best practice

Issue 4

April 2007

PPIs

Warfarin Interactions

Herceptin

bpac nz
better medicine

Contact us:

Mail P.O. Box 6032 Dunedin
Email editor@bpac.org.nz
Free-fax 0800 27 22 69

Best Practice Journal (BPJ)
ISSN 1177-5645

BPJ is published and owned by bpac^{nz}
Level 8 10 George Street Dunedin

BPJ Issue 4 April 2007

Bpac^{nz} is an independent organisation that promotes health care interventions which meet patients' needs and are evidence based, cost effective and suitable for the New Zealand context.

We develop and distribute evidence based resources which describe, facilitate and help overcome the barriers to best practice.

Bpac^{nz} has four shareholders:

Procare Health, South Link Health, IPAC and The University of Otago

Bpac^{nz} is currently funded through contracts with PHARMAC and DHBNZ.

Cover Story

Easily the most photographed site in all of Iceland, The Blue Lagoon is perhaps the most supernatural looking body of water on Earth. The temperature in the swimmable area averages about 40°C, and the soothing, mineral-rich water is rumoured to have curative powers for functional dyspepsia.

Though the lagoon looks like something born from Iceland's otherworldly landscape, it is actually man made. It was created by run-off from the Svartsengi power plant, which pumps up the geothermally heated water from a full mile below the surface. After being used to generate both heat and electricity, the excess (which is absolutely clean) is ejected into the lagoon.

Contents

Contents

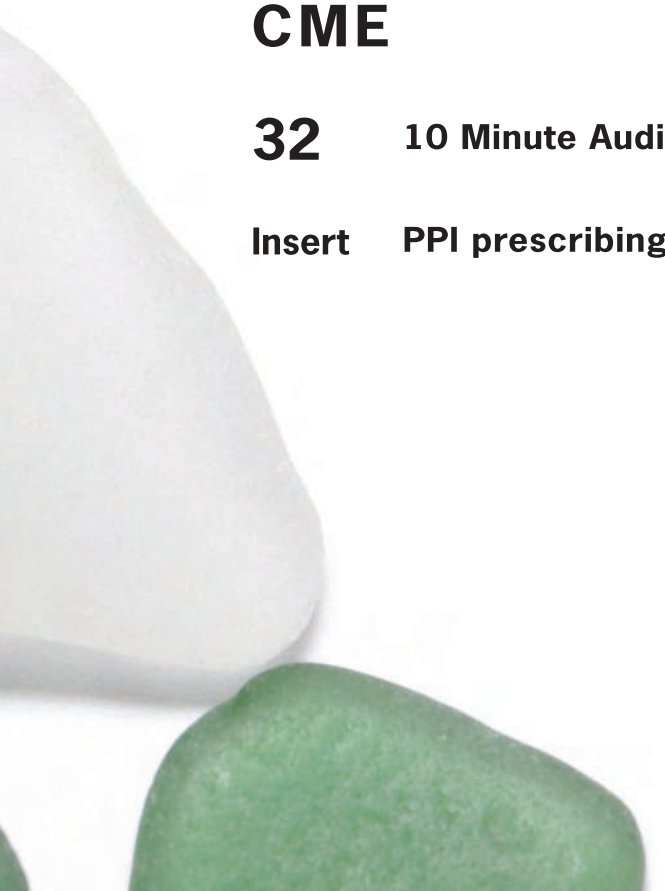
Access best practice online

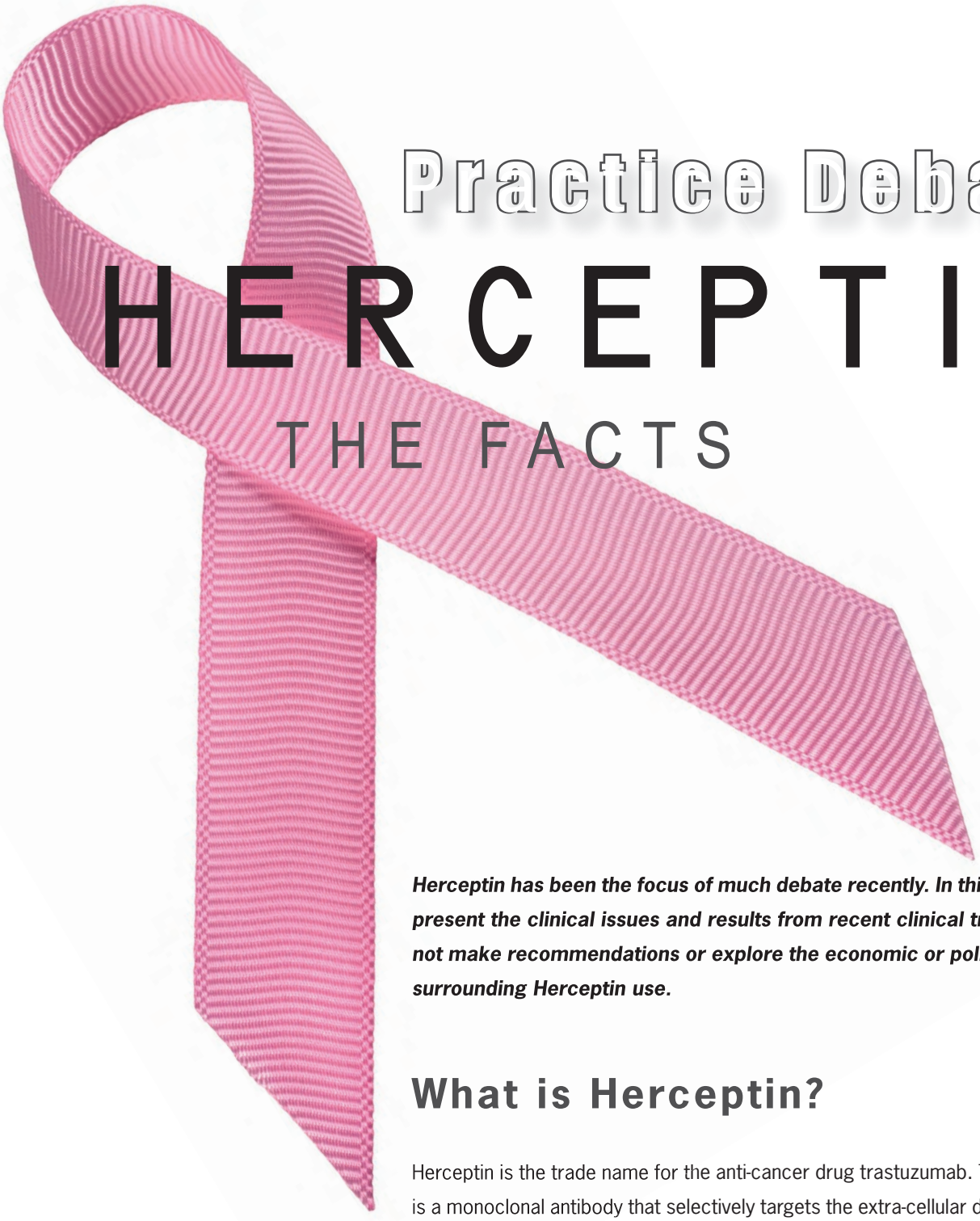
www.bpac.org.nz

Contents

Essentials

CME





Practice Debate

HERCEPTIN

THE FACTS

Herceptin has been the focus of much debate recently. In this article we present the clinical issues and results from recent clinical trials. We do not make recommendations or explore the economic or political issues surrounding Herceptin use.

What is Herceptin?

Herceptin is the trade name for the anti-cancer drug trastuzumab. Trastuzumab is a monoclonal antibody that selectively targets the extra-cellular domain of the human epidermal growth factor receptor 2 protein (HER2).[1] An over expression of HER2 is seen in approximately 15%–20% of invasive breast cancers.[2] This causes an increase of HER2 protein on the surface of the tumour cells, activating the HER2 receptor.[1] Women with tumours that over-express HER2 have been found to have a decreased likelihood of recurrence-free survival and overall survival, compared to women with HER2 negative breast cancer.[3] Trastuzumab

inhibits the proliferation of tumour cells that over-express HER2. The exact mechanism by which it does this is unclear. It appears that trastuzumab attaches itself to the HER2 protein, contributes to apoptosis (cell death), reduces HER2 expression, alters various cellular cycles and potentiates the effects of chemotherapy. Trastuzumab may also have extracellular effects, e.g, mediating immune recognition.[2]

What is Herceptin indicated for?

Herceptin is indicated for the treatment of women with metastatic breast cancer who have tumours that over-express HER2. It is used alone for patients who have already received one or more chemotherapy regimens or in combination with taxanes (e.g. paclitaxel) for those who have not received chemotherapy.

Herceptin can also be used for the treatment of HER2 positive early breast cancer in women who have a normal Left Ventricular Ejection Fraction (LVEF) following surgery (lumpectomy or mastectomy) and chemotherapy.

What is the treatment regimen for Herceptin?

Herceptin is administered by intravenous infusion once a week. New evidence has shown that a three-weekly dosing schedule is also effective.[4]

There are currently three regimens that have been investigated for adjuvant treatment of HER2 positive early breast cancer;

- Herceptin for 12 months after chemotherapy (anthracycline +/- taxane)
- Herceptin for 12 months in combination with chemotherapy (taxane), and after anthracycline
- Herceptin for 9–10 weeks in combination with chemotherapy (taxane), and before anthracycline

How effective is Herceptin?

Advanced breast cancer

The use of Herceptin in metastatic breast cancer is generally accepted by most health professionals. Its effectiveness was investigated in a randomised controlled trial (n=469) which compared standard chemotherapy with and without trastuzumab. It was found that the addition of trastuzumab to the chemotherapy regimen resulted in a longer time to disease progression (7.4 vs. 4.6 months), a longer duration of response (9.1 vs. 6.1 months) a lower death rate at one year (22% vs. 33%) and longer survival (25.1 vs. 20.3 months) than chemotherapy alone. Cardiac toxicity was observed in 27% of patients receiving trastuzumab.[5]

In a case series (n=222) investigating the use of Herceptin as monotherapy, 4% of women experienced a complete tumour response to treatment and 12% experienced a partial tumour response i.e. trastuzumab demonstrated anti-tumour effects. The median duration of survival was 13 months for all women with HER2 positive metastatic breast cancer and 16 months in a subgroup with HER2 at 3+ levels.[6]

Age does not appear to be a factor in the effectiveness of Herceptin treatment.[4]

Early stage breast cancer

Much of the evidence for the use of Herceptin in early breast cancer has been gathered from five major clinical trials. These trials have shown that Herceptin reduces the risk of recurrence in women with HER2 positive early breast cancer. Table 1 summarises the characteristics and results of the major trials.

Table 1: Summary of clinical trials investigating the use of Herceptin in early HER2 positive breast cancer.[11,15]

		HERA (Europe)	N9831 (arm C) and NSABP B31 joint analysis (USA)	BCIRG 006 (USA)	FinHer (Finland)
Trial size (n)		3401	3351	2148	231
Median follow-up years		2	2	3	3
Trastuzumab schedule		12 months, after anthracyclines +/- taxanes	12 months, concurrent with anthracyclines and taxanes	12 months, concurrent with anthracyclines and taxanes, +/- carboplatin	9 weeks, concurrent with anthracyclines +/- taxanes
Recurrence or death from any cause (%)	*Trastuzumab*	218 (12.8%)	133 (8.0%)	128 (11.9%)	12 (10.4%)
	Control	321 (18.9%)	261 (15.5%)	192 (17.9%)	27 (23.3%)
	Hazard ratio (95% CI)	0.64 (0.54–0.76)	0.48 (0.39–0.59)	0.61 (0.48–0.78)	0.42 (0.21–0.83)
All-cause mortality (%)	*Trastuzumab*	59 (3.5%)	62 (3.7%)	49 (4.6%)	6 (5.2%)
	Control	90 (5.3%)	92 (5.5%)	80 (7.5%)	14 (12.1%)
	Hazard ratio (95% CI)	0.66 (0.47–0.91)	0.67 (0.48–0.93)	NR	0.41 (0.16–1.08)
Serious, life threatening or fatal cardiac events (%)	*Trastuzumab*	10 (0.6%)	51 (3.1%)	based on 2 year data 25 (2.3%)	0
	Control	1 (0.1%)	5 (0.3%)	10 (1.0%)	0
	Relative risk (95% CI)	9.97 (1.28–77.80)	10.38 (4.15–25.91)	2.46 (1.19–5.09)	
Number Needed to Treat (NNT)	Calculated NNT (mortality)	55.6*	55.6	34.5	14.5
	Calculated NNT (Disease free survival)	16.4	13.3	16.7	7.8

* A NNT of 55, for example, means that one extra woman will be alive for every 55 treated for the period over which the NNT was calculated, in this case two years.

The Herceptin Adjuvant (HERA) Trial is one of several large trials which tested the efficacy of trastuzumab administered over a 12 month period. Results of analysis after two years follow up showed that trastuzumab, given once every three weeks after chemotherapy, achieved a significant improvement in disease-free survival compared with women treated with chemotherapy alone.[7] The joint analysis of two other trials (N9831 and B-31) showed a significant improvement in disease-free survival with trastuzumab administered concurrently with paclitaxel, every one or three weeks after chemotherapy, compared with the same chemotherapy schedule alone. Analysis of the BCIRG trial has also shown a disease-free survival benefit when trastuzumab is administered with docetaxel after chemotherapy, or with docetaxel and carboplatin.[7]

Because of the improved disease-free survival with concurrent treatment in the joint analysis of **the B31 and N9831 trials**,[8] an unplanned interim analysis of **the N9831 trial** was undertaken to assist the management of patients receiving sequential treatment in the trial.[9] The analysis compared the results of patients in the sequential Herceptin treatment arm with those in standard care (no Herceptin) and concurrent treatment arms. The results of this analysis (Table 2) showed that a Herceptin treatment regimen received concurrently with paclitaxel for 12 weeks, followed by an additional 40 weeks of Herceptin treatment provided greater disease free and overall survival benefit than a sequential regimen of 12 weeks of paclitaxel, followed by 52 weeks of Herceptin.[9]

Table 2: Concurrent vs Sequential Treatment: Unplanned interim analysis of the N9831 trial, comparing Arm B (sequential) and Arm C (concurrent).[9]

Pairwise comparison	Disease Free Survival		Overall Survival	
	*Number of events**	*Hazard Ratio (95% CI)*	*Number of events (%)*	*Hazard Ratio (95% CI)*
Concurrent vs. control**	140 (54 vs. 90)	0.55 (CI not reported)	(not reported for N9831 alone)	(not reported for N9831 alone)
Sequential vs. control	220 (103 vs. 117)	0.87 (0.67 – 1.13)	79	0.85 (0.55 – 1.33)
Concurrent vs. sequential	137 (53 vs. 84)	0.64 (0.46 – 0.91)	56	0.74 (0.43 – 1.26)

Notes

* Numbers of events differ between comparisons because of differences between times of analysis and censoring of some patients' results.

