogonadotropin alfa (Ovitrelle®)	Superovulation prior to assisted conception. Treatment of anovulatory or oligo-ovulatory women.	*Formulary* Acknowledge new formulation. Restricted to initiation by specialists.	√
Citalopram (FONDU review)	Depression.	*Formulary* Additional Drug of Choice.	√
Co-careldopa (Duodopa®)	Advanced levodopa-responsive Parkinson's disease with severe motor fluctuations and hyperkinesias or dyskinesia when available combinations of medicines have not given satisfactory results.	Non-*Formulary*	x
Cetuximab (Erbitux®)	In combination with radiation therapy for the treatment of patients with locally advanced squamous cell cancer of the head and neck.	*Formulary* Restricted to patients who are not appropriate for, or unable to tolerate, chemo-radiotherapy and who are of good performance status with no evidence of distant metastases. Restricted to use by specialists in the management of head and neck cancer.	√
Entecavir (Baraclude®)	Chronic Hepatitis B infection in adults with compensated liver disease and evidence of active viral replication, persistently elevated serum alanine aminotransferase levels and histological evidence of active inflammation and/or fibrosis.	Non-*Formulary* until consultation with the Hepatitis MCN for guidance of place in therapy and estimated patient numbers.	x
Etanercept (Enbrel®)	Severe active ankylosing spondylitis in patients who have had an inadequate response to conventional therapy. Active and progressive psoriatic arthritis in adults when the response to previous DMARD therapy has been inadequate.	*Formulary* Acknowledge new formulation. Restricted to use in accordance with British Society of Rheumatology guidelines of July 2004.	√
Etoricoxib (Arcoxia®)	Symptomatic relief of osteoarthritis, rheumatoid arthritis and the pain and signs associated with inflammation associated with gouty arthritis, in patients for whom the use of etoricoxib is appropriate taking account of current advice on the place in therapy of specific COX-2 inhibitors.	*Formulary* Acknowledge new replacement formulation. Restricted to use in acute gout.	√
Ivabradine (Procoralan®)	Symptomatic treatment of chronic stable angina in patients with normal sinus rhythm who have a contra-indication or intolerance for beta-blockers.	Non-*Formulary*	x
Lercanidipine (Zanidip®)	Mild to moderate essential hypertension.	Non-*Formulary*	x
Levetiracetam (Keppra®)	Partial onset seizures with or without secondary generalisation in adults and children from 4 years of age with epilepsy.	*Formulary* Acknowledge new formulation. Restricted to specialist use.	√
Levofloxacin (appeal)	Community acquired pneumonia, cystic fibrosis.	*Formulary* Restricted to 2nd line use by hospital specialists for penicillin allergic patients with community acquired pneumonia or for cystic fibrosis patients intolerant of ciprofloxacin where a quinolone is required.	√
Sunitinib (Sutent®)	Unresectable and/or metastatic malignant gastrointestinal stromal tumour after failure of imatinib treatment due to resistance or intolerance.	Non-*Formulary*	x
Trastuzumab (Herceptin®)	HER 2 positive early breast cancer following surgery, chemotherapy and, if applicable, radiotherapy.	*Formulary* Acknowledge new indication. Restricted to use by breast cancer specialists in line with protocol.	√
Zoledronic acid (Aclasta®)	Paget's disease of bone in patients for whom the use of a bisphosphonate is appropriate.	*Formulary* Acknowledge new indication. Restricted to specialist use.	√

Concordance: Not a recipe for a comfortable life

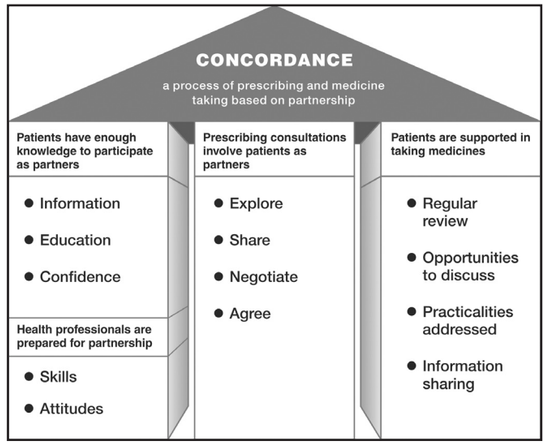
The concepts of compliance and concordance are often confused.[1] Compliance is the taking of medicines (or following advice or other treatment strategies) in accordance with the directions of a healthcare professional. This model does not allow much choice for the patient; it implies that "doctor knows best" and patients should blindly follow those instructions.

