

# Medicines Dispatch

A digest of current literature on medicines,  
prescribing and related issues

*Medicines Dispatch* aims to provide a literature alerting service for colleagues, particularly those who not have ready access to a medical library. Comments and opinions on the papers reviewed are those of the Editor alone. Colleagues are recommended to refer to the original journals for further information.



## In the Journals...

### Pharmacoeconomics

This, the second paper in a series which examines pharmacoeconomic methods, looks at one of the main four evaluation methods in health economics – cost-minimisation analysis. This is the appropriate form of economic analysis to use if two drugs have the same clinical effect. However, true equivalence studies are rare in the literature. The critical issue in cost-minimisation analysis is determining equi-effective doses for the drugs being studied.

Further papers in this series will deal with cost-effectiveness, cost-utility and cost-benefit analysis.

Newby D and Hill S Use of pharmacoeconomics in prescribing research. Part 2: cost-minimisation analysis – when are two therapies equal? *Journal of clinical Pharmacy and Therapeutics* 2003; 28: 145-50

### Safety of OTC medicines

The OTC marketing of loratadine in the USA was approved by the FDA in November 2002. However, concerns have been expressed over the OTC availability of this drug. Some clinicians believe that OTC use of loratadine may delay diagnosis and treatment of conditions that would be best treated with other agents, such as inhaled steroids. The authors of the editorial are also concerned over the problem of the cardiovascular safety of loratadine, which they consider is still not resolved. OTC availability of ranitidine is also mentioned, with a number of hypothetical scenarios where there could be problems. The authors wish to 'raise consciousness about ...these infrequent but potential dangers and to raise questions about the evidence of safety considered when drugs are approved for OTC status'.

Shader RI and Greenblatt DJ The safety of over-the-counter drugs: some reflections and unanswered

questions *Journal of Clinical Psychopharmacology* 2003; 23: 111-2

### Interpreting Incomplete Data in Studies of Diet and Weight Loss

Although most physicians recommend low-fat diets, low-carbohydrate diets such as the Atkins diet have remained very popular for many years. There are very few scientific studies however that have evaluated the long-term effects of these diets on weight and lipid levels. In this issue of the *Journal*, results from two randomized trials comparing carbohydrate-restricted diets with fat-restricted diets are reported. Foster et al. enrolled 63 obese men and women in a 12-month study of a low-carbohydrate, high-protein, high-fat diet. Samaha et al. report results of a six-month study of a carbohydrate-restricted diet in 132 severely obese subjects (with a body-mass index of at least 35). In both trials, the participants achieved limited weight loss, with evidence of rebound over the course of the trial. The average weight loss was greater in the low-carbohydrate groups than in the low-fat groups, but the difference was no longer significant at 12 months in the trial in which follow-up lasted that long. Finally, the weight loss was small relative to the amount of excess weight carried by these obese subjects. Unfortunately, large percentages of participants were lost to follow-up and the investigators did not follow participants systematically after they discontinued the study therapy which is not in accordance with good clinical trial practice.

Ware JH Interpreting Incomplete Data in Studies of Diet and Weight Loss *New England Journal of Medicine* 2003; 348: 2136-2137 (22 May)

## BNF Chapter 2

### Chest pain and ischaemic heart disease in primary care

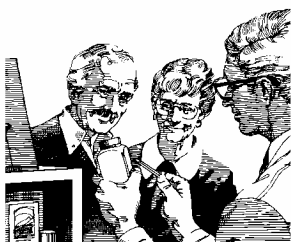
Little is known about the incidence of ischaemic heart disease (IHD) among patients consulting their GP for chest pain, although chest pain is the main symptom at first presentation with IHD. In this study, in three primary health care centres in Sweden, the investigators set out to estimate the occurrence of IHD among patients consulting for

chest pain, to study the results of the bicycle exercise test and to estimate the incidence of IHD in the population. All patients without a current diagnosis of IHD, but who presented to their GP with a new episode of chest pain, were included in the study. Out of 38,075 GP consultations, 577 (1.5%) were for chest pain. IHD was diagnosed in 41 (8%) of the chest pain patients. The diagnosis of IHD was excluded in 441 patients (83%) and was uncertain in 50 (9%), the later requiring further investigation. By combining data from primary and hospital care, the authors estimated the incidence of IHD in their population as 6.5 diagnosed per 1,000 adult inhabitants per year. They concluded that the incidence of a new episode of chest pain bringing the patient to the GP was low.