** The results for concurrent treatment vs. control are for trials B31 and N9831 jointly and do not differentiate between the two trials; hence separate results are not available for N9831.

Control = AC → T (12 weeks)

Concurrent = AC → T + H (12 weeks) → H (40 weeks)

Sequential = AC → T (12 weeks) → H (52 weeks)

AC = Anthracycline T = Taxane (Paclitaxel) H = Herceptin

The FinHer Trial involved an alternative treatment sequencing and duration to the commonly used 12-month period. Results from FinHer show that trastuzumab administered concurrently with a taxane, over a nine week treatment period, before standard chemotherapy (including anthracycline) was effective in increasing the recurrence-free survival rate among women with HER2 positive early breast cancer. No significant cardiac toxicity was observed with this shorter treatment period and this group had fewer decreases in cardiac function (LVEF) than the control group.[10] In addition the FinHer study had longer follow-up than other studies.

However this study only included 116 women treated with Herceptin and it is uncertain whether a similar result for adverse cardiac effects would be seen in a larger group of patients, especially as a wider range of pre-existing cardiac disease was excluded from the study, compared to the other trials.

Although a larger scale trial is needed the small size of the FinHer study indicates an appreciable effect, where disease-free survival was statistically significant, despite the small number of patients.[11]

The evidence of effectiveness of using Herceptin in early breast cancer has so far centred on disease-free survival. Long-term survival has yet to be adequately assessed due to the number of follow-up years since the major trials commenced. Caution is warranted in applying the results of these trials to the whole population. There may be some variability in baseline risk of recurrence of breast cancer depending on the nature of the chemotherapy regimen used prior to treatment with Herceptin. In addition long term risks of cardiac toxicity have yet to be evaluated. In some groups of women the side effects associated with trastuzumab may outweigh the benefit of treatment.[12]

What are the adverse effects associated with Herceptin?

Approximately 50% of patients can expect to experience an adverse reaction to treatment. Most often these are relatively minor infusion-related effects such as fever or chills. There have been infrequent reports of serious adverse reactions including dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress. Most adverse reactions can be treated with supportive therapy such as oxygen, beta-agonists and corticosteroids. In rare cases adverse effects can result in death.[4]

The most significant adverse effect associated with Herceptin is cardiac toxicity. After one year sequential trastuzumab therapy in the HERA study 0.6% of patients had severe congestive heart failure (CHF) and 2% had symptomatic CHF. In comparison 0.1% of control patients had symptomatic CHF and none had severe CHF. In addition 3% of patients who received Herceptin and 0.5% of controls had a significant decrease in LVEF. Seventy-two patients (4%) that were receiving Herceptin withdrew from the study due to cardiac problems.[7] After a median follow up of two years in the HERA study, it has been calculated that trastuzumab will raise the absolute risk of symptomatic CHF by 2% and by 5% including sub-clinical harms.

For symptomatic CHF the number needed to harm (NNH) is 51 and the NNH for the risk of all cardiac harms is 20. This compares with the NNT of 56.[7]

In the joint analysis of B-31 and N9831, the three year cumulative incidence of severe cardiac events (severe (grade 3/4) heart failure or cardiac death) was 4.1% and 2.9% (respectively) for patients receiving concurrent Herceptin, and 0.8% and 0% for controls. Overall results for the combined trials were not reported. In study B31 34% of the patients in the trastuzumab arm had a significant decrease in LVEF (≥10% decline to below 55%) versus 17% in the control group.[13] Two cardiac deaths occurred during these trials.[14] In the BCIRG study after 3-year's median follow-up 1.9% of patients that received concurrent Herceptin and 0.4% of controls developed CHF (grade 3/4). A LVEF decline (>10%) was seen in 10% of controls and 18% of concurrent Herceptin patients, however no cardiac related deaths occurred.[15] None of the patients in the FinHer trial suffered clinically significant cardiac events or cardiac related death.[10]

What issues still need to be resolved?

There is much evidence in support of the use of Herceptin in both metastatic and early HER2-positive breast cancer. However, the following issues require further investigation:

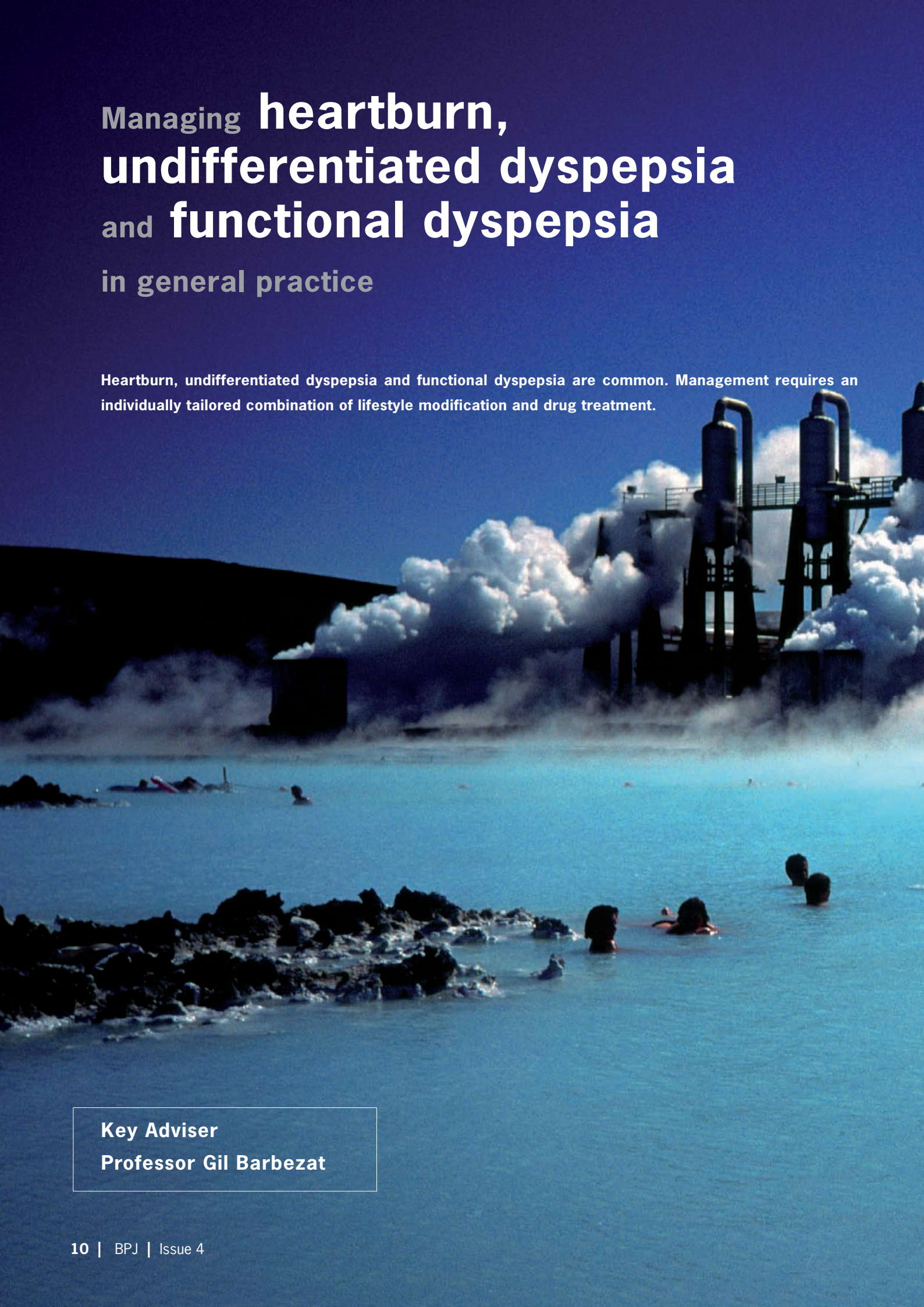
- The optimal scheduling of trastuzumab treatment with different chemotherapy regimens, concurrent with taxanes, pre/post anthracyclines or sequential treatment post chemotherapy
- The comparative clinical effectiveness of 12 months vs shorter treatment periods including assessment of adverse events
- Long-term efficacy follow up and assessment of toxicity
- The risk of recurrence in specific subgroups (e.g. tumours with nodal involvement and with or without hormone receptors)

References

1. National Institute for Health and Clinical Excellence (NICE). Guidance on the use of trastuzumab for the treatment of advanced breast cancer. NICE Technology Appraisal Guidance No. 34, 2002. Available from http://www.nice.org.uk. Accessed February 2007
2. Burstein H. The distinctive nature of HER2-positive breast cancers. N Engl J Med 2005;353(16):1652-54
3. Pritchard K, Shepherd L, O'Malley F, et al. HER2 and responsiveness of breast cancer to adjuvant chemotherapy. N Engl J Med 2006;354(20):2103-111
4. Medsafe. Herceptin. Data Sheet, 2006. Available from http://www.medsafe.govt.nz/Profs/Datasheet/h/Herceptininf.htm. Accessed February 2007
5. Slamon D, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001;344(11):783-92
6. Baselga J, Tripathy D, Mendelsohn J, et al. Phase II study of weekly intravenous trastuzumab (Herceptin) in patients with HER2/neu-overexpressing metastatic breast cancer. Semin Oncol 1999;26(4 Suppl 12):78-83
7. Smith I, Procter M, Gelber R, et al. 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. Lancet 2007;369:29-36
8. Romond E, Perez E, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 2005;353(16):1673-84
9. Perez E. Further Analysis of NCCTG-N9831. Slide presentation ASCO annual meeting, 2005. Available from http://snipurl.com/1d13u. Accessed March 2007
10. Joensuu H, Kellokumpu-Lehtinen P, Bono P, et al. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. N Engl J Med 2006;354(8):809-20
11. Hind D, Pilgrim H, Ward S. Questions about adjuvant trastuzumab still remain. Lancet 2007;369(9555):3-5
12. National Institute for Health and Clinical Excellence (NICE). Trastuzumab for the adjuvant treatment of early-stage HER2-positive breast cancer. NICE Technology Appraisal Guidance No.107, 2006. Available from http://www.nice.org.uk. Accessed February 2007
13. Belgian Health Care Knowledge Centre (KCE). Trastuzumab in early stage breast cancer. KCE reports 2006;34C:vii-viii. Available from http://snipurl.com/1d13s. Accessed March, 2007
14. Ward S, Pilgrim H, Hind D. Trastuzumab for the treatment of primary breast cancer in HER2 positive women: A single technology appraisal. NICE Technology Appraisal Report: University of Sheffield School of Health and Related Research, 2006. Available from http://www.nice.org.uk/page.aspx?o=328487. Accessed February 2007
15. Slamon D, Eiermann W, Robert N, et al. Phase III Trial Comparing AC-T with AC-TH and with TCH in the Adjuvant Treatment of HER2 positive Early Breast Cancer Patients Investigators. Second Interim Efficacy Analysis. . Slide Show Presentation: San Antonio Breast Cancer Symposium, 2006. Available from http://snipurl.com/1d13r

Managing heartburn, undifferentiated dyspepsia and functional dyspepsia in general practice

Heartburn, undifferentiated dyspepsia and functional dyspepsia are common. Management requires an individually tailored combination of lifestyle modification and drug treatment.



Key Adviser
Professor Gil Barbezat

Dyspepsia is a range of symptoms which may indicate significant organic disease but most people with dyspepsia have no underlying pathology and do not seek medical advice

Heartburn is a burning sensation rising from the epigastrium toward the neck.

Dyspepsia is pain or discomfort located in the epigastrium. Associated symptoms may include fullness after meals, bloating, belching, early satiety, anorexia, nausea and vomiting. The symptoms of dyspepsia may be episodic, recurrent or chronic and whilst many symptoms are associated with food this is not always the case.

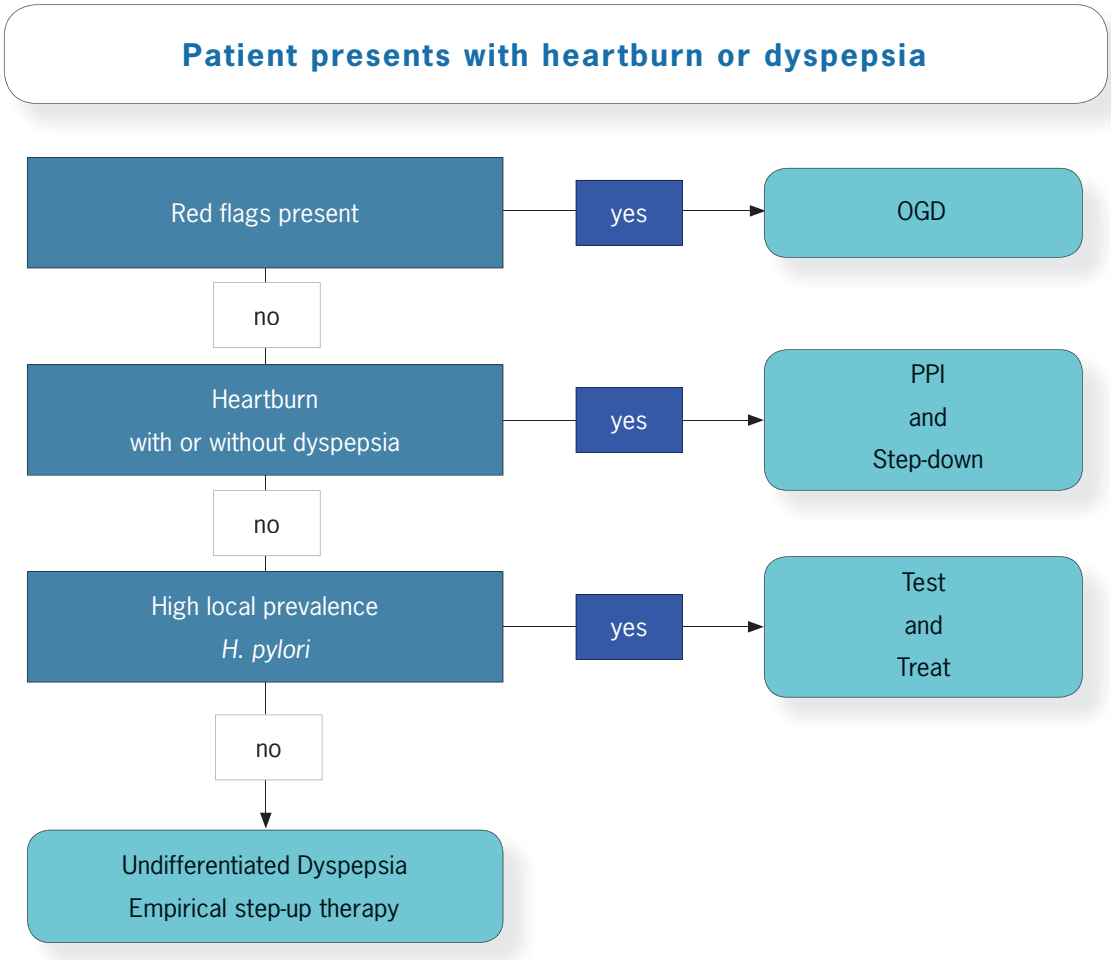
Undifferentiated dyspepsia is dyspepsia that has not been investigated. In a person at low risk of underlying pathology this can be managed empirically without further investigation.

