

NEWSLETTER

Supporting the Derbyshire Health Community

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CEPPaC update

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 CEPPaC does not recommend for use (DARK BROWN) or only in restricted circumstances (LIGHT BROWN) due to lack of data on safety, effectiveness, and/or cost-effectiveness. *All BROWN drugs are non-formulary.*

The most recent updates are in the table below:

Drug	Date considered	Decision
Metformin SR	June 2007	GREEN (2 nd line use only)
Disulfiram	June 2007	AMBER
Exenatide injection	June 2007	DARK BROWN
Sitagliptin	June 2007	DARK BROWN
Testosterone patch (Intrinsa)	May 2007	DARK BROWN
Grazax (grass pollen allergen extract)	April 2007	DARK BROWN
Lanthanum carbonate	April 2007	RED
Varenicline	April 2007	GREEN (second line use only)
Pregabalin	April 2007	LIGHT BROWN
Colief liquid	April 2007	LIGHT BROWN
Ranibizumab	April 2007	RED
Exforge (amlodipine + valsartan)	April 2007	DARK BROWN
Darifenacin	April 2007	LIGHT BROWN
Rotigotine patch	April 2007	LIGHT BROWN

Metformin SR

Metformin is the only hypoglycaemic drug that has been shown to improve total mortality in type 2 diabetes, so we need to maximise its use. Sometimes standard metformin cannot be tolerated even when a slow dose titration is used as recommended. In this minority of cases CEPPaC recommends using metformin SR rather than a glitazone. Local experience suggests it is worth checking back on patients labelled as metformin intolerant and trying metformin SR.

Amantadine for neuropathic pain

Amantadine is licensed for use in Parkinson's disease and also for the prophylaxis and treatment of influenza A (but is no longer recommended for this indication). It is very occasionally used for difficult to manage neuropathic pain. This is an unlicensed use and the evidence base is not strong.

Its use was discussed at CEPPaC and the pragmatic decision taken to allow prescribing by specialist pain services. The decision on the ongoing prescribing responsibility in successful patients was thought to be best done as a joint decision between the consultant and their GP. We were assured that there are only likely to be 10 - 20 patients per year.

Making anticoagulant use safer

The National Patient Safety Agency has issued Patient Safety Alert No. 18 "Actions that can make anticoagulant therapy safer". One of the recommendations is to amend local policies to standardise the range of anticoagulant products used, including all strengths of warfarin tablets to best meet the needs of individual patients. The alert informs us that patient and carer groups prefer using the least number of tablets each day, constant daily dosing and not alternate day dosing, and not to use half tablets.

Some years ago Derbyshire moved to a system of using only warfarin 1mg tablets as a patient safety improvement to reduce the chances of confusion and potential overdosing. I contacted the NSPA to ask what evidence there is to support their recommendations. Their response was that there is no hard evidence other than extensive consultation with patients and carers. They added that local organisations will need to make their own decisions but on balance they felt that their recommendation was likely to put fewer patients at risk. We have discussed this at CEPPaC and it was agreed that 1mg should remain the recommended strength of warfarin, but to use higher strengths when appropriate for those patients with a high tablet load. Alternate day dosing may be appropriate in a minority of cases.

Another of the NPSA recommendations is that prescribers and pharmacists should check that patients' blood clotting is being monitored regularly and that the INR level is safe before issuing or dispensing repeat prescriptions for oral anticoagulants. Community pharmacists will only need to do this if failsafe systems are not in place in GP practices. This will need careful and sensible liaison between community pharmacists and GP practices and CEPPaC advises that this should happen as soon as possible. The BSH and the NPSA have updated the patient-held information (yellow) booklet, which includes an individual treatment record. Patients are advised to always carry their 'Anticoagulant Alert Card' and show it when requesting a new prescription or having a prescription dispensed. Community pharmacists are asked to be alert for potential warfarin interactions with over-the-counter drugs and herbal remedies. The County PCT Medicines Management team are developing a local action plan for the implementation of this NPSA alert.

Rosiglitazone associated with increased risk of MI?

The goal of the treatment of type 2 diabetes is to decrease cardiovascular disease, the largest cause of death in these patients. Glitazones have already been shown to increase the risk of hospitalisations for heart failure. A new study now suggests that rosiglitazone is associated with an increased risk of MI¹.

