

PRESCRIBING and CLINICAL EFFECTIVENESS NEWSLETTER



Supporting the
Derbyshire Health Community

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JAPC Update

The Joint Area Prescribing Committee (JAPC) is a countywide group covering NHS Derbyshire County and NHS Derby City. It provides recommendations on drugs and medicines management issues.

RED drugs are those where prescribing responsibility lies with a hospital consultant or a specialist.

AMBER drugs are those that are initiated within a hospital/specialist setting but are suitable for shared care with a GP under a shared care agreement.

GREEN drugs are regarded as suitable for primary care prescribing.

BROWN drugs are those that JAPC does not recommend for use, except in exceptional circumstances, due to lack of data on safety, effectiveness, and/or cost-effectiveness.

BLACK drugs are those that are not recommended or commissioned.

The most recent updates are in the table below; the full list is available at

<http://www.derbyshiremedicinesmanagement.nhs.uk/home>

Drug	Date considered	Decision
Fingolimod	June 2011	BLACK
Pivmecillinam	June 2011	GREEN [only on microbiologist recommendation]
Tolcapone	June 2011	RED
NuvaRing	May 2011	GREEN [after specialist initiation]
Romiplostim	May 2011	RED

Guidance on missed pills

The Faculty of Sexual and Reproductive Healthcare has issued new guidance on what to do when combined oral contraceptive pills (COCs) have been missed. This applies to all COCs with an estrogen dose of at least 20 micrograms (with the exception of Qlaira), whether monophasic or phasic and including every day (ED) preparations. The guidance defines a missed pill as one that is more than 24 hours late. If more than one pill is missed, the rule applies to consecutive pills. The rule applies to active pills, not to placebo pills in ED preparations.

The following are key elements of the revised advice:

- If it is reasonably certain that the woman is not pregnant, COCs can be initiated on any day of the menstrual cycle, not just the first day. Additional contraceptive precautions are required for the first 7 days if the pills are started after Day 5 of the cycle.
- If one active pill is missed, advise the patient to take it as soon as they remember (even if it means taking two pills in one day), and there is no need to take additional precautions.

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- If two active pills are missed, advise the patient to take the last missed pill as soon as they remember (even if it means taking two pills in one day), and additional contraceptive precautions should be taken for the next 7 days.
 - Advice on use of Qlaira®, Evra® and NuvaRing® can be found in the Summaries of Product Characteristics and patient information leaflets available at <http://www.medicines.org.uk/emc>
- The full document can be found at <http://www.ffprhc.org.uk/admin/uploads/StatementCEUMissedPills.pdf>

Prasugrel hypersensitivity

Prasugrel (Efient ▼) has been rarely associated with reports of serious hypersensitivity reactions including, very rarely, angioedema; some of which occurred in patients with a history of hypersensitivity to clopidogrel. Healthcare professionals should be aware of this risk when prescribing prasugrel.

Advice for healthcare professionals¹:

- Prescribers should be aware of the potential risk of rare but serious hypersensitivity reactions with prasugrel and should monitor for signs in all patients, including those with a previous known history of hypersensitivity reactions to thienopyridines
- When prescribing prasugrel, inform patients of the potential risk of hypersensitivity reactions, including angioedema
- Suspected adverse reactions to prasugrel should be reported via the Yellow Card Scheme (see www.yellowcard.gov.uk)

Advice for patients taking prasugrel:

- Patients should inform their doctor immediately if they experience symptoms suggesting hypersensitivity or allergic reaction (e.g. swelling of the face, neck, tongue, lips, or throat; rash; itching; or shortness of breath)

1. Drug Safety Update May 2011 vol 4, issue 10:A1

Yasmin and VTE

Both the US FDA and the EMA have highlighted that drospirenone-containing pills may be associated with an increased risk of venous thromboembolism (VTE). Two observational studies have found that there is a two to three-fold increased relative risk of VTE associated with the use of drospirenone-containing combined oral contraceptives (COCs), e.g. Yasmin, compared with levonorgestrel-containing COCs. In these studies, the incidence of VTE was about 20 to 30 cases per 100,000 women-years of use with drospirenone-containing COCs and about 10 cases per 100,000 women-years of use with levonorgestrel-containing COCs. All COCs increase the risk of VTE but, in absolute terms, this risk is low and lower than that in pregnancy.