Functional dyspepsia is dyspepsia, which has been investigated and no underlying pathology found.

The management of dyspepsia associated with underlying pathology, e.g peptic ulceration or use of NSAIDs is not discussed in this article.

Key Points

- Red flags are indications for oesophago-gastro-duodenoscopy (OGD)
- People with heartburn or undifferentiated or functional dyspepsia often benefit from modification of lifestyle and drug therapies
- If heartburn is part of the symptom complex, treat initially as gastro-oesophageal reflux disease (GORD) with a proton pump inhibitor (PPI) and step down therapy
- If drug treatment for undifferentiated or functional dyspepsia without heartburn is required an H_2-receptor antagonist (H2RA) is the drug of choice
- In areas of moderate to high prevalence of *H. pylori* consider the need for a test and treat approach
- After the initial control of symptoms encourage people to step down to the lowest effective dose and/or treat symptoms intermittently 'on-demand'
- Review your patients with chronic dyspepsia annually for the appearance of alarm signals and use of aggravating drugs
- Review all patients for on-going requirement for pharmacotherapy, especially PPIs



First check for red flags of significant organic disease

A number of features in the initial history or examination of people with dyspepsia or heartburn increase the likelihood of significant organic disease. These red flags are detailed in Table 1. Red flags are indications for further investigation with OGD. In some cases, such as bleeding or severe dysphagia, this needs to be done immediately.

When there is less urgency, people need to be off PPIs or H2RAs for two weeks prior to OGD as these can mask signs of organic disease. Antacids may be continued.

Table 1: Red Flags

(Adapted from NZGG and Prodigy Guidance[1,2])

The following increase the likelihood of significant organic disease:

- Aged 50–55 years or older at first presentation
- Aged 40–45 years or older at first presentation for people of Māori, Pacific Island or Asian descent*
- Family history of gastric cancer with onset age <50 years
- Severe or persistent dyspepsia
- Previous peptic ulcer disease, particularly if complicated
- Ingestion of NSAIDs including aspririn (check OTC use) particularly those at increased risk
- Chronic gastrointestinal bleeding
- Unexplained weight loss
- Difficulty in swallowing
- Persistent or protracted vomiting
- Iron deficiency anaemia
- Palpable abdominal mass
- Coughing spells or nocturnal aspiration

**Gastric cancer tends to occur a decade earlier in these people*

Heartburn with or without dyspepsia is usually caused by GORD and step-down PPI therapy is indicated

In the absence of red flags the presence of heartburn with or without dyspepsia is the single most important feature determining management.

Heartburn with or without dyspepsia is usually related to lower esophageal dysfunction and the presence of GORD. This often follows a large meal or is related to obesity; people with a BMI of 25 or above are at much greater risk of getting GORD. Heartburn needs to be differentiated from other causes of similar symptoms such as cardiac disease.

GORD is appropriately managed empirically by lifestyle measures (Table 2) with or without a step down drug regimen. The following step down programme usually in 4–8 week steps is appropriate for most patients (adapted from NZGG, 2004).[1]

Step 1 Full-dose PPI (omeprazole 20 mg or lansoprazole 30 mg daily)

Step 2 Half-dose PPI

Step 3 H2RA (famotidine 20–40 mg, ranitidine 150–300 mg twice daily)

Step 4 antacids/alginate

If there is no response to full dose PPI after three months double the dose. Trial this for 3–6 months and review. If the person fails to respond, or if symptoms recur within one month after the end of treatment, consider OGD rather than long-term empiric treatment.

Table 2: GORD is appropriately managed empirically by lifestyle measures

Heartburn or dyspepsia is often due to or worsened by lifestyle factors. Modification of these factors may reduce or resolve symptoms without the need for drug treatment or allow the use of lower drug doses or intermittent therapy when symptoms worsen.

- Offer simple lifestyle advice; including healthy eating, weight reduction, smoking cessation and limiting alcohol intake.
- Advise avoidance of trigger factors if these are known to aggravate symptoms. These may include, bending, alcohol, chocolate, spicy food, fatty food and smoking.
- If people have reflux symptoms, weight control, eating smaller meals, avoiding fat and not eating before going to bed are often helpful.

(Adapted from Prodigy Guidance)[2]

People with heartburn can often step-down to intermittent therapy taken either in response to heartburn or when lifestyle indiscretions make it likely. Up to 20% can stop medication without recurrence of symptoms.

Dyspepsia without heartburn

How common is dyspepsia?

Dyspepsia is extremely common with a prevalence of 23–41 % in OECD countries. Most people with dyspepsia do not seek advice about it from their GPs and often accept symptoms as part of their lifestyle and dietary habits. This explains the widespread availability and purchase of over the counter (OTC) antacids, H2RAs (e.g. ranitidine) and PPIs in some countries.

It has been estimated that only 25% of people with symptoms of dyspepsia actually seek medical advice[3] but because it is so common dyspepsia accounts for between 2% and 7% of visits to GPs.

Who gets dyspepsia?

Dyspepsia can occur at any age but in older people it is more likely to be associated with organic diseases such as peptic ulcer or gastric cancer. NSAIDs are a major cause of dyspepsia and peptic ulcer and are more frequently prescribed in people over 65, who are more susceptible to complications. It should be noted that low dose aspirin is associated with dyspepsia and increased risk of peptic ulceration.

There are no accurate figures linking the prevalence of dyspepsia with ethnicity in New Zealand. However, *H. pylori* infection which is associated with peptic ulceration is more common among Māori and Pacific Island people.

Initial management of undifferentiated dyspepsia without heartburn

(Adapted from NZGG, 2004)[1]

When a person with dyspepsia presents for the first time there are two important issues to consider:

- Is there a significant underlying pathology?

  and

- Why has the person decided to present with the problem at this time?

A reasonable approach is to:

- If there are red flags (Table 1), refer to a specialist for OGD
- Review lifestyle factors (Table 2)
- Review use of antacids and H2RAs as this may guide drug treatment if this is necessary
- Review intake of other medicines, including OTC, especially NSAIDs but also calcium antagonists, corticosteroids, nitrates, bisphosphonates and theophylline
- In areas with high prevalence of *H. pylori*, test for *H. pylori*
- If *H. pylori* testing is not indicated or is negative treat as undifferentiated dyspepsia
- If there is no response to initial treatment after a reasonable trial period of 4–12 weeks refer for OGD

Test and treat for *H. pylori* in areas of high prevalence

If a person has no red flags but there is a high (> 30%) local prevalence of *H. pylori* it is worth testing for *H. pylori*.

The best tests for this are the *H. pylori* faecal antigen and the breath test. Both are available in NZ but the faecal antigen test is a lot cheaper, funded and more readily available. Patients should be off PPIs for two weeks before both of these tests. The sensitivity and specificity of both tests (about 95%) is very much better than serology. In clinical use, serology has a sensitivity and specificity ranging from 68–80%, although in some research studies can reach the 90–95% level.

The quality of serology depends on the matching of the local *H. pylori* with the commercial kit used for the assay and very few are actually validated for local consumption. Although serology is cheap and convenient it is no longer regarded as the test of choice.

People, for whom *H. pylori* testing is either not indicated or is negative, can be treated empirically as undifferentiated dyspepsia, as long as they have no red flags.

For undifferentiated dyspepsia step up therapy until symptoms are controlled and then step down or treat intermittently

The use of antacids, alginates and over the counter H2RAs are effective for many people with intermittent mild symptoms of dyspepsia. However many people do not seek medical advice and become chronic users of OTC antacids and H2RAs. Many of these people will benefit from advice on lifestyle modification or a trial of full dose drug therapy.

The preferred drug treatment for undifferentiated dyspepsia is contentious due to inconsistent study design and interpretation of the literature. A vast majority of clinical trials show a placebo response of about 40%, and some even higher[4], making any effects of drug treatment difficult to measure.

Another major problem is that many studies do not differentiate between two distinct patient groups, those with heartburn with or without dyspepsia, and those with dyspepsia alone. This is important, as heartburn is predominantly due to reflux of acid into the oesophagus, but dyspepsia without heartburn is often related to reduced GI motility and other factors. This distinction significantly affects the success of the various drug treatments available and has failed to be taken into account in some international guidelines.

Overall, prokinetics appear to be the most effective drugs for functional dyspepsia. This supports the theory that this condition is most often due to a motility disorder rather than over-secretion of acid. The two main prokinetics used in clinical trials were cisapride and domperidone. Cisapride is no longer available and there have been recent concerns about cardiotoxicity associated with domperidone. There is insufficient evidence to support the widespread use of metoclopramide for functional dyspepsia and there is a risk of extrapyramidal effects with this drug.

In practice, drug choice is usually between a PPI and an H2RA because of the adverse effects of prokinetics.

NNT for drugs used in management of dyspepsia without heartburn:

- ***Prokinetics (domperidone): NNT = 2.8***
- ***H2RAs: NNT = 5.9***
- ***PPIs: NNT = 11.1***

These figures are based on a Cochrane review in which people presenting primarily with heartburn were excluded.[5] The most recent Cochrane Review[4] did not find any conclusive evidence of superiority of either agent in the treatment of functional dyspepsia and the authors concluded that H2RAs might still be the drugs of choice in this condition on the grounds of cost.

The standard doses of H2RAs are famotidine 20 mg BD and ranitidine 150 mg BD. These doses can be doubled for severe disease.

If H2RAs do not control symptoms it is appropriate to step-up to PPIs until symptoms are under control and then to step-down again.

Functional dyspepsia is managed as for undifferentiated dyspepsia

Functional dyspepsia accounts for 45% of dyspepsia diagnosis on OGD

Functional dyspepsia is the most common diagnosis after OGD accounting for approximately 45% of cases. It refers to people with symptoms and a normal OGD (i.e. exclusion of peptic ulcer, oesophagitis and malignancy).

Other diagnoses include; oesophagitis 29%; duodenitis 3%; gastric ulcer 4–9%; duodenal ulcer 6–9%; cancer of stomach or oesophagus 0.3–2%. Erosive duodenitis and gastric erosions are considered to be part of the spectrum of peptic ulcer disease.

The role of hyperacidity in functional dyspepsia?

Although antisecretory drugs are used extensively in the treatment of functional dyspepsia, there is little evidence that excess acid secretion is involved in the aetiology of this condition.[4] The cause of functional dyspepsia is multifactorial so acid suppression with PPIs or H2RAs is not always helpful in treatment. The reason why antisecretory drugs are sometimes effective is not clearly understood but it may in part relate to the fact that a significant number of people have acid reflux symptoms associated with their dyspepsia.

Management of Functional Dyspepsia without heartburn

(adapted from NZGG, 2004)[1]

It is important to provide reassurance that there is no underlying organic pathology. Encourage lifestyle changes such as diet, weight control, smoking cessation and alcohol moderation and manage in the same way as undifferentiated dyspepsia.

Do You Prescribe Paroxetine?

The brand of subsidised paroxetine hydrochloride 20 mg tablets is changing from Aropax to Loxamine.

Timelines for this change are as follows:

- From April 1 2007 Loxamine will be available fully subsidised without the need for endorsement and Aropax will be available fully subsidised by endorsement (as it is now)
- From June 1 2007 the endorsement for full subsidy for Aropax will be removed and patients may have to pay a part-charge
- From September 1 2007 Loxamine will remain fully subsidised and Aropax will be delisted from the Pharmaceutical Schedule

Bpac has developed an education programme to support this brand change.

The resources available include information on the bioequivalence of Loxamine and Aropax, the latest research on patients perceptions of brand changing and generic drugs, practical advice for counselling patients and patient information.

To access these resources follow the link on the bpac home page

www.bpac.org.nz

Table 3: Summary of empiric drug treatment

Heartburn with or without dyspepsia

- Start with PPI and step-down and/or revert to intermittent use

Undifferentiated or functional dyspepsia but no heartburn

- If OTC antacids, alginates or H2RAs have been used prior to consultation, check these have been taken regularly and at full dose. If not, regular full dose treatment in combination with lifestyle modification, may be effective
- In areas of high prevalence for *H. pylori* test and treat
- Otherwise step-up therapy until symptoms under control
- When symptoms are under control step-down therapy to the lowest effective dose and/or intermittent use. This applies to H2RAs and PPIs
- If previous dyspepsia symptoms recur one– six months after stopping treatment, re-evaluate the person for red flags, taking in to account timing of relapse and severity of symptoms
- If previous dyspepsia symptoms recur after six months with no red flags, repeat empiric therapy

Review and reduce

- Review patients who have been taking acid suppression (PPI or H2RA) treatment for more than six weeks
- Check for lifestyle factors such as stress or drugs such as NSAIDs which may be contributing to the problem
- Reduce the dose of PPI or H2RA and assess symptom response. Some patients may only require intermittent treatment when they have symptoms and in this case an H2RA may give more rapid relief than a PPI
- Up to 20% of patients can stop therapy with recurrence of symptoms but need to be warned that stopping PPIs may lead to transient recurrence of symptoms. Slow withdrawal may be better

References

1. NZGG. New Zealand Guidelines Group Dyspepsia Guidelines, 2004
2. Prodigy Guidance. Dyspepsia – Proven non ulcer dyspepsia (July 2005) http://snipurl.com/1cee7
3. Jones R, Lydeard S. Prevalance of dyspepsia in the community. BMJ 1989;298:30-2
4. Moayyedi P, Soo S, Deeks J, Delaney B, Innes M, Forman D. Pharmacological interventions for non-ulcer dyspepsia. Cochrane Database of Systematic Reviews: 2006 Issue 4 John Wiley & Sons, Ltd Chichester, UK DOI: 0.1002/14651858.CD001960.pub3
5. Soo S, Moayyedi P, Deeks J et al. Pharmacological interventions for non-ulcer dyspepsia. The Cochrane Library, Issue 2, 2000

Management of acute asthma

In the third issue of BPJ we discussed the current debate around the management of acute asthma for people on long acting beta agonists (LABAs). In this issue we pose four scenarios and ask Respiratory Physician, Professor Robin Taylor, for his advice in these situations.

Consider how you would respond to the scenarios and then read Professor Taylor's comments.