The authors of this meta-analysis have pooled data from 42 trials to determine if use of the drug increases the risk of MI or cardiovascular death. Since the studies were not specifically designed to evaluate cardiac outcomes, most did not describe how cardiac endpoints were determined. Most studies were between 24 and 52 weeks duration, with a typical dosage range for rosiglitazone of 4 to 8 mg per day. The average age of patients was 56 years and over half were men; the mean HbA_{1c} was 8.2%.

The results showed a significant increase in the likelihood of MI (odds ratio 1.43, 95% CI 1.03 to 1.98), p=0.03 and a non-significant increase in the risk of death from cardiovascular causes (OR 1.64, 95% CI 0.98 to 2.74), p=0.06. The absolute increase in risk of MI was small. On the other hand, the studies were short and most excluded patients with pre-existing heart disease, which explains the small total number of cardiovascular events in both groups. Results were similar whether the control group took placebo or an active comparator, suggesting that the increased risk of rosiglitazone was not a function of the protective effects of active comparator drugs.

The authors of the meta-analysis conclude:

"Rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that had borderline significance. Our study was limited by a lack of access to original source data, which would have enabled time-to-event analysis. Despite these

limitations, patients and providers should consider the potential for serious adverse cardiovascular effects of treatment with rosiglitazone for type 2 diabetes.”

The authors in the discussion admit that the results are based on a relatively small number of events, resulting in odds ratios that could be affected by small changes in the classification of events, but add that the findings are worrisome because of the high incidence of cardiovascular events in people with diabetes. One potential contributing factor may be the adverse effect of rosiglitazone on serum lipids. They call for urgent comprehensive evaluations to clarify the CV risks of rosiglitazone.

The accompanying editorial recognises the possibility that the findings were due to chance cannot be excluded². The authors point out that the possibility of cardiovascular benefit associated with rosiglitazone seems remote and there are no data showing that rosiglitazone prevents microvascular disease. They conclude that the rationale for prescribing rosiglitazone at this time is unclear and call for regulatory action by the FDA.

GSK has responded by saying it “strongly disagrees” with the conclusions of the NEJM paper. An unsigned editorial in the Lancet (June 2nd) urges waiting for further results from the RECORD study before acting on the NEJM papers. The NEJM *Journal Watch Cardiology* Editor-in-Chief Harlan M. Krumholz comments on the Lancet editorial: “Why would you wait when Avandia has never been shown to avert events or save lives? And now that there is evidence of potential harm – and there are alternative meds – it seems to me that the pressure is on the company to show that it is safe and effective.”

The SPC for Avandia actually lists the adverse event of cardiac ischaemia as common ($\geq 1/100$, $< 1/10$).

An unplanned interim analysis of the RECORD study has been published on-line by the New England Journal of Medicine (June 5th). The primary endpoint was hospitalisation or death from CV causes. RECORD is planned to run for 6 years and the mean follow-up of this analysis is 3.75 years. The authors admit that it therefore has limited statistical power to detect treatment differences. At this moment in time there is no difference in the primary endpoint (HR 1.11 [CI 0.93 to 1.32]) but will this become statistically significant after 6 years? The Kaplan-Meier graphs show divergence of the lines with more primary events for rosiglitazone. There is already a doubling of the risk of heart failure with rosiglitazone (HR 2.15 [1.30 to 3.57]). The three editorials accompanying this paper all say that there is continued uncertainty about the CV safety of rosiglitazone.

The FDA alert advises that healthcare professionals should factor this new information into their individual treatment decisions for their patients. The EMEA and MHRA have both advised that patients should not stop treatment with rosiglitazone but to discuss the medication with their doctor at their next routine appointment. No specifics are given about what the doctor should advise at this appointment. This has all been discussed at CEPPaC and the recommendations are:

- to maximise the use of metformin (using SR as appropriate) and avoid unnecessary use of glitazones,
- to reiterate that glitazones should only be used as per the NICE guidance,
- and if a glitazone is indicated, pioglitazone would appear to have a better risk/benefit ratio (and is cheaper) and should be the glitazone of choice.

1. Nissen SE & Wolski K. N Engl J Med 2007; 356: e-published
2. Psaty BM & Furberg CD. N Engl J Med 2007; 356: e-published

Insulin discontinuations – advice on switching

Novo-Nordisk has announced the discontinuation of Mixtard 10, 20, 40, 50 insulins by December 2007, and Velosulin, which will no longer be available after 15th June 2007. Mixtard 30 will continue to be manufactured. The decision to cease manufacture is for commercial reasons only and not because of effectiveness or safety concerns. Novo-Nordisk will be attaching stickers to the affected products alerting patients of this discontinuation. Patients will start to consult GP practices in order to switch to alternative treatments prior to December 2007.