Moving away from this paternalistic approach is the model of concordance which is defined as an agreement on an appropriate treatment strategy reached between the patient and a healthcare professional. This model recognises the rights of the patient to have their wishes and beliefs taken into account when determining what treatment strategy, if any, is to be followed.

The outcomes of such therapeutic partnerships may not always be what the clinician believes is in the patient's best interests. However, we know that many patients do not follow their treatment strategies fully which can compromise outcomes. As the *BMJ* noted in 2003, "When the medicines that doctors prescribe fail to produce the benefit they expect, they often respond by varying the dose or selecting an alternative medicine. Thus doctors seem to behave as though non-compliance is a problem for other doctors."[2]

Concordance allows the patient to be more honest with the clinician and the two parties can reach a mutually agreeable outcome. These agreed treatment outcomes may be more realistic than the gold standard desired effect, but reasons for deviation can be understood by both patient and prescriber.

The Medicines Partnership, now part of the National Prescribing Centre (**www.npc.co.uk/med_partnership/index.htm**), suggests a multi-faceted model of concordance (as demonstrated by their graphic, reproduced here with permission). They note that research shows that patients are more likely to benefit from their prescribed medication when they understand and accept the diagnosis, agree with the treatment proposed and have had their concerns about the medicines specifically and seriously addressed.



This approach is not without disadvantages. Any acceptance of lower treatment effects must be balanced by the current pressure on achievement of targets for clinical measurements such as blood pressure, cholesterol or HbA1c to drive payment. Extra time would be required to discuss issues openly with the patient and to examine their health beliefs and expectations of treatment. Some concern has been expressed that it is not realistic with the pressure on appointments and waiting lists. But we must remember; this is not a completely new approach. Many patients and health professionals have been working this way for years.[1]

For all article references, check our website http://www.glasgowformulary.scot.nhs.uk

Trastuzumab (Herceptin®)

Trastuzumab has been at the centre of much media attention over the past 12 months. It has been accepted by the SMC and added to the Glasgow *Formulary* for patients with HER2 positive early breast cancer following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable). It is restricted to use by breast cancer specialists.

Human Epidermal Growth Factor Receptor 2 (HER2) is normally involved in the regulation of cell proliferation. Over-expression of the HER2 protein occurs in approximately 20-30% of primary breast cancers. It causes the affected cancer cell to have aggressive behavioural traits including enhanced growth and proliferation, increased invasive and metastatic capability and stimulation of angiogenesis. Trastuzumab is an engineered IgG1 monoclonal antibody directed against the extra-cellular domain of HER2. It is given as an intravenous infusion at three weekly intervals for up to one year. The average treatment cost per person is £22,000-£30,000.

The Herceptin Adjuvant Trial (HERA) was an open-label, randomised, phase III trial in women with HER2 positive early stage invasive breast cancer who had completed surgery with or without radiotherapy and at least four courses of chemotherapy. Patients (n=5,090) were randomised to three groups to receive trastuzumab once every three weeks for either one or two years or observation only. The primary end point was disease-free survival, secondary outcomes were overall survival, relapse-free survival and distant disease-free survival. There was a 5.4% absolute reduction (from 12.9% to 7.5%) in the risk of recurrence (hazard ratio (HR) 0.54, 95% CI 0.44 - 0.67). There was a non-significant 0.5% reduction in mortality from 2.2% to 1.7% (HR 0.76, 95% CI 0.47 - 1.23). The effect was independent of nodal status, adjuvant chemotherapy, hormone receptor status and patient age.