Nilsson S et al Chest pain and ischaemic heart disease in primary care  
British Journal of General Practice 2003; 53: 378-82

### Cardiovascular drugs are under prescribed for those with diabetes

This population study looked at the extent to which cardiovascular therapies are prescribed in primary care to patients with diabetes, compared to those without diabetes. All patients receiving a prescription for any diabetic therapy (8,523 patients) and those receiving no such therapies (145,756) during a one-year period in the Eastern Regional Health Authority area of Ireland were identified. A sub-set of patients receiving nitrates, a marker for ischaemic heart disease (IHD), was also identified (14,682 patients). Odds ratio and 95% confidence intervals for the prescribing of cardiovascular therapies to those with and without diabetes were calculated. Results indicated that the proportion of those with diabetes and IHD who were prescribed secondary preventative therapies was 37.3% for statins, 55.3% for ACE inhibitors, 34.7% for  $\beta$ -blockers, 73.3% for aspirin, 4.4% for angiotensin-II receptor blockers and 2.5% for fibrates. The adjusted odds ratio for prescribing in those with diabetes compared with those without were 1.44 for statins, 3.09 for ACE inhibitors, 0.82 for  $\beta$ -blockers, 1.23 for aspirin, 1.47 for angiotensin-II receptor blockers, and 1.43 for lipid lowering fibrates. The investigators concluded that, although the greater rate of prescribing for diabetic patients was, as expected, higher than for those without diabetes, the proportion of patients with diabetes, particularly those who also had established IHD, prescribed cardiovascular therapy was considerably below that recommended in both local and international guidelines.



Bennett KE et al Under-prescribing of cardiovascular therapies for diabetes in primary care European Journal of Clinical Pharmacology 2003; 58: 835-41

### The HOPE study – what impact on ACE inhibitor usage?

The HOPE (Heart Outcomes Prevention Study) trial showed that ramipril benefits patients at high risk of cardiovascular disease. The study reported in this paper examined usage and costs of ACE inhibitors in Canada before and after publication of HOPE. Data on sales of ACE inhibitors to both community and hospital pharmacies in three provinces of Canada (British Columbia, Quebec and Ontario) were examined for the period 1985 – 2001. Ten drugs were examined. Captopril, the first, was introduced in Canada in 1985. Prescription numbers had increased steadily over the study period. Usage of ramipril increased dramatically from 1999 and eventually represented 9.2% of all sales of ACE inhibitors. [The authors conclude that, whilst usage of the other ACE inhibitors increased steadily over the study period, usage of ramipril increased markedly following publication of the HOPE study.

Hemels MEH et al HOPE study impact on ACE inhibitor use  
Annals of Pharmacotherapy 2003; 37: 640-5

## BNF Chapter 4

### Efficacy and safety of olanzapine in geriatric psychosis

This study aimed to assess the effectiveness and safety of olanzapine in 94 elderly ( $\geq 65$ ) psychiatric patients with psychotic symptoms. Clinical assessment was conducted at baseline and at four weeks after commencing treatment with olanzapine, using the Brief Psychiatric Rating Scale (BPRS) and the Clinical Global Impression Improvement (CGI-I). After four weeks, a mean of 52.2% reduction in the BPRS was observed, and 91% of the patients experienced mild to substantial improvement in CGI-I. All patients were monitored for adverse effects, the most common of which were somnolence, dizziness and weakness of legs or bradykinesia. However, body weight and fasting triglycerides and sugar levels were significantly elevated after olanzapine treatment. The authors consider that it is reasonable to consider olanzapine to be efficacious for geriatric patients with psychosis. The dosage can be diagnosis-dependent.