For those patients on Mixtard insulins this leaves prescribers with several options:

1. If the patient is stable and concordant the preferred option is to switch to an alternative biphasic insulin such as Mixtard 30 or Humulin M3.

2. Consider if there is a more appropriate regimen such as basal/bolus eg Soluble S/Novorapid and human insulatard/Humulin I.

Basal/bolus is more likely to be appropriate for type 1 DM and could be considered for type 2 patients if they are not adequately controlled on large doses of insulin on a bd regime eg Mixtard 30, 60-70 units bd.

3. Long acting insulin analogues are an option for type 1 diabetics but due to their higher cost should be reserved for those experiencing severe or nocturnal hypoglycaemic attacks. NICE recommends that long acting insulin analogues are not routinely used for people with type 2 diabetes.

Patients on Velosulin should be switched to appropriate short acting insulin such as Humulin S. Rapid acting analogue insulins such as Humalog are more expensive than short acting insulins. They may be suitable for use just before meals by those patients on multiple dose regimens and should only be initiated by a specialist in diabetes.

Prescribing situations not covered by the NHS

This document has been updated and ratified by CEPPaC. It is an amalgamation of the previous north and south Derbyshire guidelines and contains a new section on travelling abroad with CDs, which is included here.

Travelling abroad with controlled drugs – implications for patients

Patients who are carrying certain controlled drugs abroad (or in the case of an import licence, into the UK) for short periods for their own personal use may require a personal licence.

Controlled drug quantity limits for travellers can be found from the following link:

<http://www.drugs.gov.uk/publication-search/drug-licences/travellers-controlled-drug-list>

In most cases the limits are set quite high, so a reasonable quantity of medication would be required to exceed this. However it is worthwhile being aware of this list as exceptions apply, for example:

- Benzodiazepine limit is 900mg for the duration abroad, 46 temazepam tablets 20mg would exceed this limit.
- Morphine limit is 1200mg for the duration abroad, 41 doses of MST 30mg would exceed this limit.

For those planning to travel with less than the limit, medication should be carried in the hand luggage and include a covering letter from the traveller's doctor.

For those planning to travel into or out of the UK with controlled drugs in excess of the set limits the traveller's doctor will need to complete an application for a personal import or export licence and sent with a covering letter to the Home Office. **Please allow two weeks for issue.** Application forms can be downloaded from:

<http://www.drugs.gov.uk/publication-search/drug-licences/Personal>

Some countries may have their own import regulations for controlled drugs and it is advised for travellers to contact a country's embassy to check.

There is no allowance in the GMS contract to reimburse GPs for providing this service. It would be up to the discretion of the GP/practice whether to charge patients in these circumstances.

Pharmaceutical sponsorship policy launched – is there any such thing as a free lunch?

Why do we need a policy?

The prescribing of drugs is the most common intervention made in the NHS and accounts for a significant proportion of resources. In Derbyshire County PCT £100 million is spent on primary care prescribing per year and these costs are rising. It is essential that these public funds are used for drugs which are safe, effective and provide value for money.

Almost all the literature available shows that the more clinicians rely on commercial sources of information, the less appropriate and less cost-effective are their prescribing decisions^{1 2 3 4}. Pharmaceutical companies see promotion of their products as important in influencing prescribing behaviour and continue to spend much of their revenue on this activity⁵. Whilst most of the evidence focuses on doctors, pharmaceutical companies target other health care professionals including PCT staff, many of whom will have supplementary/independent prescribing status.

Policy key points

- This policy applies to all PCT staff including provider services. Practice Based Commissioning groups will be required to adopt this policy or provide the PCT with an acceptable alternative policy. As a commissioner of services associated risks lie with the PCT.

