best practice

Issue 2

December 2006

Warfarin

LABAs

TCAs

bpac nz
better medicine

Best Practice Journal (BPJ)
ISSN 1177-5645

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

BPJ Issue 2 December 2006

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
Independent Practitioners Association Council
University of Otago

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

Front cover: Pohutukawa flower.
(Mainland pohutukawa, Metrosideros excelsa)

Pohutukawa are found all over New Zealand, although their natural growing range is north of a line stretching from New Plymouth to Gisborne. Pohutukawa and rata are often referred to as New Zealand's native Christmas tree because of the bright red blooms which decorate the trees during the Christmas holiday season.

For many people they rekindle memories of long summer days and holidays spent with friends and family in, on, around and under these magnificent trees.

The board and staff of bpac^{nz} wish you all a happy and fun filled Christmas and holiday season.

Why not try something different this Christmas… instead of bringing out the plastic tree, or buying a pine, why not plant a pohutukawa. For more info visit www.projectcrimson.org.nz

Back cover: Palmers Beach, Great Barrier Island …wish you were here?

Contact us:

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

Contents

Warfarin

Contents

Access best practice online
www.bpac.org.nz

Contents

Essentials

CME

UPFRONT

UPFRONT provides a forum for airing opinions on prescribing issues. The opinions expressed in UPFRONT are those of the authors alone. They do not necessarily represent the views or opinions of bpac^{nz} or its staff.
In this issue Professor Les Toop and Dr Dee Mangin share their opinions about the effects of direct to consumer advertising of prescription medicines.

Direct to Consumer Advertising In New Zealand.

Is the end in sight?

In recent years there have been few issues that match the advertising of prescription medicines directly to consumers (DTCA) in pitting the interests of public health against those of commercial gain. New Zealand and the U.S stand alone in the developed world in allowing the pharmaceutical industry to market their product ranges directly to consumers.

DTCA works by promoting messages that will increase commercial success (overstating benefits) and omitting messages likely to reduce commercial success (minimising harms). As spending on DTCA in both countries has increased from U.S $12 million in the mid 90s to U.S $4.1 billion in 2006 so consumer, health professional and political concern has grown. Internationally there have been many reviews of DTCA from health professional groups, academic institutions, governments and importantly many independent (non industry funded) consumer and patient groups. Without exception they have come to the same conclusion: the partial and potentially misleading information and the accompanying medicalisation caused by DTCA is of net public harm. The only reports and research supporting DTCA have been funded by the pharmaceutical industry, their marketing agents and others who benefit from their support.

All other jurisdictions have reaffirmed their commitment to prevent the introduction of DTCA. In 2002 European parliamentarians threw out a proposal to introduce limited DTCA by a vote of 14 to 1.

Its effectiveness is attested by the growth in expenditure on it, reportedly more than U.S $4 billion was spent on DTCA in the U.S in 2004 and tens of millions in New Zealand. Like the U.S DTCA was 'allowed' in New Zealand by default rather than by design.

DTCA is packaged and sold as 'information' with the pharmaceutical industry claiming to be acting in patients' best interests. However advertising is about manipulation not information. Its sole purpose is to increase profits by convincing consumers they want or need a particular branded drug - to drive choice not to inform it.

Supporters of DTCA argue that consumers have a right to the information contained in prescription medicine advertising to facilitate autonomous choice. Does advertising fulfil this need? Within a bioethical framework, three forms of influence on decision making have been described. The first is persuasion, which is a rational process through which someone comes to believe something, through the merit of reasons another advances. Coercion is the second form of influence. The third is manipulation - swaying a person to do something by means other than coercion or persuasion.

'In health care the key form of manipulation is information manipulation. This is a deliberate act of managing information that nonpersuasively alters a person's understanding of a situation and thereby motivates him or her to do what the agent of influence intends'.

Information gaps are no excuse however to sanction deliberate` misinformation. The presence of DTCA changes the balance of influence on decision making from persuasion to manipulation and masquerades as supporting autonomous choice when in reality it undermines it.

These issues were played out clearly for us as a case study in the recent revelations about Vioxx®, where the emergence of safety concerns occurred after large numbers of patients in many countries had been exposed, after vigorous promotion.

Physicians also have responsibilities to the community. Beneficence, which goes beyond non-maleficence ('do no harm'), confers the moral obligation to prevent harm and promote benefit. This includes advocating for policy change that will protect from harm and promote benefit. In 2002 more than half of all New Zealand GPs responded within days to a letter from Academic General Practice, setting out their intention to lobby for a DTCA ban, and asking for colleagues to share their opinions and experiences. Four out of five GPs writing back felt negatively about DTCA. In this instance New Zealand general practice has let its voice be heard and has prompted all major professional prescribing groups to consider this issue and take a position opposing DTCA. The combined weight of opinion of New Zealand GPs who responded along with the independent consumer groups, has put a ban of DTCA on the political agenda. In New Zealand we have just finished the second round of public consultation in five years which reaffirmed the unified health professional and independent consumer health organisation opposition to DTCA.