The NPC suggests the following action¹:

Healthcare professionals should review their prescribing of oral contraceptives to make sure it reflects current MHRA advice (see below). Rather than having an advantage in this regard, the VTE risk with drospirenone-containing COCs, such as Yasmin, may be higher than with levonorgestrel-containing COCs. While patient choice is an important factor in selecting a suitable contraceptive method, a levonorgestrel-containing COC is a sensible first choice for women who decide to use a COC, because of their well known safety profile.

In April 2010, the MHRA advised that:

- Prescribers should be aware of the new evidence when discussing the most suitable type of contraceptive for a woman who wants to start or switch contraception.
- Any prescribing decision should take into account each woman's personal risk factors and any contraindications.
- All combined oral contraceptives, including Yasmin, should be prescribed with caution to obese women (BMI>30), or those with a higher baseline risk of VTE for other reasons.
- All hormonal contraceptives are highly effective and safe and have important health benefits, including those from avoiding unplanned pregnancy. When used appropriately, the benefits of all COCs far outweigh the risk of VTE, which is rare.

Yasmin is relatively expensive compared with other COCs, at £63.70 for one years supply, compared with £6.46 to £27.95 for other COCs (excluding Qlaira [approx. £100]). Rigevidon is the current Derbyshire formulary choice levonorgestrel-containing COC.

1. www.npc.nhs.uk/rapidreview/?p=3549

Bisphosphonates and atypical fractures

The European Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has concluded that rare atypical fractures of the femur are a class effect of bisphosphonates¹.

The Committee confirmed that the benefits of bisphosphonates in the treatment and prevention of bone disorders continue to outweigh their risks, but that a warning of the risk of atypical femoral fractures should be added to the prescribing information for all bisphosphonate-containing medicines in the EU. Such a warning had already been included in the product information for alendronate-containing medicines across Europe, following a review in 2008. It will now be extended to the whole bisphosphonate class.

The information contains the following advice:

- Prescribers of bisphosphonate-containing medicines should be aware that atypical fractures of the femur may occur rarely. If an atypical fracture is suspected in one leg, then the other leg should also be examined
- Doctors who are prescribing these medicines for osteoporosis should regularly review the need for continued treatment, especially after five or more years of use.
- Patients who are taking bisphosphonate-containing medicines need to be aware of the risk of this unusual fracture of the femur. They should contact their doctor if they have any pain, weakness or discomfort in the thigh, hip or groin, as this may be an indication of a possible fracture

The marketing authorisation holders of bisphosphonate-containing medicines have been asked to closely monitor this issue.

1. www.ema.europa.eu/docs/en_GB/document_library/Press_release/2011/04/WC500105281.pdf

Paracetamol prescribing in primary care

Off-label prescribing of paracetamol for children is common in primary care, with relatively high levels of potential overdosing in the youngest children and underdosing in the oldest children, according to the results of a recent study¹.

Data on paracetamol prescribing in children aged 0 to 12 years were obtained from the Scottish Practice Team Information database and analysed for off-label prescribing (i.e. prescribing outside the BNFC age and dose recommendations).

The following results were reported for data collected for the year 2006:

- A total of 4,423 paracetamol prescriptions were issued to 2,761 children (52.4% males) with almost half (48.9%, 1,329 children) issued to children aged 1-5 years.
- 18% of individual prescriptions were off-label and after accounting for repeat prescriptions, 625 (22.75%) individuals were exposed to off-label prescriptions.
- 13.3% of prescriptions were underdosed and 4.4% overdosed at least once during the study year. A further 15% of prescriptions contained insufficient dosage data to determine their status.
- Age was significantly related to non-recommended dosage ($p < 0.001$).
- Children aged one to three months were at highest risk of being overdosed; 27% of prescriptions recommended actual or potential overdose and 25% of children aged six to 12 years were prescribed an actual or potential underdose.
- Overall, 57.2% of all prescriptions failed to comply with current BNFC recommendations.

The authors conclude that approximately a fifth of paracetamol prescriptions issued to children by their GP are off label, with relatively high levels of potential overdosing in the youngest children and potential underdosing in the oldest children. This is associated with risks of toxicity or under treatment, respectively.