Hwang J-P et al The efficacy and safety of olanzapine for the treatment of geriatric psychosis Journal of Clinical Psychopharmacology 2003; 23: 113-8

### Economic evaluation of antidepressants

This systematic review looked at whether experimental and observational pharmaco-economic

analyses of antidepressant drugs support the choice of one of the SSRIs or newer antidepressants as first-line treatment for patients with major depression.

Experimental data were found to indicate that tricyclic antidepressants are equivalent to SSRIs in terms of total expenditure. Database analyses failed to show any significant difference in total costs between SSRIs and tricyclics. Taken together, available pharmacoeconomic analyses indicate that SSRIs and tricyclic antidepressants have 'similar cost-effectiveness in the health care systems where these comparisons have been made'.

Barbui C et al Economic evaluation of antidepressive agents: a systematic critique of experimental and observational studies *Journal of Clinical Psychopharmacology* 2003; 23: 145-54

### **'Don't demonise DOPA'**

There is now a wide choice of therapies for Parkinson's disease and this raises several questions, such as when should the newer drugs be used, and what is the place of levodopa in treating older patients? In this editorial, MacMahon considers the evidence for using direct dopaminergic monotherapy. Drugs such as ropinirole, pramipexole and pergolide appear to show slightly less efficacy than levodopa in the relief of symptoms but with the advantage of significant reduction in motor complications. With many patients now having considerable life expectancies following their diagnosis of Parkinson's disease, choice of therapy is important. Agonists can be considered in newly diagnosed cases, but in view of the inevitable progression of the disease and the continued value of levodopa, the author urges that the latter should not be 'demonised'.

MacMahon DG The initial drug treatment of older patients with Parkinson's disease - consider an agonist, but don't demonise dopa *Age and Ageing* 2003; 32: 244-5

### **Oral topiramate for treatment of alcohol dependence: a randomised controlled trial.**

Although current psychosocial treatments for alcohol abuse and dependence have been useful in reducing alcohol use and alcohol-related morbidity and mortality, they are not always completely successful for all patients. As an alternative treatment, Bankole Johnson and colleagues evaluated topiramate, a sulphamate fructopyranose derivative, to determine whether it antagonised alcohol's rewarding effects.

So they performed a double-blind randomised controlled 12-week clinical trial comparing oral topiramate and placebo for treatment of 150 individuals with alcohol dependence

Of these 150 individuals, 75 were assigned to receive topiramate (escalating dose of 25-300 mg per day) and 75 had placebo as an adjunct to weekly standardised medication compliance management. Primary efficacy variables were: self-reported

drinking (drinks per day, drinks per drinking day, percentage of heavy drinking days, percentage of days abstinent) and plasma  $\gamma$ -glutamyl transferase, an objective index of alcohol consumption. The secondary efficacy variable was self-reported craving.

At the end of the study, participants on topiramate, compared with those on placebo, had 2.88 (95% CI -4.50 to -1.27) fewer drinks per day ( $p=0.0006$ ), 3.10 (-4.88 to -1.31) fewer drinks per drinking day ( $p=0.0009$ ), 27.6% fewer heavy drinking days ( $p=0.0003$ ), 26.2% more days abstinent ( $p=0.0003$ ), and a log plasma  $\gamma$ -glutamyl transferase ratio of 0.07 (-0.11 to -0.02) less ( $p=0.0046$ ). Topiramate-induced differences in craving were also significantly greater than those of placebo, of similar magnitude to the self-reported drinking changes, and highly correlated with them.

The authors concluded that Topiramate (up to 300 mg per day) is more efficacious than placebo as an adjunct to standardised medication compliance management in treatment of alcohol dependence. In the accompanying Commentary, Robert Swift notes that Johnson and colleagues' results are important because they suggest that "different pharmacotherapies could be targeted at different stages of alcoholism treatment--the initiation of abstinence, the maintenance of early abstinence, or the maintenance of prolonged abstinence".