If we accept the need to regulate access to and advertising of prescription medicines because of the potential for harm, then the aim should not be balancing the interests of industry and consumers, but rather the protection of consumers. For industry there are major commercial benefits from DTCA but it is ultimately patients who take all the risks.

Hopefully New Zealand politicians and regulators will be able to put aside party politics for such an important public health issue and heed the calls of the majority of health professional and consumer groups to join the rest of the world (bar the U.S) and ban DTCA. Even better would be to replace it with useful, unbiased independent consumer health information.

An announcement from the Government has been promised. Watch this space.

Dee Mangin
Les Toop

Atrial fibrillation and flutter in primary care

Atrial fibrillation is under-diagnosed and under-treated

Atrial fibrillation or flutter (AF)* occurs in approximately 1% of the general population. The prevalence doubles with each successive decade over the age of 50 years and it occurs in approximately 10% of people over the age of 80 years. An estimated 30 to 40 thousand people in New Zealand have AF and about one-third of these are unaware of it. Most GPs probably have some patients with undiagnosed AF.

People with AF are at increased risk of stroke, heart failure and other cardiovascular events. AF is associated with doubling of mortality rates, mainly due to ischaemic stroke. Overall the risk of ischaemic stroke in people with AF is approximately 5% per year but this risk is not evenly distributed across people with this arrhythmia. For people at high risk, the benefits of warfarin to lower this risk, outweighs the risks of serious bleeding from warfarin use. Therefore thromboembolic risk assessment is required for all people with AF.
Warfarin is generally considered to be underutilised

** We have used the abbreviation AF to mean atrial fibrillation or flutter because the principles of antithrombotic therapy and rate control are the same for atrial fibrillation and atrial flutter. However there are some important differences. For example, achieving rate control can be more difficult in flutter than fibrillation, choice of agents for rhythm control are different and people with lone or predominant flutter should be considered for ablation therapy.*

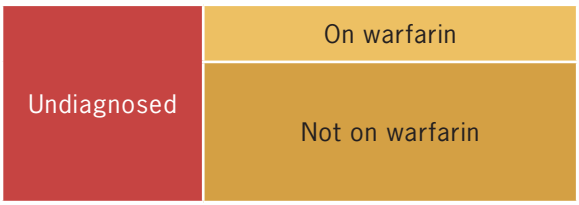
Expert Review: Dr David Heaven. Consultant Cardiologist, Middlemore Hospital

in the management of AF; it appears that approximately one-third of people with identified AF are taking warfarin. This underutilisation almost certainly results from a cautious approach to avoiding the risks of major bleeding with warfarin. These risks have probably been overstated.

Many people with AF are prescribed digoxin for its beneficial effect of lowering the heart rate. However digoxin does not control the heart rate during exercise. Its use as first-line therapy is limited to people who are unlikely to be active or have overt heart failure.

The New Zealand Guidelines Group guideline 'The management of people with atrial fibrillation and flutter' (NZGG, 2005) makes recommendations, which if implemented can be expected to improve the primary care management of people with AF. These recommendations form the basis for this article.

Table 1: People with atrial fibrillation



Of the estimated 35,000 people in New Zealand with AF only two thirds are aware of it and only about one-third of those with identified AF are on warfarin.

Opportunistic screening recommended

Opportunistic screening of the radial pulse for irregularity can help to identify people with asymptomatic atrial fibrillation. The diagnosis needs to be confirmed by ECG, which will also show the heart rate and may suggest underlying cardiac pathology.

Case finding is likely to be higher in older patients or those with cardiac or other conditions often associated with AF. AF appears to occur in Māori people at ages about ten years younger than the general population, probably related to earlier onset of heart disease.

AF is often associated with:

- Cardiac conditions including hypertension
- Hyperthyroidism
- Alcohol excess
- Severe infection
- Pulmonary pathology

AF symptoms

AF results in asynchronous atrial contractions, which reduce cardiac efficiency, and an irregular and usually rapid ventricular rate, which reduces diastolic filling time and coronary perfusion. Most people with AF, but not all, get symptoms from these effects. The most common are palpitations, breathlessness, fatigue, light-headedness and chest discomfort but at times AF can contribute to acute heart failure, myocardial ischaemia and hypotension.

When AF is paroxysmal it may not be present on a standard ECG. Some form of continuous monitoring, such as Holter monitoring or event recording, may be required for people with intermittent symptoms suggestive of paroxysmal AF.

Initial assessment for people with AF

Appropriate initial assessment for all people with AF includes checking for the common causes of AF discussed above, performing a thromboembolic risk assessment and doing any pre-treatment checks necessary before starting particular medications.