The MHRA are to introduce more exact paracetamol dosing for children. See www.mhra.gov.uk/NewsCentre/Pressreleases/CON120251

1. Br J Clin Pharmacol, published early online 18/5/11; doi:10.1111/1365-2125.2011.03993.x

LTRAs in asthma

A pragmatic randomised trial found that a leukotriene receptor antagonist (LTRA) was equivalent to an inhaled corticosteroid (ICS) as first-line preventer therapy, and to a long-acting beta-2 agonist (LABA) as add-on therapy to ICS, in adults with asthma¹. Most randomised trials of treatment for asthma study highly selected patients under idealised conditions. This pragmatic trial was designed to maximise external validity (applicability or generalisability), with the goal of studying a heterogeneous real-world population. The study was commissioned and predominantly funded by the UK Health Technology Assessment Programme.

In RCTs, LTRAs have been shown to be significantly better than placebo but usually less effective than ICS for relieving asthma symptoms and improving lung function. The accompanying editorial suggests that the LTRA showed equivalence in a real-world setting because it is easier to take a tablet once or twice a day than to use an inhaler². The rates of adherence to the LTRA were 65% and 74% in the first-line controller and add-on therapy arms, respectively, as compared with only 41% and 46% for the ICS.

However, the NPC states that this study has important limitations and does not change current recommended practice³. They advise:

‘Health professionals should continue to follow the recently revised SIGN/BTS guideline on the management of asthma. For patients not adequately controlled on a short-acting beta2-agonist (SABA) when required (step 1), ICS are the first choice regular preventer therapy (step 2). An LTRA (montelukast or zafirlukast) may be considered in children under five years if an ICS cannot be used.

A proportion of patients with asthma may not be adequately controlled on an ICS alone at step 2. For adults, adolescents and children aged 5 to 12 years, the addition of a LABA (salmeterol or formoterol) to an ICS should be considered next (step 3). For children under five years, the first choice add-on therapy to an ICS is an LTRA. However, before adding or changing treatment, practitioners should check concordance with existing therapy, check the patient’s inhaler technique and eliminate trigger factors.’

1. N Engl J Med 2011; 364:1695-707
2. N Engl J Med 2011; 364:1769-70
3. www.npc.nhs.uk/rapidreview/?p=3847

NSAIDs and MI

Patients with a history of myocardial infarction (MI) taking any non-steroidal anti-inflammatory drug (NSAID), except possibly naproxen, are at increased risk of subsequent death or recurrent MI, according to the results of an observational study¹.

NSAIDs are associated with an increased risk of cardiovascular (CV) adverse events in healthy individuals; however data on the risk profile in individuals with a previous history of CV disease are limited. This study examined the effect of duration of NSAID use on CV outcomes in patients with a previous MI.

Data from Danish healthcare registries were used to identify all patients aged 30 years and above admitted with first time MI between January 1997 and December 2006, and who were alive at discharge (n=83,677). Data on all NSAID use after index MI were obtained, and dose and duration of treatment evaluated.

Overall, there were 35,257 outcome events (including 29,234 deaths). NSAID treatment was associated with an increased risk of death/recurrent MI. This was present from the start of treatment (hazard ratio 1.45 [95% CI 1.29 to 1.62]) and persisted throughout the treatment course (1.55 [1.46 to 1.64] after 90 days).

When individual drugs were analysed, diclofenac was associated with the highest risk (HR for day one to seven, 3.26 [2.57 to 3.86]), with the increase persisting throughout treatment. Ibuprofen was associated with increased risk when continued for over seven days. Rofecoxib was associated with increased risk from day one, whereas celecoxib was associated with increased risk when continued beyond 14 to 30 days. Naproxen was the only NSAID without statistically significant increase in risk at all time points; however patients taking naproxen were generally younger and male.

The authors conclude that even short-term treatment with most NSAIDs is associated with increased risk of death and recurrent MI in patients with a previous MI. Diclofenac is associated with the greatest increase in risk, and only naproxen does not appear to increase risk. They caution, however, that the risk of gastrointestinal bleeding should also be considered, as this worsens the prognosis for patients with a history of MI. They note the limitations of their study, which as an observational study cannot ascribe causality due to the presence of unmeasured confounders. Nevertheless, they comment that these would have to have large effects to account for the measured effect. Overall, they suggest that neither short- nor long-term treatment with NSAIDs is advised in this population, and any NSAID use should be limited to the absolute minimum in patients with established CV disease.