1

Ms Rees is a 22-year-old retail assistant with asthma. You have recently been able to reduce her high inhaled corticosteroids (ICS) dose by adding an inhaled LABA and she is currently taking fluticasone (Flixotide) 250 micrograms bd and salmeterol (Serevent) 25 micrograms bd in separate inhalers. She wants to combine these into a single inhaler (Seretide 250) for the sake of convenience and you agree.

In the past she has been in the habit of doubling her daily dose of fluticasone if she gets a mild exacerbation of her asthma or a URTI. She asks what she should do now she is on a combination inhaler. **What do you recommend?**

Professor Robin Taylor's comments

The use of a combination inhaler is a logical step forward in most patients whose asthma is well controlled on both an ICS and a LABA (subject to Special Authority application). The fact that her total dose of ICS can be reduced is also an advantage.

Doubling the dose of inhaled steroid during an exacerbation has been shown not to provide any benefit in the management of exacerbations. It is now obsolete as a management strategy, thanks to the advent of evidence from appropriately designed trials.

More recently there has been a series of studies in which the use of regular plus as-required formoterol/budesonide has been compared with regular combination plus as required short acting beta-agonist (SABA). The strategy is known as adjustable maintenance therapy (AMT) — in which the patient needs to have only one type of inhaler (Symbicort). The results to date demonstrate an advantage in using the former regimen. This strategy is based on the fact that formoterol has a rapid onset of action and can be used as a 'reliever' and the patient simultaneously gets an additional dose of inhaled steroid. Thus Symbicort may be used in this way, but not Seretide.

What remains unclear is whether this approach is valid in all patients or only in selected groups. This question will probably be answered over the next 2–3 years. My own concern relates to the patients whose 'prn' use of beta-agonist is problematic. Those who rely on too much SABA and do not take enough inhaled steroid ought theoretically to gain from this — assuming that their asthma is steroid sensitive and current symptoms **are due to poor asthma control** and not something else. Some patients may be prone to taking reliever to excess for psychological as well as truly disease-related reasons, in which case the possibility of steroid overuse might arise. To date there has been only limited experience using AMT in New Zealand and it may be that increasing familiarity will help to identify where the potential problems really lie. However AMT is not suitable for this woman because she is on Seretide.

2

Mr Ingram is an 18-year-old student with asthma and features of atopy. His asthma has been present for as long as he remembers and he lost quite a lot of time from school because of it. However for the last two years he has been well controlled on budesonide 400 micrograms bd and eformoterol 12 micrograms bd in a combined inhaler (Symbicort Turbuhaler). He presents with worsening asthma that he attributes to his flatmate getting a cat.

History and examination confirm the diagnosis of asthma. He has scattered rhonchi, a pulse of 110 per minute and PEFR of 75% of his recent best result. **What do you recommend?**

Professor Robin Taylor's comments

"No amount of treatment will overcome the effects of daily exposure to high levels of allergen"

Students experience a number of potential exacerbating factors especially around age 18 or 19 when they move away from home:

- Exposure to the cat may be very important. Skin prick testing (SPT) of the patient will confirm whether he is allergic or not. If so the answer is simple — get rid of the cat. No amount of treatment will overcome the effects of daily exposure to high levels of allergen
- By definition students are poorly compliant with treatment. The figures suggest that this group take around 20% of prescribed inhaled steroid!
- Poor compliance with anti-inflammatory treatment may go hand in hand with excessive use of beta-agonist and more than 6/7 puffs per day of salbutamol or the equivalent is pro-inflammatory
- Consider whether his allergy is also giving rise to rhinitis. If so, nasal blockage can result in mouth breathing which in turn may exacerbate airway responsiveness. Treat accordingly
- Consider whether stress factors are important. This may be the case if he is facing severe academic pressures or has just moved from home for the first time

His observations suggest moderately severe asthma. A young man of 18 with a peak flow of 75% and an elevated pulse rate is in poor shape. Treat as for acute severe asthma but do not stop his maintenance treatment.

3

Ms Richards is a 22-year-old secretary who is getting married next week. She has asthma which is usually well controlled on salmeterol 25 micrograms bd and fluticasone 250 micrograms bd in a combined inhaler (Seretide 250). Her asthma is flaring up and she is concerned that it will ruin her wedding day.

History and examination do not suggest a diagnosis other than her asthma. Her chest is wheezy, her pulse is 110 per minute and her PEFR is 75% of her recent best result. **What do you recommend?**

Professor Robin Taylor's comments

All that was said about Mr Ingram applies to Ms Richards. However, in addition, there is a pragmatic aspect. Weddings are important. I would prescribe prednisone 40 mg/day as usual for three days rather than five to seven days. Then I would reduce the dose to 10 mg/day assuming there is some improvement. Thereafter I would maintain this dose for two weeks or even longer until the patient has returned from her honeymoon, before re-evaluating her inhaler maintenance drug therapy. This dose is low enough that it will not cause side effects (in a young woman headaches, bloating feelings, ankle oedema) but high enough in most young asthmatics that it will help to maintain control of her asthma.

4

Mrs Morrison had asthma as a child and thought she had outgrown it during adolescence. Five years ago when Mrs Morrison was 45-years-old the asthma returned and was quite difficult to get under control. However for the last two years she has been achieving good control with fluticasone (Flixotide) 250 micrograms bd and salmeterol (Serevent) 25 micrograms bd She has a rescue inhaler but rarely uses it. The rest of her health is good.

She is visiting her daughter on the West Coast. She arrived one week ago and her asthma has become quite troublesome and she needs to use her rescue inhaler every two hours because of wheezing and tightness in her chest.

History and examination in the surgery does not raise suspicion of anything except worsening of her asthma. She has scattered wheezing, a pulse of 110 per minute and PEFR of 75% of her recent best result. **What do you recommend?**

Professor Robin Taylor's comments

When a patient, who is well controlled rapidly becomes uncontrolled, a trigger for the poor control needs to be sought. In this woman's case the immediate possibilities include:

- She has developed a viral lower respiratory tract infection which is exacerbating her asthma
- She has forgotten to bring her inhalers to the West Coast and has been without steroid 'protection' for the previous five days. However the average time from stopping ICS till the advent of loss of control is actually longer i.e. 17 days.
- She has been exposed to a trigger which is unusual for her. This might include an allergen e.g. horses or she may have taken a NSAID (one tablet can do it!)

The management includes:

- Removing identifiable triggers if present
- A course of oral prednisone for five to seven days
- Use of a spacer to deliver inhaled steroids especially if her peak flow is very low

There is no particular comment to be made regarding LABA in this case. The standard dose may continue as already prescribed. There is no good reason to change the dose of inhaled fluticasone. There is no particular advantage to be gained from a combination product.

CLOZAPINE – Safe and Effective Use

GPs Can Make The Difference

Contributed by Nikki Holmes, Mental Health Pharmacist Coordinator, Waitemata DHB, on behalf of DHBNZ Safe and Quality Use of medicines Group (SQM)

http://www.safeuseofmedicines.co.nz

Clozapine is the gold-standard treatment for people with schizophrenia who are unresponsive to or intolerant of other antipsychotics. It is effective in one-third of people after six weeks[1] and around 60% of people after one year.[2] Unfortunately there can be some significant adverse effects and interactions associated with its use. GPs have a vital role in detecting and managing these.

Significant adverse effects

Constipation – Constipation is common, predictable and is related to anticholinergic effects. Poor diet and inactivity can increase the risk of constipation, which should be monitored for and actively managed. Note that lactulose takes 48 hours to be effective; in some situations this may be too slow. Although helpful when used acutely, ongoing stimulant use (e.g. senna) should be avoided as the bowel will become dependent. Inadequately treated constipation may lead to life-threatening sequelae such as a toxic megacolon – there have been several such cases recorded, all of which have necessitated emergency colectomies. Most people were taking other anticholinergic agents as well as clozapine – this should be avoided wherever possible especially if there is a history of constipation.

Metabolic Syndrome – Weight gain, hyperglycaemia and dyslipidaemia are all associated with clozapine. Relevant parameters should be regularly monitored and diet and exercise interventions made as clinically indicated. It may also be appropriate to use pharmacological management.

Seizure Threshold – Clozapine lowers the seizure threshold dose dependently. If seizure activity develops or pre-existing seizures worsen, this should be followed up. Carbamazepine should not be used with clozapine due to the significant increased risk of blood dyscrasias[3,4] and the effect on serum concentrations.

Blood dyscrasias – These are rare but can be fatal. If a person taking clozapine presents with an infection, a full blood count should be performed to exclude neutropenia/agranulocytosis. Should an antibiotic be indicated it is worth remembering that some are more likely than others to cause blood dyscrasias (e.g. co-trimoxazole) and some may interfere with clozapine metabolism and therefore serum concentrations (e.g. erythromycin).

Myocarditis – This adverse effect is rare but cases have been reported in New Zealand. If a person develops signs or symptoms (e.g. chest pain, shortness of breath) or cardiac insufficiency or a pre-existing cardiac condition worsens, this should be followed up urgently.

There are also some interactions of note with clozapine

Smoking – Cigarette smoke (not nicotine) induces the enzymes that metabolise clozapine. Stopping smoking will cause serum clozapine concentrations to rise and increase the risk of concentration-related adverse effects such as drowsiness and seizures. Stopping smoking should always be planned with the clinical team so that this effect can be monitored for and managed.

Selective serotonin reuptake inhibitors (SSRIs) – Some SSRIs inhibit the enzymes that metabolise clozapine, thereby causing serum concentrations of clozapine to rise. Citalopram is the preferred SSRI in this situation as this does not interact.

References

1. Kane J, Honigfeld G, Singer J, et al. Clozapine for the treatment-resistant schizophrenic. Arch Gen Psych 1988;45:789-96
2. Meltzer HY, Bastani B, Young Knon K et al. A prospective study of clozapine in treatment-resistant patients. 1: preliminary report. Psychopharmacology 1989;99:568-72
3. Clozaril® data sheet dated 15/2/06 from www.medsafe.govt.nz
4. Junghan U, Albers M, Woggon B. Increased Risk of Hematological Side-Effects in Psychiatric Patients Treated with Clozapine and Carbamazepine. Pharmacopsychiatry 1993;26:262

etc

evidence that counts

Antipsychotics and cognitive decline in Alzheimer's disease: the LASER-Alzheimer's disease longitudinal study

National Electronic Library for Medicines

Bottom line: A study published in the Journal of Neurology, Neurosurgery and Psychiatry has investigated whether taking antipsychotics is associated with more rapid cognitive deterioration in Alzheimer's disease. The researchers concluded that those taking antipsychotics were no more likely to decline cognitively over 6 months.

Researchers studied 224 people in a longitudinal cohort of people with Alzheimer's disease, and compared those taking antipsychotic drugs for more than six months to those who were not, in terms of change in three measures of cognition: Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog), Mini-Mental State Examination (MMSE) and Neuropsychiatric Inventory (NPI).

The following results were reported:

- No statistically significant difference was observed in cognitive decline between those taking antipsychotics (atypical or any) and others on any measure of cognition.
- The only predictor of more cognitive decline was greater baseline cognitive severity ($p<0.05$).
- Although mortality was higher in those treated with antipsychotics, this reflected their greater age and severity of dementia. The results were the same when the whole cohort was included, rather than the select group with potential to change, who had been taking antipsychotics continuously.

The researchers concluded that those taking antipsychotics were no more likely to decline cognitively over 6 months. Although clinicians should remain cautious when prescribing antipsychotic drugs to people with Alzheimer's disease, any increase in cognitive deterioration is not of the magnitude previously reported.

Reference *Livingston G, Walker AE, Katona CL, Cooper, J Neurol Neurosurg Psychiatry. 2007 Jan;78(1):25-9*

A New Treatment for Colic?

Journal Watch, Volume 27, Number 4, 2007

Bottom line: Are these results too good to be true? Colic is likely a heterogeneous disorder, yet in this study, *lactobacillus* was remarkably effective. Additional confirmatory double-blind studies are needed before this treatment is widely adopted.

Infantile colic is difficult to treat. In a randomised non-blinded trial Italian investigators assigned 83 breast-fed infants with colic (>3 hours of crying on >3 days/week) to receive the probiotic *Lactobacillus reuteri* (5 drops once daily 30 minutes after feeding) of the anti-gas medication simethicone (60 mg/day as 15 drops twice a day after feeding) for 28 days. Mothers also were asked to adopt a diet free of cow's milk.

By day 28 after randomisation, mothers of infants in the probiotic group were significantly more likely than mothers of infants in the simethicone group, to report a reduction from baseline in average crying times to less than 3 hours par day (95% vs. 7%). In addition, median crying times were significantly shorter in the probiotic group than in the simethicone group on days 7, 14, 21 and 28 (e.g., 51 vs. 145 minutes/day on day 28).

Reference *Savino F et al. Lactobacillus reuteri versus simethicone in the treatment of infantile colic: A prospective randomised study. Pediatrics 2007;119:e124-30*

Meta-analysis: aspirin added to anticoagulant no benefit for most patients

National Electronic Library for Medicines

Bottom line: Based on their analysis, the authors conclude that combined therapy is not appropriate for most patients, as the benefits are minimal and there is a significant increase in major bleeding. For patients with mechanical heart valves there is a significant reduction in arterial thromboembolic events and in this group the benefits may outweigh the risks.

Most patients taking oral anticoagulant therapy do not seem to benefit from addition of low-dose aspirin, and they are at higher risk of major bleeding, according to a meta-analysis of trial evidence. The authors of the study note that whether or not to add low dose aspirin to oral anticoagulation therapy is a common clinical dilemma without accepted guidelines. They therefore carried out a systematic review and meta-analysis to determine whether there was published evidence on benefits and risks to guide practice. Eligible studies were defined as randomised controlled trials that included comparison of oral anticoagulant therapy plus low-dose aspirin with oral anticoagulant alone. Studies had to have at least three months follow-up, with anticoagulation either titrated to the same INR in both arms, or was given as the same standard dose in each arm. Main outcomes were arterial thromboembolism, all-cause mortality and major bleeding, calculated as pooled odds ratios (OR).

A comprehensive search located ten eligible studies including a total of 4,180 patients. The analysis found that overall risk for arterial thromboembolism was lower in patients receiving combined aspirin + anticoagulant therapy compared with anticoagulation therapy alone (OR, 0.66; 95% CI, 0.52-0.84). When different patient groups were analysed these benefits were limited to patients with a mechanical heart valve (OR, 0.27; 95% CI, 0.15-0.49). There was no significant difference in the risk for arterial thromboembolism in atrial fibrillation (OR, 0.99; 95% CI, 0.47-2.07) or coronary artery disease group (OR, 0.69; 95% CI, 0.35-1.36). There was no difference in all-cause mortality with either treatment (OR, 0.98; 95% CI, 0.77-1.25).