Johnson B et al Oral topiramate for treatment of alcohol dependence: a randomised controlled trial. *Lancet* 2003; 361: 1677-85 (17 May)

### **Paracetamol or ibuprofen as analgesic after dental surgery**

The effect of a three-day regimen of ibuprofen 600mg four times a day was compared with paracetamol 1g four times a day on acute postoperative swelling and pain and other inflammatory events after third molar surgery. The study group consisted of 36 patients (aged 19-27 years) who were to have surgical removal of bilateral third molars. Patients acted as their own controls, since after one operation they received the ibuprofen regimen, with the paracetamol regimen after the second removal. Swelling was measured objectively with a standardised face bow and the patients scored their pain intensity on a 100mm visual analogue scale. There was no statistically significant difference between the two treatments with respect to acute postoperative swelling or in pain relief on the day of surgery. Two patients developed fibrinolysis of the blood clot (dry socket) with ibuprofen but none did with paracetamol. There was no noticeable difference between treatments with respect to appearance of haematomas/ecchymoses or adverse effects. The authors concluded that a three-day regimen of ibuprofen offered no clinical advantages over paracetamol with respect to alleviation of acute

postoperative swelling and pain after third molar surgery.

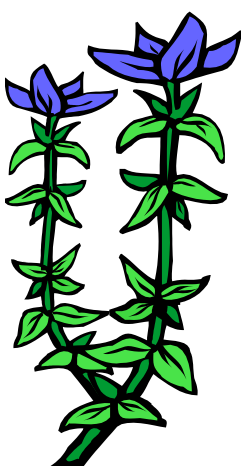
Björnsson GA et al A randomised, double-blind crossover trial of paracetamol 1000mg four times daily vs ibuprofen 600mg: effect on swelling and other postoperative events after third molar surgery *British Journal of Clinical Pharmacology* 2003; 55: 405-12

## BNF Chapter 5

### Improving antibiotic use

Problems with antibiotic resistance led this Veterans' Affairs medical centre to devise a multi-disciplinary intervention program to align usage of vancomycin and fluoroquinolones with the hospital guidelines for use of these agents. The program encouraged early discontinuation of inappropriate vancomycin and fluoroquinolone therapy and to decrease inappropriate duplicate coverage of Gram-negative infections. Following a retrospective review of all antibiotic prescriptions during 1998, new guidelines were drawn up. All requests for vancomycin or fluoroquinolones were then reviewed by a clinical pharmacist. Results indicated a significant reduction of inappropriate use of both groups of drugs. A reduction of 43% was achieved in usage of intravenous vancomycin over the subsequent four years was achieved, along with a reduction of 22% in courses lasting more than five days. The interventions by the clinical pharmacist were deemed successful, with 76% of the recommendations being accepted by the prescribers.

Feucht CL and Rice LB An interventional program to improve antibiotic use *Annals of Pharmacotherapy* 2003; 37: 646-51



## Alternative and complementary therapy

### Quality, safety and efficacy of complementary medicines

This, the second of two papers which review issues regarding complementary medicines, considers evidence for the efficacy of several well-known complementary medicines (herbal medicines,

essential oils, melatonin and dietary supplements such as glucosamine) and discusses issues in pharmacovigilance with complementary medicines. Several herbal preparations, e.g. Kava, have been withdrawn in recent years because of toxicity. Some interactions between complementary medicines and conventional drugs (e.g. the range of drugs with

which St John's wort interacts) are well known. However, for many other preparations such evidence is lacking.