Apart from history, examination and ECG the assessment would usually include:

- Transthoracic echocardiogram
- CBC, TSH, renal function, LFTs, INR
- Thromboembolic risk assessment

Transthoracic echocardiography is performed to identify any underlying structural heart disease, which may need further evaluation and information on disorders such as left ventricular hypertrophy, which may impact on thromboembolic risk assessment. When there is likely to be delay in obtaining this examination warfarin therapy does not need to be delayed for people who already meet the criteria for a strategy of rate control and warfarin therapy. Echocardiography is required before a rhythm control strategy is instituted.
Other investigations may also be clinically indicated from this initial assessment.

Antithrombotic therapy and control of rate is the most appropriate strategy for most people with AF

The focus of AF management is to control symptoms and reduce the risk of serious complications such as stroke or heart failure, as well as managing associated pathology. The major components of AF management are antithrombotic therapy, to reduce the risk of stroke, and rate or rhythm control, to reduce haemodynamic disturbance. Antithrombotic therapy and control of rate is the most appropriate strategy for most people with AF.

Choosing between warfarin and aspirin for antithrombotic therapy in AF

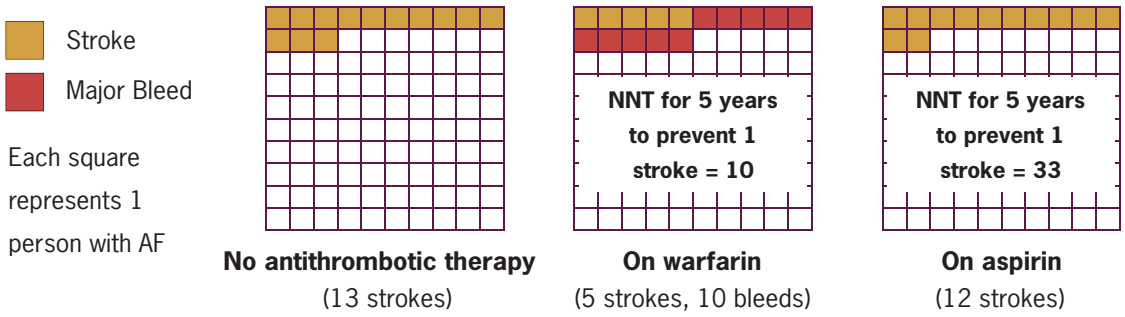
Anticoagulation therapy with warfarin reduces the risk of stroke by approximately two thirds whilst aspirin reduces it by one fifth. There is no difference in stroke risk between paroxysmal, persistent or permanent AF. Therapy should be based on absolute stroke risk rather than current rhythm. The greater risk reduction by warfarin over aspirin must be balanced against the increased risk of serious bleeding. In the average population this is approximately 1% per year.

The risk:benefit ratio for warfarin is most advantageous for people with a high absolute risk of stroke

The risk:benefit ratio for warfarin is most advantageous for people with a high absolute risk of stroke (>15% five year stroke risk). Table 2 shows that when people with a 15% five-year stroke risk receive warfarin therapy there is a significant decrease in stroke incidence. This stroke reduction is matched by an increase in major bleeding. However, although some of this major bleeding will be intracranial haemorrhage, most will be GI or GU bleeding. At stroke risks of greater than 15% there is a greater absolute risk reduction in stroke, without a matching increase in major bleeding, which remains at 10%.

Risk:benefit of antithrombotic therapy

Table 2: Strokes and major bleeds for 100 people with AF and a 15% five-year stroke risk

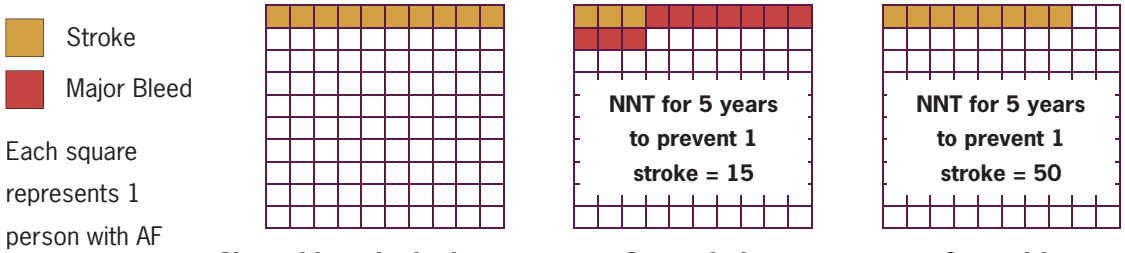


No antithrombotic therapy (13 strokes)

On warfarin (5 strokes, 10 bleeds)

On aspirin (12 strokes)

Table 3: Strokes and major bleeds for 100 people with AF and a 10% five-year stroke risk



No antithrombotic therapy (10 strokes)

On warfarin (3 strokes, 10 bleeds)

On aspirin (8 strokes)

At low levels of stroke risk (<10% five year stroke risk) the risks of warfarin outweigh its benefits and aspirin is a more appropriate choice. See Table 3. At intermediate levels of risk the benefits are not so clear-cut.