Reference *Dentali F, et al. Combined Aspirin–Oral Anticoagulant Therapy Compared With Oral Anticoagulant Therapy Alone Among Patients at Risk for Cardiovascular Disease. M Arch Intern Med. 2007 Jan 22;167:117-24*

Patients taking venlafaxine may have a higher risk of suicide - but it's probably not drug-related

National Electronic Library for Medicines

Bottom line: A large retrospective cohort study found that patients prescribed venlafaxine were at a higher risk of suicide, than those prescribed some other antidepressives, but also that they had more suicide risk factors.

The authors of the study note that while SSRI have been shown to be associated with an increased risk of suicidal ideation and behaviour in clinical trials, a range of studies have found no increase in the risk of actual suicide with these drugs. Data suggest that venlafaxine is prescribed to patients at higher risk (e.g. those unresponsive to other agents) but there are limited data on the relative risk of suicide with this drug.

There were 219,088 patients in the study cohort with consistent distribution of basic characteristics across the drug groups. Most were diagnosed as depressed (90.5%); about 25% had mixed depression and anxiety and in this group venlafaxine was more often prescribed (35.4% vs. 22% to 27.3% for the others). There were 54 completed suicides over a total of 173,452 person-years use of any study drug and 3,060 first attempted suicides over 169,735 person-years of risk. Before adjustment for potential confounding factors, venlafaxine was associated with a significantly higher risk of suicide (incidence 0.64 vs. 0.23 to 0.27 per 1000 person-years) and attempted suicide (incidence 26.6 vs 13 to 17.4 per 1000 person-years) compared to the other study drugs. When potential confounding factors were used to adjust the estimates, however, the relative risks fell considerably. The results of the analysis confirmed previous findings that risk was significantly increased during the first 30 days of treatment and by severe psychiatric morbidity.

Reference *Rubino A, et al. Risk of suicide during treatment with venlafaxine, citalopram, fluoxetine, and dothiepin: retrospective cohort study. BMJ. 2007;334:242*

etc

evidence that counts

FDA urges caution in unlicensed use of quinine to treat leg cramps

National Electronic Library for Medicines

Bottom line: The FDA has ordered companies to stop marketing unapproved drug products containing quinine, citing serious safety concerns including deaths, associated with quinine products. As part of that action, the agency is also cautioning consumers about unlicensed use of quinine to treat leg cramps.

In the US there are several unapproved products containing quinine currently marketed but only one is approved by the FDA. In June 2006 the agency had issued new guidance, 'Marketed Unapproved Drugs – Compliance Policy Guide' which made clear that firms illegally marketing drugs without FDA approval, needed to submit applications showing that their products were safe and effective, before continuing to market those products.

The agency also stressed that quinine is approved for the treatment of malaria; the risks associated with quinine in this setting are justified but not for preventing or treating leg cramps. Since 1969, the FDA has received 665 reports of adverse events with serious outcomes associated with quinine use including 93 deaths. Serious side effects associated with quinine drugs include arrhythmias, thrombocytopenia and severe hypersensitivity reactions. There is also the potential for serious drug interactions and there are conditions under which quinine should not be used.

The Director of the FDA's Centre for Drug Evaluation and Research said in a statement "we believe unapproved quinine products represent a serious health risk because of the widespread use of this product for treating leg cramps. Quinine needs to be dosed carefully and FDA-approved labelling reflects the fact that the risks associated with the use of this drug for treatment of leg cramps outweigh the benefits."

Opioids and Chronic Back Pain

Journal Watch, Volume 27, No. 4, 2007

Bottom line: Clearly, we need better treatments for chronic back pain. Opioids are an option at least in the short term, but their efficacy for chronic back pain is not particularly convincing, and the possibility of a coexisting substance disorder has to be considered.

Opioids are sometimes prescribed for chronic back pain that persists despite treatment. In a systematic literature review, researchers identified 38 studies that examined the prevalence of opioid prescribing for chronic back pain, the efficacy of opioids, and the prevalence of substance disorders in these patients.

In 11 studies, the prevalence of opioid prescribing for chronic back pain ranged from 3% to 66%. In four of the six studies that compared opioids to placebo or non-opioids, opioids had superior efficacy; none of these studies lasted more than 16 weeks. A meta-analysis of data from four studies found that opioid treatment was associated with decreased pain, but this decrease was not significant. The prevalence of a current substance disorder ranged from 3% to 43% in patients receiving opioids for chronic back pain; the researchers note that these data came from studies judged to be of generally poor quality. In the highest-quality study, the prevalence of current substance disorder was 23%, both in patients receiving opiates and in those who did not. The prevalence of aberrant medication-taking behaviours was 5% to 24% in five studies; only one study controlled for the possibility that the behaviour was motivated by inadequate pain relief.

Reference *Martell BA et al. Systematic review: Opioid treatment for chronic back pain: Prevalence, efficacy, and association with addiction. Ann Intern Med 2007 Jan 16;146:116-2*

Stopping drugs associated with falls in the elderly does reduce fall risk

National Electronic Library for Medicines

Bottom line: A range of drugs is known to increase the risk of falls in the elderly: this study shows that stopping such drugs can reduce the risk of falling. The authors note that various drugs have been linked with increased risk of falling in the elderly, but that there is little trial evidence on the effect of withdrawing them. They therefore carried out a prospective cohort study in a group of high-risk patients from a Dutch geriatric centre.

The study population came from patients attending the outpatient clinic or day centre who were aged over 65, had a history of falling, had no significant cognitive impairment (MMSE >20), and could walk at least 10 m without an aid. At baseline, a list of all medication being taken by a patient was compiled and checked, to identify drugs that could potentially increase risk of falling. These drugs were then stopped, if possible, or reduced to the minimum effective dose, over a one-month period. The patients were then followed-up for falls over a further three months.

A total of 201 patients were eligible for inclusion during the study recruitment period (April 2003–November 2004). Of these, 139 agreed to participate. In this group one or more relevant drugs could be stopped in 67 patients and dose reduction was possible in a further eight. No change was possible in the remaining 64, as they were either not using a relevant drug, or they were using one but it could not be stopped. Over the follow-up period patients who had drugs withdrawn or reduced were significantly less likely to fall - 17 (23%) vs. 20 (31%) reported one or more falls. They also had fewer falls - after correction for confounding factors mean numbers of falls over the two months was 0.3 vs. 3.6.

The authors note that at baseline the group in whom drug withdrawal/ dose reduction was possible were at higher risk: for example, they used more drugs, had a history of more falls and had more co-morbid conditions. They conclude that their study indicates withdrawal of fall-inducing drugs to be a potentially effective intervention for reducing the risk of falls in elderly people. Analysis indicated that the drug group for which withdrawal gave the greatest benefit was cardiovascular drugs.

Reference *Aronson JK. Adverse drug reactions–no farewell to harms. Br J Clin Pharmacol 2007; 63:131-5*

PPIs and Risk for Hip Fracture

Journal Watch, Volume 27, No. 3, 2007

Bottom line: Although this case-control study may not have accounted for all factors affecting hip fracture risk, clinicians should note the possible association between proton-pump inhibitor (PPI) use and hip fracture. Use of PPIs is so widespread that confirmatory studies are needed. In the meantime clinicians should consider minimising both the dose and the duration of PPI use in older patients.

Through the mechanism of hypochlorhydria, PPIs theoretically can reduce calcium absorption and decrease bone density. These investigators sought to clarify the relation between PPI use and risk for hip fracture by using a UK population-based registry of 1.8 million patients aged 50 or older. Roughly 400,000 patients received at least one prescription for a PPI, a histamine 2–receptor antagonist (H2RA), or both. A total of 13,556 patients who suffered a hip fracture after at least 1 year of complete data collection were compared with 135,386 controls matched for age and sex.

After adjustments for medications and health conditions affecting the risk for hip fracture the risk was 44% higher among patients who had used a PPI for at least one year (with or without an H2RA) than among those who did not use any acid-suppression therapy. The relation between PPI use and hip fracture was particularly strong for high-dose use (defined as >1.75 times the average daily dose; adjusted odds ratio, 2.65) and for increased duration of use (AOR for four years of use 1.59).

Reference *Yang YX et al. Long term proton pump inhibitor therapy and risk of hip fracture. JAMA 2006 Dec 27;296:2974-53*

Interactions with Warfarin

Warfarin has the potential to interact with numerous drugs resulting in significant morbidity and potentially serious bleeds. Loss of anticoagulant control is one of the most frequent causes of drug related hospital admissions in New Zealand and in many cases the event is precipitated by an agent which alters the anticoagulant effect of warfarin.

Mechanisms include inhibition or induction of warfarin metabolism, additive or synergistic antiplatelet effects (e.g. aspirin) and changing vitamin K status (e.g. dietary changes and antibiotics). Individual susceptibility may increase the risk of an interaction in some people. For many drugs the supporting evidence for an interaction is relatively weak and based on poor quality case reports. However, the consequences of an interaction are potentially severe so any change (starting or stopping) in drug therapy, diet or herbal/dietary supplement intake should be checked for the potential to alter anticoagulant control.

Rather than an extensive list of individual drugs we have focused on the major drug classes (plus some individual drugs which don't fit) to give some indication of the relative potential for interactions. Hopefully this will be easy to read and digest and prompt the need for further advice on management when necessary. As this 'list' is not totally comprehensive or inclusive our advice is to check any agents's potential to interact with warfarin, especially if you are unfamiliar with the combination.

Acid regulating drugs

Cimetidine inhibits the metabolism of warfarin and increases its anticoagulant effect. Ranitidine appears not to interact but there have been isolated cases of bleeding.

There have been some reports of bleeding with proton pump inhibitors (PPIs) and warfarin but an interaction is relatively uncommon. An awareness of the slight possibility of bleeding along with the usual monitoring of the INR are required when PPIs are given with warfarin.

Alcohol

Anticoagulant control can be affected by changes in alcohol consumption. Poor diet and liver damage in alcoholics may also be factors.

Allopurinol

Most patients are not affected. Clinically important increases in INR are rarely reported.

Monitor the INR when allopurinol is first added.

Antiarrhythmic Drugs

Amiodarone inhibits the metabolism of warfarin and this interaction occurs in most patients. The onset may be slow (about two weeks) and it may persist for weeks or even months after the amiodarone has been stopped. The anticoagulant effect of warfarin is possibly enhanced by quinidine.

Analgesics

Most analgesics can increase the bleeding risk when given with warfarin but by different mechanisms. Aspirin and NSAIDs have antiplatelet effects so an increased risk of bleeding can occur without an increase in the INR. Warfarin can increase the severity of a GI bleed caused by aspirin, NSAIDs and COX-2 inhibitors. Other than occasional case reports there is little evidence that NSAIDs increase the INR in people taking warfarin. There is some evidence that the COX-2 inhibitors (e.g. celecoxib, etoricoxib) can cause a significant increase in the INR in some people on warfarin, especially the elderly. Consider monitoring the INR if a COX-2 inhibitor is added to warfarin.

Recent case reports indicate that tramadol can inhibit the metabolism of warfarin and increase its anticoagulant effect.

Regular use of paracetamol can increase the effect of warfarin in some patients. Occasional doses of paracetamol for two to three days are unlikely to have a significant effect, but regular use for a week or more may increase the INR in some patients. Monitor the INR in people starting or stopping regular use of paracetamol.

Antibacterials

Most antibiotics have been reported to alter the anticoagulant effect of warfarin and the usual mechanism proposed is reduction of vitamin K synthesis by gut flora. Monitoring is recommended when an antibiotic is started or stopped. Clinically significant interactions appear to be more likely with ciprofloxacin, norfloxacin, macrolides (e.g. erythromycin) and metronidazole, where enzyme inhibition is also possibly involved.

Rifampicin is a potent enzyme inducer and can reduce the effect of warfarin.

Antidepressants

Selective serotonin reuptake inhibitors (SSRIs) have antiplatelet effects and as well as increasing the risk of bleeding *per se* they can enhance the risk if bleeding with warfarin without increasing the INR. There are also isolated case reports of SSRIs causing an increase in INR. Advise people to report signs of bleeding and consider monitoring the INR when an SSRI is added.

The effects of warfarin are occasionally increased by venlafaxine, sometimes with an increase in the INR.

With tricyclic antidepressants (TCAs) there are isolated reports of changes in the INR but the evidence for an interaction is poor and inconclusive. Monitor INR as normal.

St John's Wort can decrease the effect of warfarin in some people. The CSM in the UK advise against concurrent use.

Antidiabetics

There are isolated reports of enhanced anticoagulant effect or hypoglycemia with sulphonylureas but evidence of a clinically significant interaction with warfarin is very weak and appears to be very unlikely.

Antiepileptics

The metabolism of warfarin can be increased by carbamazepine, phenytoin and phenobarbitone (reduced anticoagulant effect). Enhanced anticoagulant effect has been reported with phenytoin and sodium valproate.

The evidence for clinically significant drug interactions is strongest with carbamazepine and phenobarbitone (reduced anticoagulant effect) but consider monitoring all patients started on concurrent therapy.

Antifungals

Fluconazole inhibits the metabolism of warfarin and a clinically significant interaction occurs in most patients. A reduction in the dose of warfarin (20–70%) is usually required. Miconazole also inhibits the metabolism of warfarin and potentially serious bleeds have been reported when miconazole preparations (including oral gel and vaginal preparations) have been given in combination with warfarin. Miconazole or fluconazole should not be co-administered with warfarin unless the INR can be very closely monitored.

Apart from isolated case reports, there is very little evidence that itraconazole or ketoconazole interact in the same way.

Antivirals

The anticoagulant effect of warfarin can be enhanced or reduced by ritonavir and nevirapine.

Clopidogrel

The anticoagulant effect of warfarin is enhanced due to antiplatelet action.

Corticosteroids

The anticoagulant effect of warfarin may be enhanced or reduced by low to moderate oral doses of corticosteroids (e.g. prednisone, methylprednisolone, dexamethasone), although the supporting evidence is weak and a clinically significant interaction does not usually occur. High doses of corticosteroids appear to be more likely to cause a significant effect (increased INR).

Cytotoxics

Anticoagulant effect possibly enhanced by etoposide, fluorouracil and ifosfamide and reduced by azathioprine and mercaptopurine.

Dipyridamole

Increased bleeding risk due to antiplatelets effects.

Disulfiram

Disulfiram enhances the anticoagulant effects of warfarin and an interaction (increased INR) probably occurs in most people.

Enteral Foods

These are often high in vitamin K which may reduce the effect of warfarin.

Foods and Juices

A change in diet, especially changing intake of vegetables, fruits and juices high in vitamin K can affect anticoagulant control. The range of possible foods that interact ranges from avocados to ice cream. Generally only significant or sustained dietary changes are likely to have an effect so people should be advised to discuss planned dietary changes with their GP or pharmacist. Patient information leaflets provide further advice.

Cranberry juice seems to have a different effect and compounds in the juice may inhibit the metabolism of warfarin. There have been several reports of bleeding and although information is limited the Committee on Safety of Medicines (CSM) in the UK advise against drinking cranberry juice whilst taking warfarin.