- For directly sponsored events, products to be promoted and method of promotion must be submitted to the PCT Clinical Effectiveness, Prescribing, and Prioritisation Committee (CEPPaC) or delegated representative for approval.
- PCT and provider staff should not accept any significant gifts, inducements or inappropriate hospitality.
- No supplies or samples of products (pharmaceuticals/appliances/diagnostics) must be left in the hospital/clinic/other PCT premises nor be accepted by any PCT staff employee unless approved by CEPPaC or nominated representative.
- No member of PCT and provider staff shall engage with a non-NHS organisation or representatives without approval from their line manager. Where that interaction is likely to influence the use of pharmaceuticals/diagnostics/appliances/reagents then, unless previously authorised, all requests should be referred to CEPPaC or nominated representative. For example, a sponsorship arrangement to fund the purchase of portable DEXA scanners will affect the use of osteoporosis treatments.
- Mandatory training is being developed for PCT managers regarding sponsorship and working with non-NHS organisations.
- If there is any doubt check with a Derbyshire County PCT Prescribing Adviser.

The Pharmaceutical Sponsorship Policy for Working with Non-NHS organisations can be found at: www.derbyshirecountypct.nhs.u.k under "policies and procedures".

N.B. This is a County PCT (not City PCT) policy.

- 1 BMJ 31st May 2003; 326
- 2 Physicians and the pharmaceutical industry is a gift ever a gift? JAMA 2000; 283: 373-80
- 3 Doctors and detailers : therapeutic education or pharmaceutical promotion? Int. J. Health Serv. 1989; 19: 663-79
- 4 Reasons for not seeing drug representatives. BMJ 1999; 319: 69-70
- 5 www.nofreelunch.org/facts.html

Contributed by Steve Hulme

Glucose tolerance test

The GTT involves giving anhydrous glucose 75g (equivalent to glucose BP 82.5g) by mouth to a fasting patient. Lucozade (394ml) is often used to provide the required amount of glucose. The formulation of Lucozade has changed slightly and patients now need to drink 410ml to deliver 75g glucose. However, both formulations are in circulation and will be until the end of the year. If you perform the GTT please check the formulation if you use Lucozade. An alternative recommended by the BNF, is 113ml of Polycal with extra fluid to administer a total volume of 200-300ml.

Antenatal and postnatal mental health

NICE issued clinical guideline No. 45 on this subject back in February (see April PACE Newsletter). Since publication, the recommendation on screening questions for depression has been corrected (this is recommendation 1.2.1.3 in the NICE guideline), and the guideline has been reissued.

This recommendation now reads:

At a woman's first contact with primary care, at her booking visit and postnatally (usually at 4 to 6 weeks and 3 to 4 months), healthcare professionals (including midwives, obstetricians, health visitors and GPs) should ask two questions to identify possible depression.

- During the past month, have you often been bothered by feeling down, depressed or hopeless?
- During the past month, have you often been bothered by having little interest or pleasure in doing things?

A third question should be considered if the woman answers 'yes' to either of the initial questions (*PB note: it said both previously*).

- Is this something you feel you need or want help with?

The electronic versions of the guideline on the NICE website contain the correct recommendation on screening.