Thromboembolic risk assessment necessary to choose therapy

It can be seen from Table 4 that in order to choose the appropriate antithrombotic therapy a thromboembolic risk assessment is necessary. Table 5 indicates factors which are useful in this assessment.

Table 4: Choice of therapy guided by thromboembolic risk

Thromboembolic risk – five years	
High risk of stroke (≥15%)	Warfarin usually advantageous
Intermediate risk (10-14%)	Discuss patient preferences
Low risk of stroke (<10%)	Aspirin usually preferred
Very low risk of stroke	Antithrombotic therapy not indicated

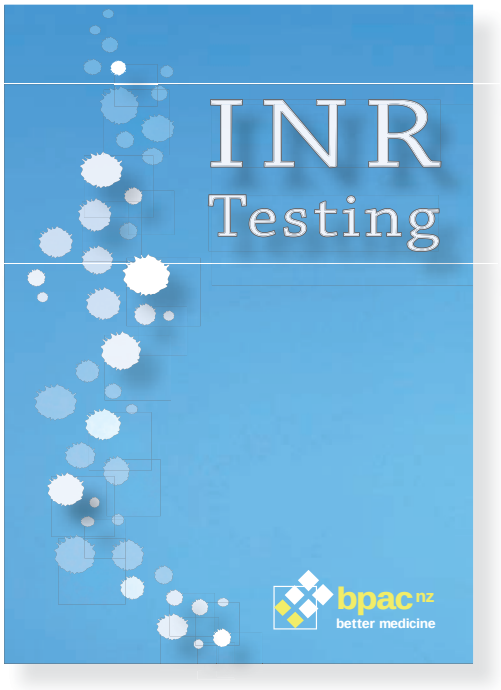
Table 5: Risk factors for thromboembolic risk assessment

High risk factors	
- Significant valvular heart disease (including mitral stenosis and prosthetic valves) - Previous stroke, TIA or pulmonary embolus - Heart failure or significant LV dysfunction	People with AF and one or more of these factors are at high risk of stroke
Medium risk factors	
- Woman >64 years - Man >74 years - Hypertension - Diabetes mellitus	People with AF and two or more of these factors are at high risk of stroke. People with AF and only one of these factors are at intermediate risk of stroke
Very low risk of stroke	
- Under 60 years with lone AF and no identified underlying cause, no hypertension and no clinical or echocardiographic evidence of heart disease	Very low risk of stroke and unlikely to benefit from antithrombotic therapy

Anticoagulation with warfarin requires a systematic practice-wide approach to INR monitoring.

Warfarin therapy for stroke prevention in AF can usually be initiated and maintained in primary care. This is discussed in bpac[nz] publication 'INR Testing'. This and an audit for your practice's system for monitoring INRs can be obtained by faxing 0800 bpac nz or from www.bpac.org.nz.

It is not always safe to give people warfarin even if their stroke risk is high; however the dangers of warfarin therapy are often overstated. Discussion of when to exclude people from warfarin therapy is included in a separate article in this issue of 'best practice journal'.



Rate control is usually preferred to rhythm control to reduce the haemodynamic disturbance of AF

Rate control is the recommended strategy for most, but not all people with AF. Compared to rhythm control it reduces morbidity and future hospitalisations and there appears to be no difference in the effects on mortality. However some people will benefit from control of rhythm.

First identify people who are likely to benefit from rhythm control

People with any of the following are likely to benefit from pharmacological or non-pharmacological rhythm control, which is conversion to and maintenance of sinus rhythm:

- Significant haemodynamic compromise, angina, MI or acute pulmonary oedema as a result of rapid AF; immediate cardioversion is usually indicated, and warrants immediate referral to hospital
- Wolff Parkinson White Syndrome (WPW) with AF can lead to sudden death and warrants immediate referral to hospital
- Unacceptable arrhythmia related symptoms despite satisfactory rate control
- Possibly young patients without structural heart disease (lone AF)

If a rhythm control strategy is chosen for people who are not yet anticoagulated, they should be cardioverted within 48 hours of onset of AF. If this deadline cannot be achieved, cardioversion will need to be delayed until an INR ≥2 has been achieved for four weeks or transoesophageal echocardiogram (TOE) has excluded atrial thrombi. The patients must be fully anticogulated at least four weeks post cardioversion even if TOE shows no thrombus.