Herbals and supplements

All people taking warfarin should check with their GP or pharmacist before taking herbal preparations or dietary supplements.

Fenugreek, dong quai, ginkgo biloba and garlic are amongst those reported to increase bleeding risk, without a change in INR (i.e. due to antiplatelet effect). Ginseng has been reported to decrease the INR.

St John's Wort can decrease the effect of warfarin in some people. The CSM in the UK advises against concurrent use.

Hormone Antagonists

Anticoagulant effect can be enhanced by danazol (inhibits metabolism of warfarin), flutamide and tamoxifen. All these interactions are established and clinically important and concurrent therapy requires close monitoring of the INR. Tamoxifen and warfarin is the commonest combination seen in practice and dose reductions of warfarin of 30–50 % or more are sometimes required.

Leflunomide

Anticoagulant effect of warfarin possibly enhanced. In case reports an increased INR has occurred after just two or three doses.

Lipid lowering drugs

Simvastatin can cause small increases in the INR in some people taking warfarin but a dose reduction of the latter is not usually required. Atorvastatin does not appear to interact with warfarin. The interaction with fluvastatin and lovastatin may be more significant.

Cholestyramine has been reported to enhance or reduce the effect of warfarin.

Bezafibrate has been occasionally reported to increase the INR in people taking warfarin.

Oestrogens and progestogens

Anticoagulant effect is antagonised

Orlistat (Xenical)

Pharmacokinetic studies indicate no interaction but fluctuations in anticoagulant control may occur in practice. Consider monitoring the INR if orlistat is added to warfarin treatment.

Thyroid Hormones (thyroxine)

A well documented and clinically important interaction. In people with hypothyroidism who are also taking warfarin, the addition of thyroxine usually results in an increased anticoagulant effect and a reduction in the dose of warfarin is necessary. The change in anticoagulant effect may be gradual as the dose of thyroxine is titrated. The addition of an antithyroid drug (e.g. carbimazole) may necessitate an increase in the warfarin dose.

Sibutramine (Reductil)

There is an increased risk of bleeding when sibutramine given with warfarin.

Vitamin preparations

Vitamin K containing preparation can antagonise the effects of warfarin. Check the vitamin K content of multivitamin preparations and dietary supplements.

Bibliography

This information is based on;

Stockley's Drug Interactions. 7th Edition, 2006. Pharmaceutical Press

British National Formulary (BNF). BMJ Publishing Group and Royal Pharmaceutical Society of GB

Bachmann KA (Ed). Drug Interactions Handbook. Lexicomp, Ohio.

Ten Minute Audit

Identifying your patients on omeprazole

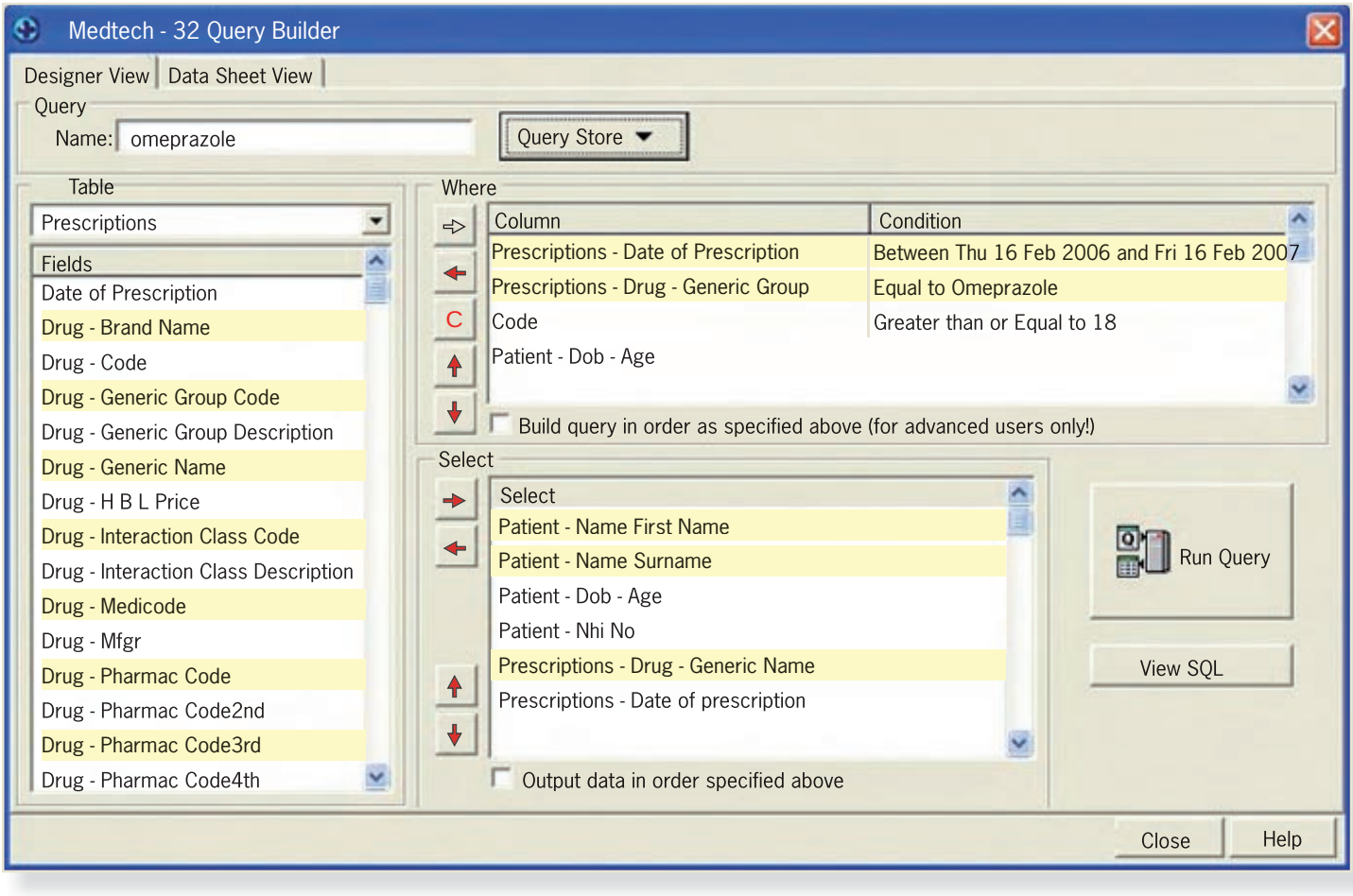
This audit is designed to identify people in your practice taking omeprazole with the aim of considering them for “Review and Reduce” (see page 18) when they need a prescription renewal.

If you are using MedTech you simply complete the query builder form as shown on the opposite page.

Select items from the box on the left and transfer them to the appropriate box on the right of the screen.

Identifying your patients on omeprazole

Medtech 32 Query Builder



Dyspepsia and Heartburn practice audit packs (endorsed by the RNZCGP as a CQI activity for the allocation of MOPs points) available online

visit **www.bpac.org.nz**

Opportunistic interventions in primary care can reduce stoke risk

Particularly for Māori and Pacific peoples and women

Stroke is the third leading cause of death in New Zealand, after ischaemic heart disease and all cancers combined, and is the most important cause of adult disability. Clearly a concerted effort is required across all population groups but there are specific issues for Māori, Pacific people and women.

Trends in stroke rate show ethnic disparities

There has been a modest decline in the rates for both lifetime incidence of stroke and stroke attacks in Auckland over the last two decades.[1] This decline is consistent with the decline reported in Northern European populations. However in Auckland the changes were not consistent across all ethnicities. Figure 1 clearly shows the increasing rates of stroke attacks in Māori and Pacific peoples. What is more, the mean age at onset of stroke for Māori is 60 years and Pacific people 65 years, compared to 75 years for New Zealanders of European ethnicity.[2]

Downward stroke trends linked to improved primary and secondary prevention

Downward stroke trends reported among European populations have been attributed to improved primary and secondary prevention, particularly improved blood pressure control, reduced cigarette smoking, lower cholesterol and greater use of blood pressure, anti-platelet and cholesterol lowering medications.[3]

Figure 1: Trends in ethnic-specific stroke attack rates by study period

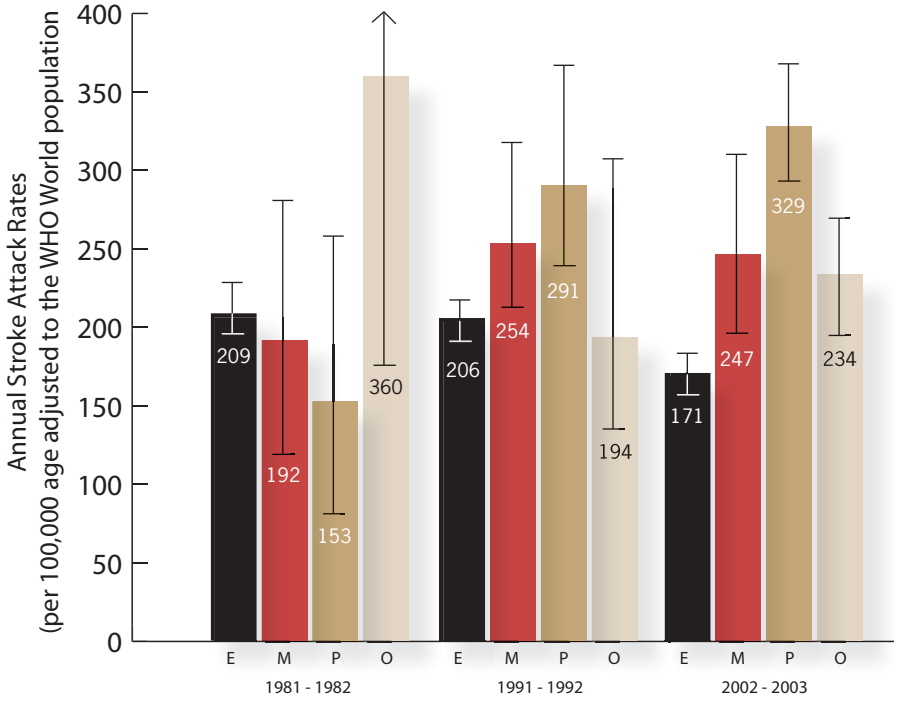
Rates were age-standardised to the WHO world population and shown with 95% CI. Ethnic groups defined as:

E = NZ/European,

M = Maori,

P = Pacific peoples, and

O = Asian and other



Favourable NZ trends for some risk factors counterbalanced by obesity and smoking

The trends in some cardiovascular risk factors in New Zealand Europeans in Auckland were studied between 1982 and 2003.[4] Trends in systolic blood pressure, raised blood pressure, serum cholesterol, HDL-cholesterol levels and use of antihypertensive and cholesterol lowering drugs have generally been favourable. Unfortunately however these favourable trends were counterbalanced by less favourable trends in body mass index, obesity and cigarette smoking.

Important risk factors for stroke

The important modifiable risk factors for stroke are:

- Hypertension
- Atrial fibrillation
- Diabetes
- Smoking
- Adverse lipid profile

Hypertension most important risk factor for stroke

Non-optimal control of blood pressure is the most important risk factor for stroke. There is a strong, direct and near-continuous association between stroke incidence and level of blood pressure. Non-optimal control of blood pressure levels accounts for almost two-thirds of the global burden of stroke.

Atrial fibrillation confers a five-fold increase in stroke risk

An estimated 15% of strokes are attributed to atrial fibrillation (AF) and when people with AF have a stroke they have much worse outcomes. Stroke rates with AF are higher in women than in men, although men have slightly higher rates of AF. Warfarin treatment is effective for both men and women but appears to be underused in women, although risk of major bleeding appears to be no greater than in men.[7]

Warfarin significantly reduces the risk of stroke for people with AF but comes at a cost of increased bleeding risk. Doctors appear to be poor at balancing the risks of stroke and bleeding[6], even though major bleeding can usually be managed by alteration of medication and a few days in hospital, whereas stroke is likely to cause permanent disability or death.

Conclusions for primary care

The most cost-effective approaches for the primary prevention of stroke and other chronic diseases such as coronary heart disease are population-based strategies to modify risk factors. However interventions during day-to-day consultations also make a difference. Useful opportunistic strategies to add to any population-based strategies are:

- Opportunistic screening for risk factors during the consultation
- Starting this 10–15 years earlier for Māori, Pacific people and people from the Indian subcontinent
- Managing hypertension aggressively
- Checking for AF and managing it appropriately for both men and women

References

1. Craid S et al, Trends in stroke incidence in Auckland - New Zealand, during 1981 to 2001. Stroke. 2005;36:2087-93
2. Carter K et al. Trends in ethnic disparities in stroke incidence in Auckland, New Zealand, during 1981 to 2003. Stroke. 2006;37:56-62
3. Fink J. Ethnic trends in stroke in New Zealand: closing the gaps or widening? NZMJ. 2006;119:1245
4. Metcalf P, Scragg R, Schaaf D, Dyall L, Black P. Trends in major cardiovascular risk factors in Auckland, New Zealand: 1982 to 2002–2003. NZMJ. 2006;119:1245
5. World Health Organisation. The world health report 2002: reducing risks, promoting healthy lifestyle. Geneva: WHO; 2002
6. Lip G et al. Physician variation in the management of patients with atrial fibrillation. Heart. 1996;75:200-205
7. Gomberg-Maitland M et al. Anticoagulation in women with non-valvular atrial fibrillation in the stroke prevention using an oral thrombin inhibitor (SPORTIF) trials. European Heart Journal, 2006;27:1947-53

Bandolier

Independent evidence-based thinking about health care

Healthy survival

Bandolier 154, Volume 13, Issue 12 www.ebandolier.com

Suppose for a moment you are a man (Bandolier readers who are not will excuse us for a moment for a little reverie). Suppose you are 55 years old and healthy. Suppose you have developed a burning desire to:

A Make sure that you get the very last drop out of your pension fund, or
B To see Macclesfield win the European Championship (any other extremely remote sporting achievement), or
C Want to see documents about the present UK government released under the present 30-year embargo.

Whichever you choose, you need to live for another 30 years, and since you are going to do that, you need to remain free of physical or mental problems. This has also been called exceptional survival, exceptional because so few actually achieve it. Bandolier 78 examined findings of the US Nurses' Study that showed that women with healthy lifestyles lived far longer than those who did not. We now have a similar finding for men [1].

Study

This was a report of the Honolulu Heart Program, which recruited over 8,000 Japanese-American men in 1965-1968. The men were aged 45 to 68 years old (average 54 years). In subsequent years it has recorded mortality and development of major physical illness and cognition, during eight follow up visits up to 2005. A physical examination was performed at baseline, as well as biochemical and other variables.