The MEDAL study

Citation:	Laine L et al. Assessment of upper gastrointestinal safety of etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. <i>Lancet</i> 2007;369: 465-73
Type of study? E.g. RCT, meta-analysis, diagnostic	Double-blind RCT – pre-specified pool intention-to-treat (ITT), 34,701 patients in 2 arms: etoricoxib 60mg (OA) 90mg (RA) od vs diclofenac 150mg od, over 18 months.
What is the question to be answered? (Main outcome measure)	To assess effects of etoricoxib and diclofenac on GI outcomes in a population that includes patients taking GI protective therapy and/or low dose aspirin. GI events stratified into complicated and uncomplicated.
Are results valid? Was the question answered?	No, uncertainty on significance of results. Results based on 3 pooled studies of which upper GI events were <u>not</u> primary endpoints therefore bias introduced. Study was not powered for GI events. ITT follow up 14 days after stopping study medication – is this long enough? Treatment arms further analysed into smaller sub groups dependant of severity of GI event, % of study period patients taking PPI and/or aspirin may further dilute significance and relevance. Also investigated symptom discontinuations (e.g. reflux) but did not look at GI symptom differences for those who continued to take study medication.
What were the important results (ARR, NNT)?	<ul style="list-style-type: none"> • Patients with any clinical GI event: HR 0.69 ARR 0.41 NNT 243 • Patients with complicated GI event: not significant • Patients with uncomplicated GI event: HR 0.57 ARR 0.39 NNT 256 • The addition of GI protective therapy and/or aspirin did not appear to alter the difference in event rate per sub-group, but this sub-group analysis is not powered and p-values are not quoted so significance is questioned.
Are the results relevant to the local population?	Study carried out across 1380 sites in 43 countries so may not reflect local population mix. 74% of cohort studied were female. GI protective therapy and aspirin were not randomly allocated (authors say reflects real life) with a possible non-random selection of groups introducing confounding by indication. Uncomplicated GI events were determined by endoscope, surgery, upper GI contrast radiography, or autopsy. In real life these may never be investigated/diagnosed and maybe of little clinical relevance.
Does this add to current knowledge, should it change clinical practice?	Raises more questions than answers, results may not be valid and statistical significance may not translate to clinical significance. Does not answer if a coxib is safer than a NSAID.
Other comments?	<ul style="list-style-type: none"> • Benefits of etoricoxib are small: to prevent <u>1</u> complicated GI event would need to treat <u>256</u> pts with etoricoxib rather than diclofenac over 18 months. This uncomplicated event event may or may not be clinically significant. • Complicated events were not significant which may be a result of an underpowered study. • There was significant pharmaceutical industry involvement throughout this study including study design, steering committee and statistical analysis of results. Two of the main study investigators were employed by Merck (MSD) who manufactures etoricoxib. • Consider an NSAID + PPI which is cheaper, less cardiotoxic, and more effective at reducing dyspepsia than a coxib alone (Cochrane).
<u>The bottom line</u>	This is a good example of industry driven research to assist in the marketing of a pharmaceutical product. The study was not primarily designed to determine GI events nor the effects of PPIs or low dose aspirin in combination with a coxib/PPI on these outcomes. As such these results should not be used as a basis to inform prescribing decisions.

Contributed by Steve Hulme

Inhaled corticosteroid use in COPD

Further to the review of the drug management of COPD in last month's PACE Newsletter, two other publications are of relevance.

The TORCH study showed an increased rate of pneumonia among patients receiving treatment containing fluticasone. A recently published analysis assessed, using a large cohort of patients with COPD, whether the use of inhaled corticosteroids (ICS) is associated with an increased risk of serious pneumonia requiring hospitalisation¹. This was a population-based cohort design with a nested case-control analysis. The cohort consisted of 175,906 COPD patients aged 72 (\pm 4.4) years at cohort entry, 50% men, and the duration of follow-up was 7.1 (\pm 4.04) years.

Current use of ICS was associated with an increase of 70% in the rate of a hospitalisation for pneumonia; rate ratio (RR) 1.70 (CI 1.63 to 1.77). There was a dose-response relationship, with the rate of pneumonia greatest with the highest doses of ICS, equivalent to fluticasone 1000mcg per day or more; RR 2.25 (2.07 to 2.44). When restricting the analysis to cases of pneumonia who died within 30 days of hospitalisation, an increase of 53% (RR 1.53 [1.30 to 1.80]) was seen with current use of ICS, while use of higher doses were associated with a 78% increase (RR 1.78 [1.33 to 2.37]) in the risk of pneumonia hospitalisation followed by death within 30 days. These adverse effects seemed to largely dissipate once treatment is stopped for six months or more.

The authors point out that the adverse effects of ICS need to be considered when prescribing these medications to patients with COPD and the impact on health care costs of an excess of pneumonia is large. They quote that 1000mcg of fluticasone is estimated to be equivalent to approximately 10mg of prednisone per day when the systemic effect is evaluated by suppression of serum cortisol.

COPD is characterised by a different type of airway inflammation than seen in asthma, with predominant neutrophils and significantly fewer eosinophils, and this inflammatory response appears to be relatively resistant to treatment with corticosteroids. Several RCTs has assessed whether ICS slows the rate of decline in FEV₁ seen in patients with COPD. A pooled analysis of patient-level data from 7 long-term RCTs of ICS versus placebo in patients with moderate-to-severe COPD has been published². It aimed to assess whether ICS modifies the natural history of COPD, characterised by an accelerated decline in FEV₁.