The pharmacological and non-pharmacological techniques used to cardiovert patients in AF to sinus rhythm are not available to New Zealand GPs. Specialist referral is required. Antiarrhythmic therapy for maintenance of sinus rhythm should generally be guided by physicians or cardiologists because of potential serious complications of new or more frequent occurrence of pre-existing arrhythmias and non-cardiac side effects.

Rate control is recommended for most people with AF

Good rate control in AF can not only control symptoms but also improve outcomes by decreasing adverse results of AF such as left ventricular dysfunction and cardiomyopathy.

Measures of good control of ventricular rate in AF are ongoing maintenance of:

- Resting ventricular rate of 60 – 80 bpm
- Ventricular rate during moderate exercise (6 minute gentle walk) 90 – 115 bpm
- No symptomatic palpitations or dyspnoea during exercise

These measures need to be reviewed regularly. Ventricular rate cannot be measured at the wrist as the radial pulse rate significantly underestimates ventricular rate because of intermittent short coupling intervals. Ventricular rate must be measured either at the apex or from the ECG.

In primary care apical pulse measurement immediately following a six minute walk is optimal and is validated in clinical trials. If there are clinical concerns ventricular rate can be measured by Holter monitor (target 24 hour average <100 bpm) or exercise heart rate with a treadmill ECG.

Choice of rate control agent is guided by comorbidities

Table 6 lists rate-control agents in order of preference taking into account other conditions that may be present. A combination of these may be required to achieve good control. People who only get occasional paroxysmal AF, may be reluctant to take ongoing rate control medication for their intermittent problem, and can use medication as needed to control symptoms. However there is little evidence for the benefit of this approach and most people with paroxysmal AF are still likely to benefit from appropriate antithrombotic therapy.
Table 7 gives additional information about the use of rate-control agents.

Table 6: Choice of rate-control agent

Comorbidity	First-line	Second-line	Less effective or desirable
No heart disease	Beta-blockers* OR Calcium channel blockers**		Digoxin*** (can be first-line in people unlikely to be active)
Hypertension	Beta-blockers* OR Calcium channel blockers**		Digoxin***
Ischaemic heart disease	Beta-blockers*	Calcium channel blockers** OR Digoxin***	Ablation and pacing
Congestive Heart Failure	Digoxin in overt heart failure Carvedilol or metoprolol in stable heart failure	Beta-blockers* (excluding carvedilol and metoprolol) OR Diltiazem	Amiodarone Ablation and pacing should be considered
COPD	Calcium channel blockers**	Beta-blockers* (unless there is reversible bronchospasm)	Digoxin***

* excluding sotalol

** diltiazem or verapamil

*** as monotherapy (can be used in combination with other rate-control agents)

Table 7: Oral pharmacological agents for rate control in people with atrial fibrillation/atrial flutter

Drug	Oral loading dose	Onset of action	Commonly used oral maintenance doses	Adverse effects	Comments
Beta-blockers					
Atenolol	N/A	2 - 3 hr	25 - 50 mg	Hypotension, heart block, bradychardia, asthma, heart failure	In people with heart failure lower doses may be advisable (negative inotropic effect)
Carvedilol	N/A	60 - 90 min	6.25 - 25 mg/bd		
Metoprolol	N/A	4 - 6 hr	23.75 - 200 mg/day*		
Nadolol	N/A	3 - 4 hr	20 - 80 mg/day		
Propranolol	N/A	60 - 90 min	80 - 240 mg/day		
Calcium channel blockers					
Diltiazem	N/A	1 - 4 hr	120 - 360 mg/day	Hypotension, heart block, heart failure	In people with heart failure, lower doses may be advisable
Verapamil	N/A	1 - 2 hr	120 - 360 mg/day	Hypotension, heart block, heart failure, digoxin interaction	In people with heart failure, lower doses may be advisable (negative inotropic effect)
Other					
Digoxin	0.5 - 1.0 mg	2 hr	0.0625 - 0.375 mg/day	Digoxin toxicity, heart block, bradychardia	First-line therapy only for people unlikely to be active (e.g, older people or infirm) and for people with heart failure. Less effective in hyperadrenergic states
Amiodarone	400 - 800 mg/day for 1 week	1 - 3 week	200 mg/day	Photosensitivity and other skin reactions, pulmonary toxicity, polyneuropathy, gastrointestinal upset, bradychardia, hepatic toxicity, thyroid dysfunction, torsades de pointes (rare)	Although there is fairly good evidence of efficacy, this is an agent of last resort in this indication, due to its long-term toxicity

* The controlled release presentation of metoprolol is most commonly used.

N/A = Not applicable

Oral therapy usually provides effective rate control in AF. Other interventions such as IV administration of anti-arrhythmic agents or atrioventricular nodal ablation and pacemaker implantation may be required.