Participants were classified into one of four types:

1 Non survivors, who died before a specified age (75, 80, 85, 90 years).
2 Usual survivors but disabled with a physical or cognitive disability.
3 Usual survivors with chronic disease but no disability.
4 Exceptional survivors who survived to a specified age without major chronic disease or cognitive or physical impairment.

Chronic disease of interest included coronary heart disease, stroke, cancer, COPD, Parkinson's disease, and diabetes. Physical impairment was defined as difficulty walking half a mile (about 800 metres).

Figure 1: Percentage of men in the cohort with different outcomes by age 85 years

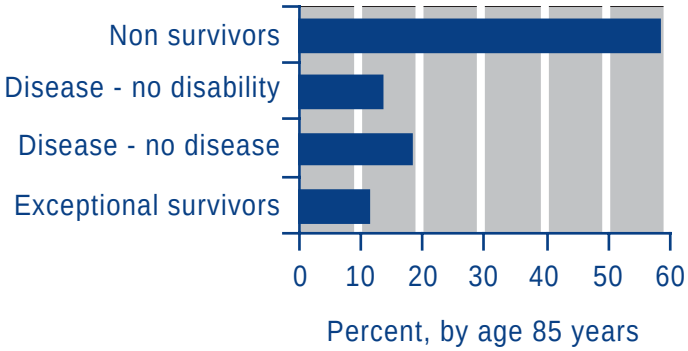


Figure 2: Probability of 55 yr man being alive at 75, 80, or 85 years, with 0 or ≥6 risk factors

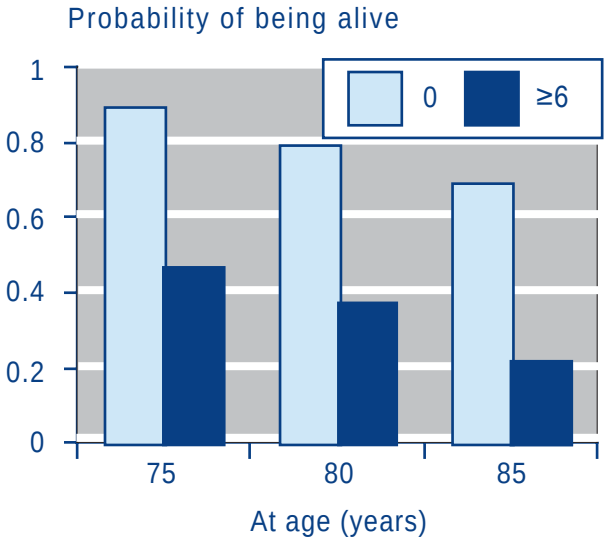


Figure 3: Probability of 55 yr man being free of serious disease at 75, 80, or 85 years if alive, with 0 or ≥6 risk factors

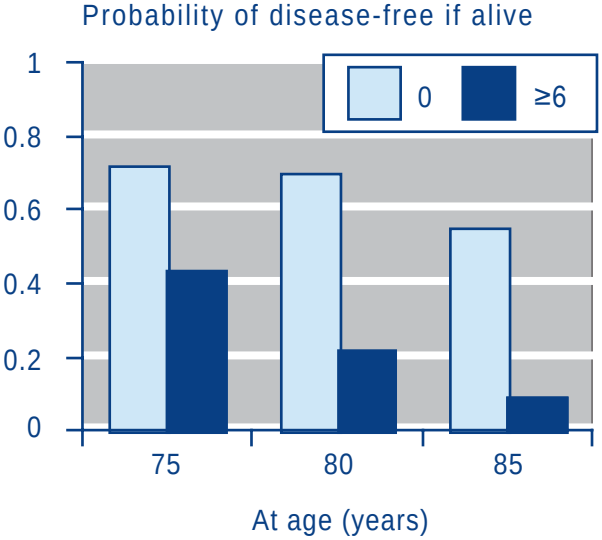
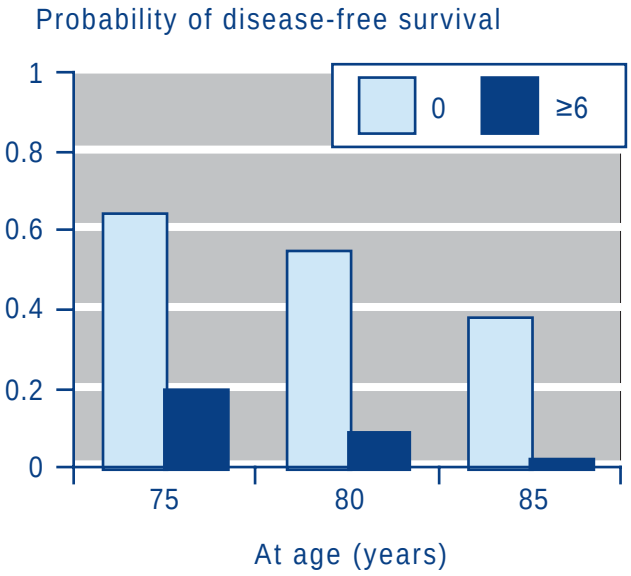


Figure 4: Probability of 55 yr man being alive at 75, 80, or 85 years and free of serious disease, with 0 or ≥6 risk factors



Results

Of 8006 original participants, 5,820 were healthy at baseline, did not die within one year, and had full baseline information including physical functioning. The classification at age 85 years is shown in Figure 1. Only 11% of men were exceptional survivors.

A set of risk factors was created after analysis of 29 different variables at baseline:

- Hyperglycaemia
- Hypertension
- High alcohol consumption (more than three drinks a day)
- Low education
- Overweight
- High triglyceride level
- Low grip strength
- Unmarried

In the absence of any of these risk factors, a man aged 55 would have a high probability of survival to age 85 years (69%), and of exceptional survival among those alive at 85 years free of disease and cognitive impairment (55%); the probability of being alive at age 85 and being free of major disease was the product of these (38%). With six or more risk factors, there was much less likelihood of any of these outcomes (22%, 9%, and 2% respectively).

Figures 2, 3, and 4 show the results graphically. With between 1 and 5 risk factors, the probabilities gradually declined, in a more or less linear manner. Thus for a man aged 55 years with three risk factors, the chance of survival to 85 years would be 50%, of being an exceptional survivor if alive at 85 years 30%, and of being both alive and free of major disease at 85 years about 15%.

Comment

The major benefits of healthy living for men in this study were not dissimilar to those for women in the US Nurses' Study (Bandolier 78). In the end it all comes down to the usual healthy living advice. Don't smoke, drink moderately, don't be overweight, exercise, eat sensibly, and, for men, get married (helps with all the above).

Most of all, there is a steep relationship between both survival and being free of major disease and the number of risk factors. In the range 0-2 risk factors, the decline is moderate. With additional factors, the decline becomes steep. The lesson is to keep them to a minimum.

Essentially this is the Bandolier healthy living advice, available from the website. So, if you want to know the winner of the 2035 FA Cup, Ashes, or World Series, you know how to do it.

Reference:

1 BJ Willcox et al. Midlife risk factors and healthy survival in men. JAMA 2006 296: 2343-2350.

STATINS AND ALBUMINURIA

Bandolier 150, Volume 13, Issue 8 www.ebandolier.com

There are times when you just don't know what to think of evidence, especially when it comes on a topic that one's tired mind has not considered before. Is it overwhelming, underwhelming, or something in between? A systematic review [1] looking at the effects of statins on urinary albumin or protein excretion is a useful example of how to look at evidence, over and above being of interest in itself.

Systematic review

Many databases were searched for randomised studies in adults of statin compared with placebo, with urinary excretion of albumin or protein as an outcome. Information required was the mean baseline and final excretion rates for statin and placebo groups. Prior intent was to analyse according to the level of albumin or protein excretion, with below 30 mg/day as normal excretion, between 30 and 299 mg/day as microalbuminuria, and 300 mg/day or more being macroalbuminuria.

Results

Fifteen trials with 1,384 participants were found. Three trials with 938 patients had normal urinary albumin excretion (based on average of all patients), six (171 patients) had microalbuminuria, and six (275 patients) had macroalbuminuria or proteinuria above 300 mg/day. Two of the trials were not double blind, and one had no clear eligibility criteria.

There was clinical heterogeneity between studies, with causes of raised albumin including diabetes, IgA nephropathy, hypertension, and complex kidney disease, or not being reported in one trial. There was one large trial, but most were small, with only eight patients treated with statins in two trials. Trial duration was three to 46 months, with most between three and 12 months.
The results of the statin treatment arms in individual trials are shown in Figure 1, using a logarithmic scale because baseline excretion varied between <10 mg/day and more than 5,000 mg/day.

With placebo, urinary albumin or protein excretion changed but

little. No trial where baseline urinary albumin excretion was normal had any meaningful change in excretion with statin. Most trials where patients had raised baseline urinary albumin excretion showed substantial reductions with statin treatment.

The weighted mean percentage reduction was about 50% for both microalbuminuria and macroalbuminuria or raised protein excretion compared with placebo. The exceptions were two trials. One was neither double blind nor had clear eligibility criteria in 36 patients with type 2 diabetes and apparently a mean age of 24 years. The second was in 30 patients with complex renal problems.

Comment

The authors of the paper do a good job of making sense of their data, but perhaps miss the obvious problem when assessing an outcome of urinary albumin excretion. For instance, if an excretion is reported as 5,000 mg/day, with a standard deviation of 2,500 mg/day, the chances are that data used for these calculations are not normally distributed. Some individual urinary excretions could be very high, while many could be lower; in the circumstance an average may not be representative of urinary excretion values of most patients.

Is the mean meaningful, in that case? It probably is much less useful than a median, and the mean may mislead. The fact that we see means falling by 50% in most trials should therefore give us some confidence, because results are consistent. Moreover, the two trials not in overall agreement are one with the lowest quality, and the only one in complex kidney disease, quite different from the others.

However, this is an excellent example about how one could lose a potentially important effect by lumping together clinically heterogeneous groups. Almost 70% of participants had normal urine protein excretion, and here there was no change. Had the analysis lumped these together with those with increased urine protein excretion, the effect may have been missed. It emphasises that we need always to ask the question whether these patients in the trial are like ours, and always to ask for the most appropriate analysis of data.

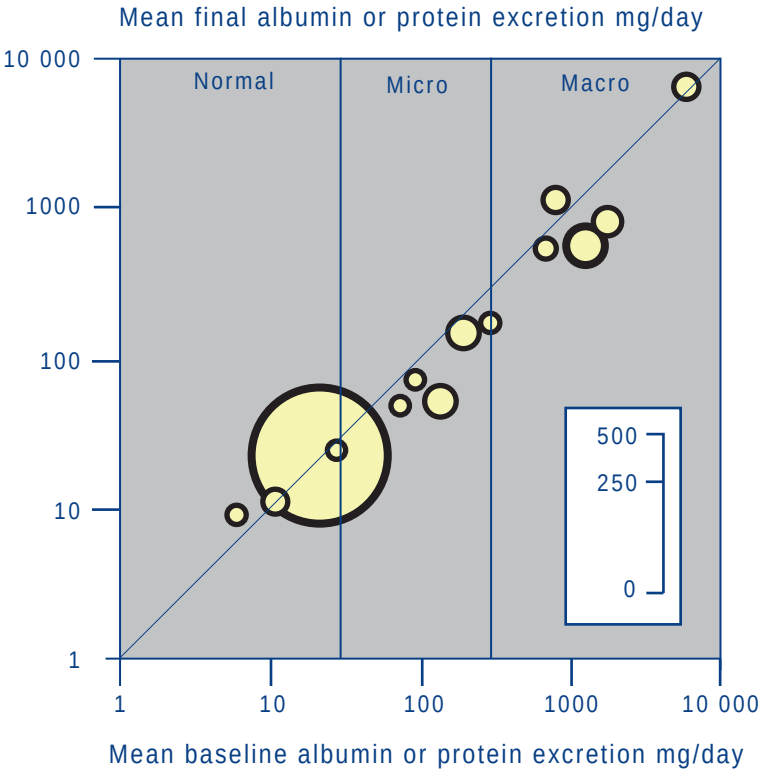
Reference 1. K Douglas et al. Meta-analysis: the effect of statins on albuminuria. Annals of Internal Medicine 2006 145: 117-124.

Antibiotics for acute otitis externa

Bandolier 150, Volume 13, Issue 12 www.ebandolier.com

Acute otitis externa is an inflammation of the external ear canal, commonly known as swimmer's ear. It can be treated with systemic or topical antibiotics, and topical treatment can involve several different types of antibiotic or antiseptic, sometimes combined with cortiocosteroid. A systematic review reveals just how little we know about what works best [1].

Figure 1: Individual studies showing baseline and final urinary albumin excretion, by normal albumin excretion, and micro- and macroalbuminuria



Systematic review

Searching involved using different databases for studies in any language. Articles were limited to topical treatments for acute otitis externa, parallel group design, comparing antimicrobial and placebo, antiseptic and antimicrobial, or steroid plus antimicrobial versus antimicrobial alone or steroid alone. Outcomes used included clinical cure (absence of all signs and symptoms) or improvement (partial or complete relief). Different end points over 3 to 21 days were examined, with the intention to combine the final results.

Results

Twenty trials described as randomised were found, 18 with the required information for data pooling. The median size was 79 patients (range 28 to 842), all but one including children and adults. Half did not explicitly define acute otitis externa, and only half were described as double blind.

Using the Oxford quality scoring system for randomisation, blinding, and withdrawal description, only 10 trials scored 3 out of 5 points, associated with a relative lack of bias. The proiportion of higher quality trials (3, 4, or 5 out of 5) did not improve with time (Table 1).

There were 13 meta-analyses of these 18 trials, all without sensitivity analysis according to quality score. The effect of topical antibiotic (neomycin) plus corticosteroid compared with placebo was described in only two good quality studies, with only 89 patients. Cure rates were much higher for antibiotic plus steroid than with placebo at 3-10 days. The NNT calculated for these two trials was 2.2 (1.6 to 3.7).

The only other comparisons of at least two treatments in relatively unbiased trials was for antiseptic versus antibiotic in three

trials, with identical cure rates of about 60% at 7-10 days and 80% at 14 to 28 days.

Table 1: Trial quality over five decades

Decade	Quality score (range 1-5)	
	1 or 2	3-5
1960s	0	1
1970s	1	3
1980s	1	1
1990s	4	2
2000s	4	3

Comment

Another example where we have a paucity of data to guide therapy for a relatively common condition. Most trials were performed since 1990, yet most had poor quality scores indicating at best poor reporting quality, and at worse inadequate conduct. If anything, the quality of more recent trials was worse than those published earlier (Table 1). These are simple trials, and the influence of quality is well known. How can it be that trials of inadequate quality continue to be performed or reported? This shows a clear failure by ethics committees and journals, and a disservice to patients and professionals.

Reference 1 RM Rosenfeld et al. Systematic review of topical antimicrobial therapy for acute otitis externa. Otolaryngology – Head and Neck Surgery 2006 134:S24-S48.