Barnes J Quality, safety and efficacy of complementary medicines: fashions, facts and the future. Part II: Efficacy and safety *British Journal of Clinical Pharmacology* 2003; 55: 331-40

## Adverse reactions

### Do statins increase the risk of breast cancer?

This study, based on a cohort of patients in Saskatchewan, investigated the possibility of an association between statins and breast cancer. Women who received at least one statin prescription between 1989 and mid-1997 were included in the study group (13,592 women), which was matched by age and sex with a group of 53,880 non-users of statins. Patients in both groups were followed for up to 8 ½ years. Relative rates of breast cancer were estimated and stratified by age, statin exposure time and prior hormone use. A total of 879 cases of breast cancer were identified. Results indicated that statin use was not associated with breast cancer risk in women under 55 years. However, amongst women aged over 55, the relative risk for breast cancer was 1.15. Stratified analysis revealed increases in risk in short-term statin users and in statin users with long-term exposure to hormone replacement therapy.

Beck P et al Statin use and the risk of breast cancer *Journal of Clinical Epidemiology* 2003; 56: 280-5

### Skin breakdown and blisters from senna-containing laxatives in young children

This paper looked at the clinical outcomes of unintentional ingestion of senna-containing laxatives in children under five years. All such incidents recorded at six poison centres in the USA over a nine-month period were studied. During this period, 111 cases were recorded, of whom 52 were under two years old. Nineteen children experienced no diarrhoea; four were lost to follow-up and 88 cases were evaluated by telephone discussion with parents. Of these, 29 (33%) experienced severe nappy rash and ten children had blisters and skin sloughing. These reactions were worse in children wearing nappies. The authors concluded that unintentional ingestion of senna-containing laxatives by young children may potentially cause severe nappy rash, blisters and skin sloughing. [All medicines, including OTC, should be kept well away from children!! – Ed.]

Spiller HA et al Skin breakdown and blisters from senna-containing laxatives in young children *Annals of Pharmacotherapy* 2003; 37: 636-9

### Zolpidem-induced distortion in visual perception

A 50-year old woman took one dose of zolpidem 10mg for insomnia along with two paracetamol

tablets at bed-time and within 20 minutes she developed distortion of visual perception (the shapes of objects appeared crooked to her). The effect lasted for about 30 minutes and then her vision returned to normal. She had never taken zolpidem before and had had no such experience in the past. The authors state that there have been 21 case reports of zolpidem-related psychotic symptoms; however, the mechanism whereby such effects are produced is not known. Clinicians should be aware of the potential of zolpidem to cause visual disturbances.

Huang C-L et al Zolpidem-induced distortion in visual perception  
Annals of Pharmacotherapy 2003; 37: 683-6

## Drug Interactions

### Psychiatric drugs and alcohol

This overview looks at the interaction of alcohol with antidepressants and antipsychotics. Both acute and chronic alcohol ingestion combined with psychiatric drugs may lead to several clinically significant toxicological interactions. The metabolism of these groups of drugs is generally, but not always, delayed by acute alcohol ingestion. Drugs undergoing metabolism may also show increased metabolic clearance with chronic alcohol ingestion. The net effect of alcohol ingestion when psychiatric drugs are being taken may be influenced by a variety of factors - internal (disease, age, gender), external (e.g. diet) and pharmacokinetic.

Tanaka E Toxicological interactions involving psychiatric drugs and alcohol: an update  
Journal of Clinical Pharmacy and Therapeutics 2003; 28: 81-95

### Phenytoin – diazepam interaction

This case report is of a 44 year old man who presented to the emergency room with headache, nystagmus, diplopia and ataxia. He was on a stable regimen of phenytoin, phenobarbitone and lamotrigine which had been unchanged for five months. Phenytoin serum concentration had been measured two weeks previously and found to be 8 µg / l. Two days prior to admission he had been prescribed amoxicillin and diazepam. The serum phenytoin concentration measured on admission to the hospital was found to be 37 µg / l. Both diazepam and phenytoin were stopped and the symptoms resolved.

The authors comment that the literature on potential interactions between diazepam and phenytoin are conflicting. Phenytoin is known to induce the metabolism of drugs by CYP2C, CYP2D and CYP3A, but its own metabolism may be altered by drugs influencing CYP2C9 or CYP2C19, such as diazepam.