Contraindications to warfarin therapy

The major contraindication to warfarin therapy is where risk of haemorrhage outweighs the benefits of anticoagulation

In some people, for example those with a bleeding disorder the risk is obvious, for others the risk is less overt.

The NZGG gives a list of conditions, which have been used to exclude people from the trials of warfarin use in AF (Table 8). We therefore cannot conclude that people with these conditions are likely to benefit from warfarin therapy.

Advance age is, in itself, not a contraindication to warfarin therapy

Not everyone with AF at high risk of stroke is able to take warfarin. However it is generally considered that warfarin is under utilised for this indication in both primary care and hospital practice. For example many clinicians are reluctant to prescribe warfarin for older people with AF because of fear of bleeding. It is true that bleeding risk from warfarin does increase with age but paradoxically older people are at increased risk of stroke, and potentially have much to gain from anticoagulation.

In primary care we are often concerned that participants in clinical trials are not like the people we see in our practices. However, although it is true that people with AF in the community are older and have more comorbidities than participants in the clinical trials of stroke prevention in AF, we can be reassured that reviews of the evidence confirm that stroke and bleeding rates with AF are comparable between trial participants and those in the community.

The NZGG document 'The management of people with atrial fibrillation and flutter' presents a useful table of contraindications to warfarin therapy because of bleeding risk in older people (Table 9). Reference to this table can give us more confidence in the use of warfarin.

Table 8: Exclusion criteria used for trials of warfarin in AF.

- Significant Thrombocytopenia (platelet count <100x10^9/L)
- Unexplained anaemia (Hb <100g/L)
- Bleeding disorders
- Past intracranial or retinal haemorrhage
- GI or GU bleed in previous six months
- Previous severe bleeding on warfarin with INR in target range
- Recurrent unexplained syncope
- Uncontrolled hypertension
- Renal failure
- Alcoholism
- Expected poor compliance
- Pregnancy

Table 9: Contraindications to warfarin therapy in older people

Absolute Contraindication	Relative Contraindication	No Contraindication
Bleeding diathesis	Conventional NSAID use	Predisposition to falls
Thrombocytopenia (<50 x 10^3/μL)	Participation in activities with high risk of trauma	Advanced age
Hypertension (untreated or poorly controlled, consistently >160/90)	Unexplained anaemia	NSAID plus PPI
Non-adherence to treatment & monitoring	Dementia	Coxib use
Previous intracranial or retinal bleed	Multiple comorbidities	Recent resolved PU bleeding (with *H. pylori* testing and treating)
Recent GI or GU bleeding	Unexplained recurrent syncope	Previous ischaemic stroke

Warfarin is contraindicated in pregnancy

Warfarin is teratogenic and should not be used in pregnancy.

Stroke Risk Stratification

The Baseline Risk of Stroke in People with New-onset AF (and without prior TIA or stroke) from Framingham Data (5-year stroke risk in %)

People with AF and either significant valvular disease, prior stroke or TIA are at **VERY HIGH** risk of stroke and don't need risk stratification. They should receive long-term warfarin unless contraindicated.