1. Circulation 2011; 123: 2226-35

Beta-blockers in COPD

Patients with COPD often also have cardiovascular (CV) disease, for which beta-blocker treatment would potentially be beneficial. Due to the known risks of beta-blockade in patients with airways disease, clinicians have historically been reluctant to prescribe these drugs. Some evidence suggests that beta-blockers improve mortality in patients with COPD, whether or not they have CV disease. A new study examines whether the drugs improve major clinical outcomes including mortality, in patients with COPD¹.

This was a retrospective cohort study using a disease specific database of COPD patients (TARDIS) linked to the Scottish morbidity records of acute hospital admissions, the Tayside community pharmacy prescription records, and the General Register Office for Scotland death registry. The study population comprised of 5,977 patients aged >50 years with a diagnosis of COPD. Mean follow-up was 4.35 years, mean age at diagnosis was 69.1 years, and 88% of beta-blockers used were cardioselective.

Use of a beta-blocker was associated with a 22% reduction in all-cause mortality overall. Compared with controls (given only inhaled therapy with either short acting beta-agonists or short acting antimuscarinics), the adjusted hazard ratio for all-cause mortality was 0.28 [95% CI 0.21 to 0.39] for treatment with inhaled corticosteroid, long-acting beta-agonist, and long acting antimuscarinic plus beta-blocker vs. 0.43 [0.38 to 0.48] without beta-blocker. Similar results were obtained for other treatment groups. There were similar trends showing additive benefits of beta-blockers in reducing oral corticosteroid use and hospital admissions due to respiratory disease. Beta-blockers had no harmful impact on lung function at all treatment steps when given in conjunction with either a long-acting beta-agonist or antimuscarinic agent.

The authors conclude that beta-blockers may reduce mortality and COPD exacerbations when added to established inhaled stepwise therapy for COPD, independently of overt CV disease and cardiac drugs, and without adverse effects on pulmonary function.

The accompanying editorial states that, together with other data, these results indicate that the use of beta-blockers may help reduce the morbidity associated with COPD. Beta-blockers should not be withheld for CV indications but using them directly for COPD is premature².

1. BMJ 2011; 342:d2549

2. BMJ 2011; 342:d2655

Ambulatory oxygen in COPD

Patients with chronic obstructive pulmonary disease (COPD) who are not severely hypoxaemic at rest may experience significant breathlessness on exertion, and ambulatory oxygen is often prescribed in this circumstance despite a lack of conclusive evidence for benefit. A recent study aimed to determine whether such patients benefit from domiciliary ambulatory oxygen and, if so, which factors may be associated with benefit¹.

This was a 12 week, parallel, double-blinded, randomised, placebo-controlled trial of cylinder air versus cylinder oxygen, provided at 6L/min intranasally, for use during any activity provoking breathlessness. Patients underwent baseline measurements of arterial blood gases and lung function. Outcome measures assessed dyspnoea, health-related quality of life, mood disturbance, functional status and cylinder utilisation.

Authors' conclusion:

This randomised controlled trial found that domiciliary ambulatory oxygen provided no additional benefit over air in terms of dyspnoea, quality of life or function in patients with COPD experiencing exertional dyspnoea without severe resting hypoxaemia. Of six factors examined (gender, exertional desaturation, severity of airflow obstruction, severity of dyspnoea, volume or exercise response to hyperoxia), none was predictive of therapeutic benefit. Our findings do not support the use of domiciliary ambulatory oxygen as a treatment for dyspnoea in this group of patients and challenge the use of exertional desaturation as a primary criterion for its prescription. Our results were suggestive but not conclusive of placebo benefits from having domiciliary gas cylinders.

1. Thorax 2011; 66:32-37

Management of tuberculosis

NICE has produced a new clinical guideline (March 2011) which offers evidence-based advice on the diagnosis and treatment of active and latent tuberculosis in adults and children, and on preventing the spread of tuberculosis, for example by offering tests to people at high risk, and by vaccination. New recommendations on using interferon-gamma tests for the diagnosis of latent tuberculosis have been added.

See: <http://www.nice.org.uk/guidance/index.jsp?action=byID&o=13422>

These are the key priorities for implementation:

Management of active TB

6-month, four-drug initial regimen (6 months of isoniazid and rifampicin supplemented in the first 2 months with pyrazinamide and ethambutol) should be used to treat active TB in:

- adults not known to be HIV positive
- adults who are HIV positive
- children.