There were 3,911 randomised participants (29.2%) female in the analysis. In the first 6 months after randomisation, ICS use was associated with a statistically significant ($p < 0.01$) but small absolute increase in FEV₁ (42ml in men and 29ml in women). From 6 to 36 months, there was no significant difference between placebo and ICS therapy in terms of FEV₁ decline ($p = 0.86$). Smokers who continued to smoke had a smaller increase in FEV₁ during the first 6 months than did ex-smokers, emphasizing the importance of smoking cessation in modifying the natural history of COPD. The use of ICS in COPD does not modify the long-term rate of decline in FEV₁. The accompanying editorial to this study comments that it is reasonable to conclude that numerous primary studies and secondary analyses have identified the inability of inhaled corticosteroids to modify FEV₁, the primary defining and descriptive physiologic variable in COPD³. The risk/benefit ratio for ICS in COPD is very finely balanced. Please refer to the COPD algorithm in last month's newsletter.

1. Ernst P et al. Am J respire Crit Care Med 2007, doi:10.1164/rccm.200611-1630OC
2. Soriano JB et al. Chest 2007; 131:682-9
3. Sutherland ER. Chest 2007; 131:648-9

Key points: ICS does not reduce the long-term rate of decline of FEV₁ in COPD but does seem to increase the rate of serious pneumonia requiring hospitalisation.

Management of patients on oral anticoagulants requiring dental surgery

The British Committee for Standards in Haematology (BCSH) has published a document to provide healthcare professionals, including primary care dental practitioners, with clear guidance on the management of patients on oral anticoagulants requiring dental surgery.

The key recommendations made are:

- The risk of significant bleeding in patients on oral anticoagulants and with a stable INR in the therapeutic range 2-4 (i.e. <4) is very small and the risk of thrombosis may be increased in patients in whom oral anticoagulants are temporarily discontinued. Oral anticoagulants should not be discontinued in the majority of patients requiring out-patient dental surgery including dental extraction
- For patients stably anticoagulated on warfarin (INR 2-4) and who are prescribed a single dose of antibiotics as prophylaxis against endocarditis, there is no necessity to alter their anticoagulant regimen
- The risk of bleeding may be minimised by:
 - The use of oxidised cellulose (Surgicel) or collagen sponges and sutures
 - 5% tranexamic acid mouthwashes used four times a day for 2 days
NOTE: The Guidance notes that 5% tranexamic acid mouthwash is not readily available in primary care
- For patients who are stably anticoagulated on warfarin, a check INR is recommended 72 hours prior to dental surgery
- Patients taking warfarin should not be prescribed non-selective NSAIDs and COX-2 inhibitors as analgesia following dental surgery

Vitamin D alone may not be enough to prevent hip fractures

A complex analysis of trial data suggests that vitamin D supplementation may only reduce the risk of hip fracture when calcium supplements are given with it¹. The authors of the paper note that both calcium and vitamin D are important in the maintenance of bone strength, but that it is uncertain whether the vitamin alone is sufficient to prevent fractures. There are limited trial data comparing the two directly: they have therefore carried out meta-analyses to summarise the literature and from these, carry out indirect comparisons to clarify the role of each. Indirect comparisons of pooled data can, if adjusted by a common control, provide evidence about the relative efficacy of two treatments that have not been directly compared.

The two analyses performed, of vitamin D alone, and vitamin D plus calcium, both compared active to placebo or no treatment. Data were derived from a comprehensive literature search for randomised controlled trials that examined the relative risk of hip fracture in men, postmenopausal women, or both, given vitamin D with or without calcium, vs. placebo or no treatment. Primary outcome was relative risk of hip fracture in patients receiving the supplement vs. control.

Vitamin D alone had no significant effect on hip fracture (relative risk 1.10, 95% CI 0.98 to 1.36, p=0.38). Vitamin D plus calcium, however, reduced hip fracture risk by about a fifth (RR 0.82, 95% CI 0.71 to 0.94, p=0.0005). The adjusted indirect comparison of the pooled estimates suggests that the combination reduces the risk by about a quarter compared to vitamin D alone (RR 0.75, 95% CI 0.58 to 0.96, p=0.021).

The authors conclude from their analysis that vitamin D given alone does not reduce hip fractures. This reflects the outcome of most of the included trials. Combined supplementation with vitamin D and calcium however, seems to have a clear benefit. The combination reduces hip fractures by about a fifth compared to placebo or no treatment, and a quarter compared to vitamin D alone. They note that this result is consistent with the close physiological relationship between vitamin D and calcium metabolism. Based on the results, daily doses should be 800 units vitamin D plus 1,000 to 1,200mg elemental calcium. This is what we have recommended for a number of years.

1. J Clin Endocrinol Metab 2007; 92: 1415-23