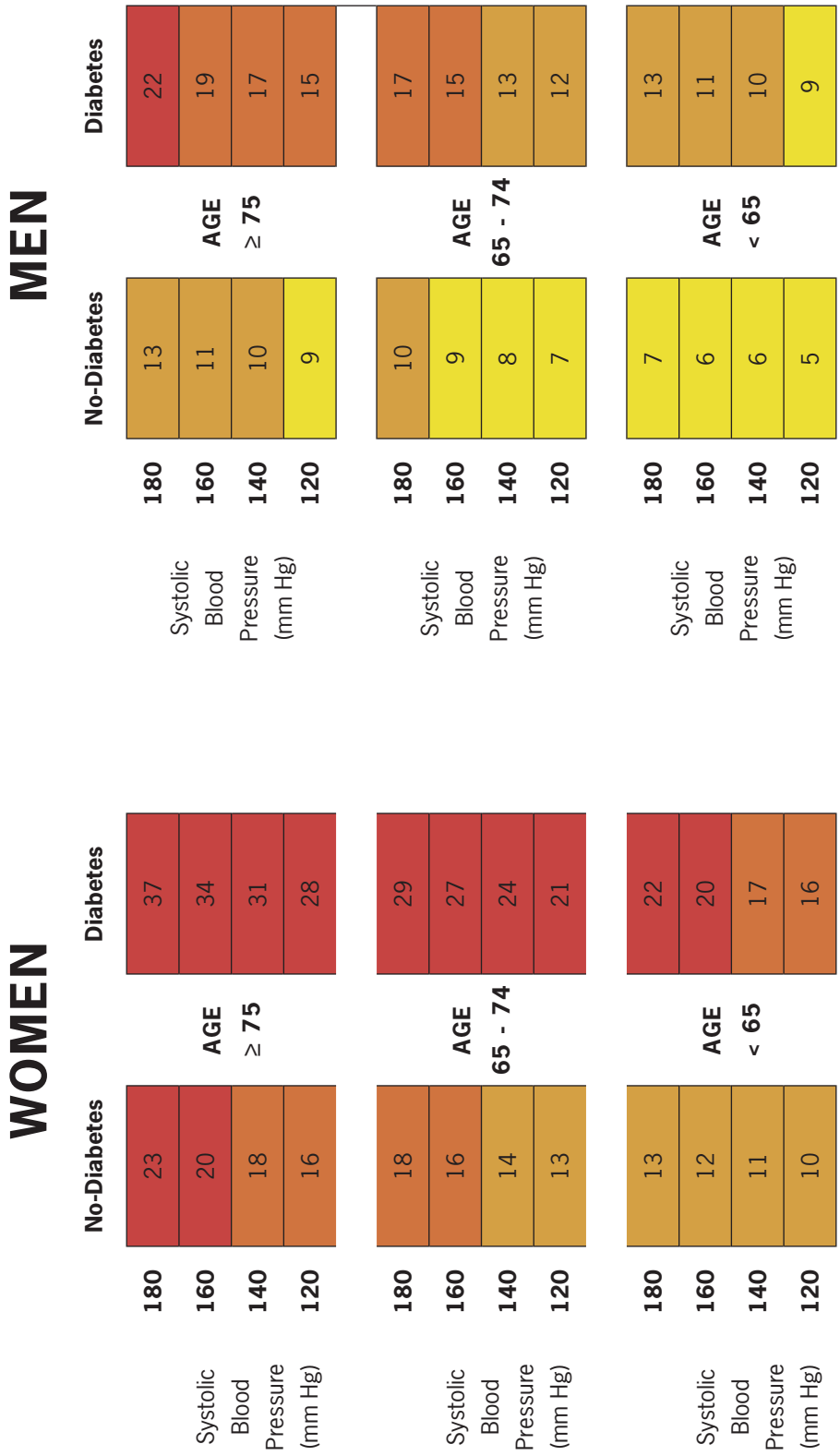
People with AF and either left ventricular dysfunction (LVEF ≤ 40%) or a past episode of decompensated heart failure are at **HIGH** risk and should receive long-term warfarin unless contraindicated.

Choice of warfarin or aspirin depends on stroke risk*

Stroke Risk	% Risk	Treatment
VERY HIGH	**≥ 20%**	Long-term anticoagulant treatment with adjusted dose of warfarin aiming for an INR 2.5 (range 2.0 to 3.0) unless there are clear contraindications
HIGH	**15 - 19%**	
INTERMEDIATE	**10 - 14%**	Discuss the individual's potential benefits, risks and preferences for or against anticoagulant or aspirin treatment
LOW	**< 10%**	Commence aspirin (75 mg to 300 mg) after discussion

Note: In people with a contraindication to warfarin, consider using aspirin (75 mg to 300 mg) after discussion.
* Even when risk of stroke is high careful consideration of contraindications is required before warfarin is commenced.

5-year Stroke Risk (%)



Reference

1. New Zealand Guidelines Group (NZGG). The management of people with atrial fibrillation and flutter. 2005. Available from http://snipurl.com/127p6

Update on the use of LABAs for the treatment of Asthma

The current literature regarding the use of LABAs in asthma can only be described as 'busy'. Central to the debate are two issues – firstly how safe are LABAs in the treatment of asthma and secondly how should exacerbations be managed in patients currently using combination LABA/ICS inhalers.

Key Points

- Long acting beta agonists (LABAs) are not indicated as first-line therapy for any asthmatic patient.
- Adverse reactions to LABAs such as hyper-responsiveness, bronchospasm and respiratory arrest are rare but patients should be closely monitored for the first 6 – 12 weeks after the initiation of treatment.
- LABAs should only be prescribed for people who are already on inhaled corticosteroids (ICS).
- LABAs may be indicated as add-on therapy if symptoms do not respond to low to moderate doses of ICS (e.g. in adults 400 - 800 micrograms beclomethasone or equivalent).
- Patients on LABAs should be counselled and reminded on the importance of continuing their ICS.
- LABAs should be discontinued after a trial period if no benefit is seen.
- Patients with acutely deteriorating asthma should not be started on a LABA.
- Review the asthma management plans of people on combination LABA/ICS inhalers.

Expert Review: Associate Professor Jim Reid. Associate Professor of Graduate Education, Dunedin School of Medicine

Adding a LABA improves symptom control, lung function and reduces the need for rescue medication

Randomised controlled trials (RCTs) have found that adding a LABA improves symptom control, lung function and reduces the need for rescue medication compared with placebo in people with asthma that is poorly controlled by ICS. There was no significant difference in the exacerbation rates between the two groups in any of the RCTs (Clinical Evidence, 2006).