Murphy A and Wilbur K Phenytoin – diazepam interaction  
Annals of Pharmacotherapy 2003; 37: 659-63



## Review articles

Staesson JA et al **Seminar - essential hypertension** Lancet 2003; 361: 1629-41

*Essential hypertension is a lasting increase in blood pressure. It is a chronic condition, usually related to age, which often involves cardiovascular and renal complications. The pathophysiology of essential hypertension depends on the primary or secondary inability of the kidney to excrete sodium at a normal blood pressure. The central nervous system, endocrine factors, the large arteries and the microcirculation all have roles in this complex yet very common disorder. This review covers epidemiology, diagnosis, pathophysiology, sodium and fluid balance, genetic factors and clinical interventions. The latter covers lifestyle changes and the range of antihypertensive drug treatments now available.*

Jessup M and Brozena S **Heart Failure**  
New England Journal of Medicine 2003; 348:2007-2018 (15 May)

Bolton-Maggs P and Pasi KJ **Haemophilias A and B** Lancet 2003; 361: 1801-09 (24 May)

Hardman P et al **Polycystic ovary syndrome and endometrial carcinoma** Lancet 2003; 361: 1810-12 (24 May)

## Department of negative results

*Knowing that something doesn't work, or doesn't do something that we might reasonably have expected, can be as important as a 'highly significant' positive result.*

### Fish consumption - no effect on incidence of CHD and all-cause mortality?

The study investigates the relationship between fish consumption, all-cause mortality and incidence of coronary heart disease (CHD) in a cohort of almost 9,000 men and women aged 30-70 years and living in Copenhagen County, Denmark. The subjects were followed from 1982-92 until 2000 for all-cause mortality and until 1997 for first admission to hospital for CHD, or death from CHD. Information on fish consumption was obtained from a self-administered questionnaire. Analysis of results indicated that, after adjustment for confounders, there was no evidence of an inverse association between fish consumption and all-cause mortality or incident CHD. However, among subjects at high risk

of CHD, there was a non-significant inverse relationship between fish intake and CHD morbidity; however there were relatively few subjects in this group. The authors concluded that their data provide no evidence for a protective effect of fish consumption on all-cause mortality or incident CHD in the population as a whole, but they could not exclude the possibility that frequent consumption of fish benefits those at high risk of CHD.

Osler M et al. No inverse association between fish consumption and risk of death from all-causes, and incidence of coronary heart disease in middle-aged, Danish adults. *Journal of Clinical Epidemiology* 2003; 56: 274-9

### **Did you see....?**

*We assume that most readers will have access to the British Medical Journal, either as a paper copy or on-line ([www.bmj.com](http://www.bmj.com)). This is a reminder of interesting articles that have appeared in recent issues.*

Manes G et al. **Empirical prescribing for dyspepsia: randomised controlled trial of test and treat versus omeprazole treatment** BMJ 2003; 326: 1118 (24 May)

*Eradication treatment allows resolution of symptoms in a large number of patients with dyspepsia and reduces the endoscopic workload.*

*After a trial of omeprazole, symptoms recur in nearly every patient. Such treatment is also likely to mask an appreciable number of peptic ulcers and cases of oesophagitis.*

Verdon F et al. **Iron supplementation for unexplained fatigue in non-anaemic women: double blind randomised placebo controlled trial** BMJ 2003; 326: 1124 (24 May)

*Non-anaemic women with unexplained fatigue may benefit from iron supplementation.*

Hawkins G et al. **Stepping down inhaled corticosteroids in asthma: randomised controlled trial** BMJ 2003; 326: 1115 (24 May)

*By adopting a stepdown approach to the use of inhaled steroids at high doses in asthma a reduction in the dose can be achieved without compromising asthma control.*

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**Published by Trent Medicines Information Service** Leicester Royal Infirmary, Leicester LE1 5WW

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