Antibiotics for acute otitis media

Bandolier 150, Volume 13, Issue 12 www.ebandolier.com

The Achilles' heel of pooled analysis is that we concentrate on averages. No individual is average, and we could do with much less concentration on whether interventions work on average, and more on which patient characteristics determine where the intervention works best. Not does it work, but in whom does it work? How can this be done? The answer is individual patient meta-analysis. Theoretically this can provide really useful information. Such an analysis for acute otitis media in children [1] gives little indication that antibiotics are useful in any children.

Review

Investigators of trials were approached for individual patient data if their trials randomised children aged 0-12 years with acute otitis media, compared antibiotics with no treatment or placebo, and had pain and fever as outcomes. Of 10 such trials, six provided data.

Outcomes calculated were presence of pain (yes/no), fever (greater or less than 38˚C), or both at 3-7 days. A series of pre-defined subgroup analyses were planned, together with logistic analysis to identify important correlates of treatment efficacy.

Results

The six trials essentially tested amoxicillin versus delayed treatment or placebo. These six trials randomised 1,633 children. Overall, antibiotics reduced the incidence of an extended episode of acute otitis media at 3-7 days by 13%, with an NNT of 8 (95% confidence interval 6-11).

Table 1 shows the overall result in more detail, together with those subgroups where there was a lower (better) NNT. The analyses indicated that the effect of antibiotics was modified by age, bilateral disease, and otorrhoea.

Comment

The authors of this analysis go to great pains to describe possible limitations, despite their individual patient analysis, and the great care they have taken in a detailed and sophisticated analysis. The take-home message, though, is that antibiotics seem to be most beneficial in younger children with bilateral acute otitis media, and where there is otorrhoea.

How much weight should we place on this? Not much, because differences between antibiotics and placebo disappeared by five or six days, numbers were small, and what differences there were came from differences with placebo (look at Table 1 carefully). This analysis nails down that there is no subgroup of children for whom antibiotics can be really useful in acute otitis media, unless there are complications or other consideration. It proves the utility of individual patient analysis.

Table 1: Results of sub group analyses for antibiotics vs placebo in AOM

Subgroup	Number in analysis	Extended episode of acute otitis media (%)		Relative risk (95% CI)	NNT (95% CI)
		Antibiotic	Placebo		
Overall result	1663			0.83 (0.78 to 0.89)	8 (6 to 11)
<2 years with bilateral AOM	273	30	55	0.64 (0.62 to 0.80)	4 (3 to 7)
<2 years with unilateral AOM	261	35	40	0.92 (0.76 to 1.1)	not calculated
Otorrhoea present (any age)	116	24	60	0.52 (0.37 to 0.73)	3 (2 to 5)
Otorrhoea absent (any age)	439	28	42	0.80 (0.70 to 0.92)	8 (4 to 20)

Outcome was pain, fever, or both at 3-7 days

Reference: 1. MM Rovers et al. Antibiotics for acute otitis media: a meta-analysis with individual patient data. Lancet 2006 368:1429-1435.

bpac^{nz} Executive Board

The board currently comprises of one nominated representative from each partner, an Independent Chair and the bpac^{nz} Chief Executive Officer. The board meets on a regular basis and is assisted in its deliberation by the CEO and the BPAC Administration Manager.

Executive Board

Alison Paterson - Independent Chair

Associate Professor Jim Reid - University of Otago

Dr Dean Millar-Coote - South Link Health

Dr Doug Baird - IPAC

Dr Peter Didsbury - ProCare Health

Co-opted board member Dr Paul McCormack - Pegasus Health

Chief Executive Officer - Professor Murray Tilyard

Alison Paterson FCA, QSO Independent chair

Alison Paterson is chair of bpac^{nz}, the Electricity and Gas Complaints Commission, Abano Healthcare Ltd, the Governing Board of the Centre of Research Excellence for Growth and Development (University of Auckland) and the Oversight Committee at Ambulance NZ. She is also Deputy Chair of the Reserve Bank of New Zealand Ltd, a board member of Vector, Metrowater Ltd and Nga Pae o Te Maramatanga (Māori CoRE) and a Massey University councillor.

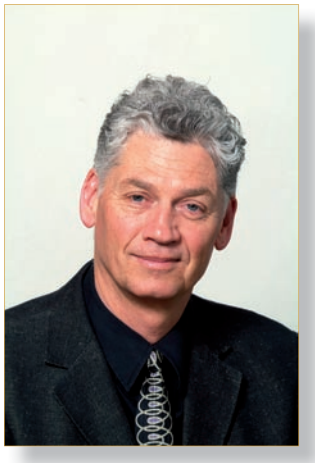
Alison Paterson has a strong background in health including previous appointments as Chair of Waitemata District Health Board and District Health Boards New Zealand Inc. She has also served as a Deputy Chair for Health Waikato and as a Director of Health Benefits.

Dr Peter Didsbury MBChB Dip Obst FRNZCGP

Peter has been a general practitioner in Manurewa, South Auckland for 17 years. He is the Clinical Director and Deputy Chairman of ProCare Health Ltd. One of the ProCare initiatives he has been involved with, the ProCare Dyspepsia Programme, won the Supreme Award in the 2004 Health Innovations Awards. Peter has an interest in evidence-based healthcare, has chaired several top national guideline projects and is past Chair of the New Zealand Guidelines Group.

Dr Doug Baird MBChB Dip Obst FRNZCGP

Doug Baird has been in general practice in Freemans Bay since 1979 and has been consulting in several other areas of medical practice since 1980. His interests are in innovation and change management in the delivery of health care. He is a founding member of ProCare Health Ltd and has been a Director since its inception. He is past Chair of IPAC and Chair of Homecare Medical Limited and Dr Ponsonby/White Cross Ltd.



Dr Jim Reid MBChB FRNZCGP

Jim Reid graduated in medicine at the University of Otago Medical School in Dunedin. He had previously trained as a pharmacist. He undertook his postgraduate work at the University of Miami in Florida. Currently he heads the Department of General Practice at the Dunedin School of Medicine and he is also Associate Dean for Postgraduate Education. He has a private family medical practice at the Caversham Medical Centre, Dunedin, New Zealand.

He is a Distinguished Fellow of the Royal New Zealand College of General Practitioners and is also a Fellow of the American College of Chest Physicians. He has a special interest in respiratory medicine. He is a member of the Medical Advisory Panel of the Asthma and Respiratory Foundation of New Zealand.

Dr Dean Millar-Coote

MBChB FRNZCGP

Dean has been a general practitioner in Dunedin for the last 16 years. He is Deputy Executive Director of South Link Health and is a Clinical Tutor for the Department of General Practice, University of Otago. He has interests in diabetes and heath promotion.

bpac^{nz} Annual Report 2006

Strategic Commentary From The Chair

bpac^{nz} is a national demand management organisation which is committed to the delivery of quality information which is relevant, timely and useful to the main clinical providers of primary health care in New Zealand. The organisation is contracted by PHARMAC in respect of demand-side management in pharmaceuticals until 2009 (with the potential to extend until 2011). The contract with DHBNZ in respect of its management programme in laboratories is for the period July 2005 until June 2008.

Strategic Goals

The long term goal is to establish bpac^{nz} nationally and internationally as a resource and co-ordinating centre for information about best clinical practice in New Zealand primary healthcare.

Conscious of the need to offer security of employment to our staff the organisation continues to endeavour to diversify funding sources to protect the revenue base. The focus of the organisation is on:

- The maintenance of intellectual capacity
- Establishing an effective corporate structure and business model
- Consistently exceeding all contracted service delivery requirements
- Ensuring that the bpac^{nz} programme is meeting market expectations in terms of content and method of delivery
- Studying, measuring, assessing and documenting the impact of bpac^{nz} programmes on provider behaviour and the health outcomes of New Zealanders.

People

We welcome Dr Paul McCormack of Pegasus Health to the board. We record our appreciation of the considerable ability, contribution and leadership of CEO Murray Tilyard. He is supported by a very committed and competent team which we value highly. The organisation enjoys a positive working relationship at all levels within PHARMAC.

Alison Paterson
Chair

CEO's Overview

I am pleased to present the CEO's report for bpac^{nz} for the 2005/2006 financial year. This is the second annual report that bpac^{nz} has produced. It is primarily intended for shareholders and other interested parties.

In the first report I gave a short history of the origins of bpac^{nz}. In particular I commented that bpac^{nz} was incorporated under the Companies Act in September 2003. As a not-for-profit organisation. bpac^{nz} was successful in gaining the national contract for demand-side management of pharmaceuticals and commenced activities in October 2003.

In last year's report I also commented on our success in gaining the contract for the laboratory demand-side management programme. This programme commenced in July 2005 and has been extremely well received.

Highlights of the 2005/06 Financial Year

The major highlight of the past year was our successful proposal to PHARMAC for the ongoing delivery of the Pharmaceutical Demand-Side Management programme.
The initial contract with PHARMAC for three years was due to cease on June 30, 2006. In March 2006 PHARMAC put out a Request for Proposal to the sector seeking responses from parties interested in providing services to promote the responsible use of pharmaceuticals. As part of that response bpac[nz] considered the following issues:

- Review of representation at board level. Following the review we offered a co-opted position on the board to Pegasus Health. I am pleased to announce that Dr Paul McCormack of Pegasus accepted that offer and Dr McCormack was appointed as the Pegasus representative on the bpac[nz] board in April 2006.

- The subcontract between bpac[nz] and BPAC Inc. In last year's report I commented that since the inception of bpac[nz] a significant proportion of the activity was undertaken by BPAC Inc. via a sub contract. In moving forward the board thought it was an appropriate time to negotiate the transfer of staff and assets from BPAC Inc. to bpac[nz].

- Māori health initiatives and website development. The board noted the positive development which had occurred in regards to Māori health initiatives and website development. The board wished to ensure that these two areas were highlighted in the proposal

Following the evaluation of proposals, bpac[nz] was chosen as the preferred provider and we were successful in negotiating a three year contract commencing on October 1 2006.

I am also pleased to say that we were successful in negotiating and achieving an agreement with BPAC Inc. for the transfer of staff and assets to bpac[nz].

In developing bpac[nz]'s proposal the team determined how best to deliver the information to the target audience. We had received feedback that the information was of very high quality, but that the frequency resulted in some of the audience feeling overloaded with information.
In response we proposed launching a new publication called 'best practice' which would be published six weekly and would incorporate all of the pharmaceutical material. The first edition of 'best practice' will be produced in mid-October 2006. This will build on our other publication 'best tests' which is highly thought of by the target audience. The development of 'best practice' will I'm sure pose some issues for the team, but there is nothing that we believe that we cannot overcome. We are committed to producing high quality educational material which assists practitioners in their day to day caring of patients.

In conclusion I believe that bpac[nz] has now firmly established themselves as a key producer of high quality information on Pharmaceutical and Laboratory use in the primary sector. In reaching this stage I would like to thank the board and in particular Alison Paterson. I would also like to thank all the bpac[nz] team for all the hard work they undertake for their commitment and support.

Professor Murray Tilyard
CEO

Dear Dave

Dave and other members of the bpac[nz] team answer your clinical questions

If you have a clinical question email it to
dave@bpac.org.nz

Dear Dave

Is there an association between the use of the combined oral contraceptive and reduced Vitamin B_{12} deficiency

Contributed by Linda Bryant MClinPharm FPSNZ Clinical Advisory Pharmacists Association (CAPA)

The reduction in serum Vitamin B_{12} in women using the combined oral contraceptive is not usually clinically significant as vitamin metabolism and stores are normal. Further investigations are warranted if there are signs and symptoms suggestive of deficiency or other factors such as diet.

An association between use of the combined oral contraceptive and reduced Vitamin B_{12} serum concentrations has been noted since 1969[1], but the clinical significance of this is debated.

Mean serum B_{12} concentrations may be 33–40% lower in women using the combined oral contraceptive compared to non-users[2,3]. One study of 71 women using low dose (20 micrograms ethinyl estradiol) oral contraception vs. 170 control non-users found that 13% of combined oral contraceptive users had Vitamin B_{12} concentrations less than 130 pmol/L compared to none in the control group; 15% had subnormal Vitamin B_{12} concentrations (130–170 pmol/L) compared to 4% in the non-users; and 72% had normal Vitamin B_{12} concentrations compared to 92% of the non-users.[4] Another study found 50% of combined oral contraceptive users have serum B_{12} concentrations less than normal (< 170 pmol/L) and 15% were clearly deficient (< 70 pmol/L).

Despite apparent low serum B_{12} concentrations in some users of the combined oral contraceptive, clinical symptoms and macrocytosis are rare and tend only to be reported as case studies.[5] An early study of 201 cases of megaloblastic anaemia found only one case to be associated with oral contraceptive use.[6]

It is now accepted that the reduced serum B_{12} concentrations observed in OC users do not usually represent a true deficiency as absorption, excretion and stores of Vitamin B_{12} are usually normal. In addition, metabolic markers for deficiency (methylmalonic acid and homocysteine) remain unchanged and clinical symptoms are rare.[6]

It is postulated that the low serum B_{12} is due to a reduction in Vitamin B_{12} binding proteins in serum. In particular it may be due to reduced haptocorrin, the major binding protein for Vitamin B_{12}, although the mechanism is still unknown and under investigation.[6]

The reduction in serum B_{12} in women using the combined oral contraceptive is not usually clinically significant as vitamin metabolism and stores are normal. Further investigations are warranted if there are signs and symptoms suggestive of deficiency or other factors such as diet.

References

1. Hjelt K, Brynskov J, Hippe E, Lundstrom P, Munck O. Oral contraceptives and cobalamin (Vitamin B_{12}) metabolism. Acta Obstet et Gynecol Scand. 1985;64:59-63
2. Green T, Houghton L, Donovan U, Gibson R, O'Connor D. Oral contraceptives did not affect biochemical folate indexes and homocysteine concentrations in adolescent females. J Am Diet Assoc. 1998;98:49-55
3. Wynn V. Vitamins and oral contraceptive use. Lancet. 1975; 1(7906):561-4
4. Sutterlin M, Bussen S, Rieger L, Dietl J, Steck T. Serum folate and Vitamin B_{12} levels in women using modern oral contraceptives (OC) containing 20 micrograms ethinyl estradiol. Eur J Obstet Gynecol Reprod Biol. 2003;107:57-61
5. Kornberg A, Segal R, Theitler J et al. Folic acid deficiency, megaloblastic anaemia and peripheral polyneuropathy due to oral contraceptives. Isr J Med Sci. 1989;23:142-5
6. Bor M. Do we have any good reason to suggest restricting the use of oral contraceptives in women with pre-existing Vitamin B_{12} deficiency? Eur J Obstet Gynecol Reprod Biol. 2004;115:240-1

bpac online

www.bpac.org.nz

bpac nz
better medicine