This regimen is referred to as 'standard recommended regimen'. For the management of active *meningeal* TB, please see NICE guidance. This involves a longer duration of treatment, with four anti-TB drugs initially for 2 months, followed by two drugs for 10 months. It also includes a course of a glucocorticoid e.g. prednisolone.

Improving adherence

Use of directly observed therapy (DOT) is not usually necessary in the management of most cases of active TB. All patients should have a risk assessment for adherence to treatment, and DOT should be considered for patients who have adverse factors on their risk assessment, in particular:

- street- or shelter-dwelling homeless people with active TB
- patients with likely poor adherence, in particular those who have a history of non-adherence.

The TB service should tell each person with TB who their named key worker is (TB nurse specialist) and how to contact them.

New entrant screening

New entrants should be identified for TB screening from the following information:

- Port of Arrival reports
- new registrations with primary care
- entry to education (including universities)
- links with statutory and voluntary groups working with new entrants.

BCG vaccination

Neonatal BCG vaccination for any baby at increased risk of TB should be discussed with the parents or legal guardian. Primary care organisations with a high incidence of TB should consider vaccinating all neonates soon after birth.

IMPORTANT LOCAL ISSUES

Key messages on awareness of TB symptoms to prevent delays in diagnosis

The key messages for health care professionals from the recent TB Alert charity campaign are '*think, suspect, refer*'. Typical TB symptoms can include a persistent *cough* (longer than 3 weeks), *pyrexia, night sweats, poor appetite, unexplained weight loss, haemoptysis* and *lymphadenopathy*. Sputum samples sent on three separate days for 'AAFB' are an excellent aid for diagnosing pulmonary TB.

TB Services in Derbyshire

All cases of active TB are managed by the TB services in North and South Derbyshire.

Southern Derbyshire

In Southern Derbyshire there is a well established TB Service comprising of two Adult Respiratory Physicians and one Paediatrician with a team of TB Nurse Specialists. The team was previously based at the Chest Clinic on Green Lane, Derby, but are now based in the Medical Outpatients Department at the Royal Derby Hospital. Although the TB Nurse Specialists have recently transferred from the PCT to the Hospital Trust, the service offered remains unaltered.

Cases are followed up in the Friday morning TB clinic. Each diagnosed case of TB is allocated a key worker (the TB Nurse Specialist) who will provide education to the patient and the family and facilitate adherence to drug treatment. The TB Nurse Specialist will provide all TB medication throughout the course of treatment, observe for side effects and monitor LFTs, as well as encouraging clinic attendance. Those who have been in contact with active TB will be identified by the nurse specialists and offered screening comprising of symptom checks, Tuberculin Skin Tests, Chest X-rays and interferon gamma tests according to the NICE (2011) algorithms. Weekly Nurse Led clinics are held at the London Road Community Hospital site. Those with positive results will be referred either into the adult or paediatric clinic for treatment.

Many referrals for New Entrant Screening are via the Port of Arrival reports from the HPA. Several GP practices refer new entrants directly to the service for TB screening. The nurse specialists also attend Derby University on a twice yearly basis to offer new entrant screening.

In Southern Derbyshire there is a 'selective' Infant BCG vaccination policy. If either parent or grandparent is from a high risk TB incidence country (see HPA WHO estimates of TB incidence by country, available on the internet) or if there has been a history of TB in the household within the last 5 years, BCG is offered. Babies are identified at birth by the midwifery and health visiting services. To discuss any aspect of the TB service, to discuss a suspected case or to make a referral to the Southern Derbyshire Team, the TB Nurse Specialists can be contacted on 01332 787995/ 787996. Fax: 01332 789693

North Derbyshire

In North Derbyshire the service has recently transferred from Derbyshire Community Health Services to Chesterfield Royal Hospital NHS Foundation Trust (CRHFT) and has become established within the Infection Prevention and Control team.

The services are very similar to those offered in Southern Derbyshire, with a TB Matron providing individual support to each patient on TB treatment as above. There is not a specific Consultant TB clinic; referrals and follow ups are seen within the general respiratory clinics, both adult and paediatric. Nurse Led clinics are held fortnightly at CRHFT and involve screening of new entrants to the UK, screening of contacts, high-risk infant/ children BCG vaccination (selective policy as in Southern Derbyshire) and screening of TB contacts.