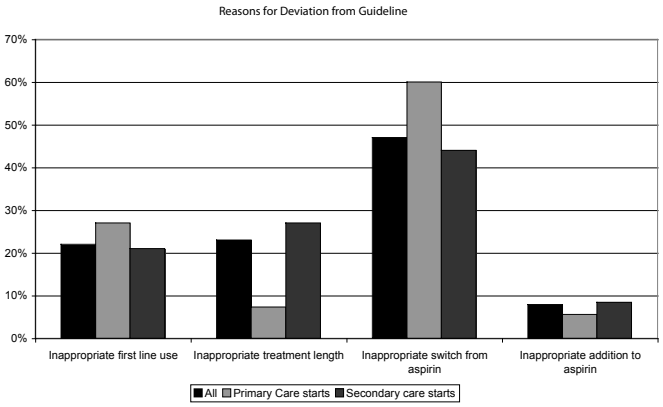
The incidence of serious cardiac adverse events for trastuzumab versus control was 0.6% versus 0.1% respectively. Patients with documented CHF, high-risk uncontrolled arrhythmias, angina pectoris requiring medication, clinically significant valvular disease, evidence of transmural MI on ECG or poorly controlled hypertension should not be recommended for trastuzumab. All patients should receive cardiac assessment at baseline, three monthly during treatment and at 6, 12 and 24 months following cessation. Other adverse effects include abdominal pain, asthenia, chest pain, chills, fever, headache, diarrhoea, nausea, vomiting, arthralgia, myalgia and rash.

The Beatson Oncology Centre has developed a protocol for the West of Scotland for trastuzumab in early breast cancer. This is based explicitly on the HERA trial exclusions and inclusions.

Summary

• Trastuzumab is included in the Glasgow *Formulary* for use according to protocol for treatment of HER2 positive early breast cancer following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable), restricted to use by breast cancer specialists.
• Trastuzumab significantly reduces the risk of recurrence (from 12.9% to 7.5%) and provides a non-significant 24% relative reduction in mortality (from 2.2% to 1.7%).
• Patients with cardiac conditions may have contra-indications to trastuzumab therapy; all patients prescribed the drug must undergo regular cardiac monitoring.

Clopidogrel *contd from page 1*



The most common reasons for prescribing being deemed inappropriate were:
• Clopidogrel prescribed first line for an indication where aspirin as effective but not tried and no contra-indication.
• Clopidogrel prescribed post ACS and/or intervention and continued beyond guideline recommendations.
• Aspirin changed to clopidogrel for inappropriate reasons, eg dyspepsia, history of GI bleed and PPI not tried first or patient suffered CVA/TIA while on aspirin and dipyridamole not added to aspirin.
• Clopidogrel added to aspirin but not indicated.

Interventions were made to stop or switch clopidogrel in 79% of inappropriate cases, resulting in a potential annual saving of £235 per patient reviewed. This equated to £207K in the 16 practices evaluated. Savings cannot be assumed at this level for all practices.

A number of actions are planned to follow up this work:
• Ongoing reviews and education in primary care.
• Further evaluation quantifying levels of appropriateness pre- and post-guideline with follow-up to identify outcomes of changes three months later.
• Feedback to address high levels of secondary care prescribing outwith the guidelines.
• The new indication for clopidogrel in combination with aspirin in medically treated patients with STEMI eligible for thrombolytic therapy is outwith the guidelines and has not yet been considered by SMC, ADTC or the MCNs.

NHS Greater Glasgow and Clyde

Area Drug & Therapeutics Committee
Chair: Professor M J Brodie

Communications Sub-group
Chair: Mrs A Thompson

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PostScript Editor: Mrs A Thompson
Prescribing Team, NHS Greater Glasgow & Clyde
Pharmacy & Prescribing Support Unit
Queen's Park House, Victoria Infirmary, Langside Road
Glasgow G42 9TY Tel: 0141 201 5214 Fax: 0141 201 5338
E-mail: audrey.thompson@nhs.net

PostScript Web editor: Dr A Power

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Concordance

1 BMJ 1999;319:787
2 BMJ 2003;326:348-349

Trastuzumab

http://www.scottishmedicines.org/updocs/trastuzumab%20150mg%20vial%20(Herceptin)%20(278-06).pdf

NSAIDs

http://www.mhra.gov.uk/
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