Referrals to the Nursing Service are received from health professionals based within Derbyshire County PCT, Stepping Hill and Sheffield. Other referrals are identified through contact tracing or public enquiry. A referral form for the nurse led service is accessible via the GP intranet site. To discuss any aspect of the North Derbyshire TB service, to discuss a potential case or to make a referral the team can be contacted on 01246 516157/ 516163. Fax: 01246 516186.

Contributed by Diane Harris, Specialist Antimicrobial Pharmacist, diane.harris@derbyshirecountypct.nhs.uk

Pioglitazone and bladder cancer

Further to the article in last month's PACE newsletter, the French and German licensing agencies have taken the decision to suspend the use of pioglitazone-containing medicines. This follows receipt of results of a retrospective cohort study carried out in France that suggests an increased risk of bladder cancer with pioglitazone. The decision has been taken whilst the outcome of the ongoing European review of the benefits and risks of pioglitazone is awaited. In addition, the NPC reports that use of glitazones is associated with an increased risk of pneumonia. See www.npc.nhs.uk/rapidreview/?p=3909

Safety of tiotropium Respimat

A systematic review and meta-analysis of RCTs suggests that there is an increased risk of mortality associated with tiotropium mist inhaler (Respimat) compared with placebo¹. For the usual dose of 5 microgram daily there was a 46% relative increase in risk (RR 1.46, 95% CI 1.01 to 2.10). However, the absolute difference was only 0.8%. This translates to an annual NNH of 121. There is considerable uncertainty around this estimate, with 95% CIs of 51 to 5556². The MHRA currently advises caution when using the Respimat in patients with arrhythmias and that the recommended dose should not be exceeded³. The accompanying editorial advises that pending the results of a head to head trial, the indirect evidence that is currently available suggests that the Handihaler is a safer bet than the Respimat. If patients have a strong preference for the mist inhaler, the possible increased risk in mortality will need to be shared with them².

1. BMJ 2011; 342: d3215

2. BMJ 2011; 342: d2970

3. Drug Safety Update Volume 4, issue 4, November 2010

Publication of the month

Top tips for GPs – strategies for safer prescribing:

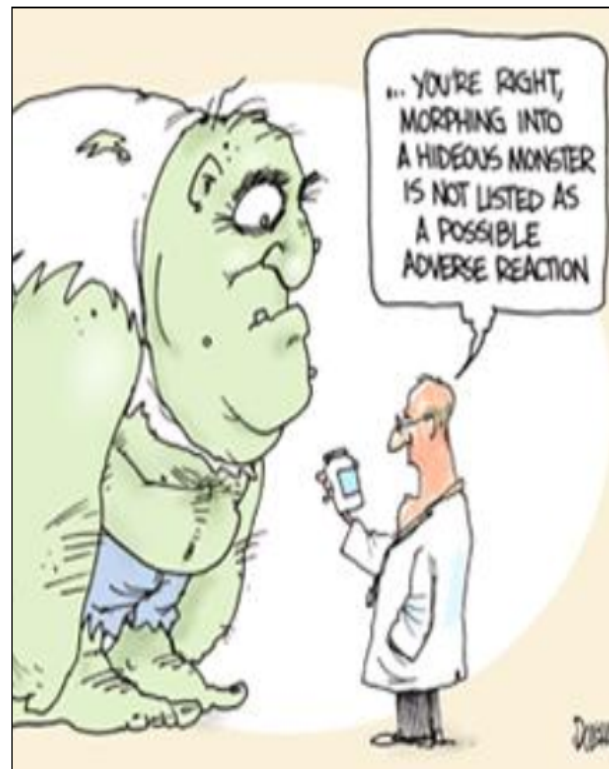
http://www.npc.nhs.uk/evidence/resources/10_top_tips_for_gps.pdf

Goodbye and good luck!

This is my last PACE Newsletter as I am taking voluntary redundancy and early retirement.

I hope you have found this newsletter useful over the many years I have been producing it.

Remember to use Barber's boxes and beware of new drugs – we don't know whether they work (POOs) and we don't know if they are safe. Only commission interventions that are effective, cost-effective and affordable!



To be, that is the answer!

;-)