Furthermore, adding regular doses of LABA improves lung function and symptoms, decreases exacerbation episodes and reduces the need for rescue medication compared with increasing the dose of ICS (Clinical Evidence, 2006).

Adding a LABA is more effective than doubling the dose of ICS (at a dose of 400 micrograms beclomethasone per day or equivalent) and should always be considered if a dose of ICS greater than 800 micrograms per day is required (NZGG, 2002). In this regard LABA can be considered to have two advantages; improved symptom control along with a steroid sparing effect.

Adverse respiratory reactions to LABA possible

There have been occasional reports of deterioration in asthma control, impairment of response to short acting bronchodilators and even respiratory arrest following commencement of a LABA. Several mechanisms may be implicated including paradoxical bronchospasm, increased bronchial responsiveness and tolerance, but none of these have been identified in prospective trials. Prescribers need to be aware of the possibility of these rare adverse reactions and monitor patients closely especially during the first 6 – 12 weeks after starting a LABA (Taylor, 1999).

Peak flow monitoring should be encouraged and patients should be advised to seek advice if they perceive a lack of benefit from using their reliever (short acting bronchodilator) medication. When people are put on a LABA symptoms often improve and compliance with ICS may be reduced. It is therefore important to remind patients to continue to take their inhaled steroids regularly in addition to the LABA. The LABA should be withdrawn if asthma control continues to deteriorate in the absence of other explanations (Taylor, 1999).

Latest trials question safety of LABA

Two recent trials have raised awareness of the possible safety concerns regarding the use of LABAs, and prompted regulatory authorities in some countries to reiterate warnings about their appropriate use, especially the need for concurrent use of an ICS.

Salpeter et al conducted a meta-analysis of 19 RCTs involving almost 34,000 asthmatic patients. The primary objective was to estimate the risk of serious adverse events associated with LABA use. The use of LABA was associated with increased asthma exacerbations and asthma related deaths. In addition, statistically significant increases in hospitalisations occurred in both adults and children with salmeterol or formoterol, compared with placebo (Salpeter, 2006). It was estimated that LABAs cause an excess of approximately one death per 1000 years of patient use.

The Salmeterol Multicentre Asthma Research Trial (SMART) compared the addition of salmeterol or placebo to existing asthma treatment in over 26,000 patients aged 12 years and over (mean age 39 years) (Nelson, 2006). All patients had a current diagnosis of asthma and were receiving asthma medication. Exclusion criteria included the previous use of inhaled LABA and a history of adverse reactions to sympathomimetic amine drugs. The intervention group received 42 micrograms of salmeterol twice daily by metered dose inhaler and the control received a matched placebo inhaler. All subjects were followed for 28 weeks and continued to use their current asthma drugs.

The composite primary end point was respiratory related death or life threatening experience (i.e. intubation and mechanical ventilation). Secondary endpoints included all cause mortality, asthma related death, respiratory related death, life threatening experiences and combinations of these.

The trial was stopped early after the interim analysis due to enrolment problems and preliminary findings from a subgroup analysis which indicated a significant risk of harm in African-Americans. In this group there were more respiratory deaths (24 vs 11) and asthma related deaths (13 vs 3) in the salmeterol group than the placebo group (Table 1).

Table 1: SMART trial results: addition of salmeterol vs placebo to usual pharmacotherapy in patients with asthma

Outcomes at 28 weeks	Salmeterol	Placebo	RRI (95% CI)	NNH (95% CI)
Combined respiratory related death or life threatening experience	0.4% (n = 50)	0.3% (n = 36)	40% (-9 – 114)	NS
Asthma related death	0.1% (n = 13)	0.02% (n = 3)	337% (25 – 1434)	1239 (705 - 5126)
Respiratory related death	0.2% (n = 24)	0.1% (n = 11)	116% (6 – 341)	965 (515 - 7861)
Combined asthma related death or life threatening experience	0.3% (n + 37)	0.2% (n = 22)	71% (1 – 189)	810 (415 - 16050)

RRI = Relative Risk Increase, CI = Confidence Interval, NNH = Number Needed to Harm (Lipchik, 2006)

As the trial was stopped early there are insufficient data to indicate whether the apparent increased risk in African-Americans applies to other populations.

Taken together SMART and the meta-analysis indicate that LABAs may be responsible for a small increase in the absolute risk of asthma related deaths and serious exacerbations. In both trials the number of adverse events was small and it is not possible to ascertain if inappropriate use of LABAs (e.g. monotherapy, poor adherence to ICS use or continued use of LABAs despite lack of response) was a contributing factor.

The important messages are to ensure that LABAs are prescribed and used in accordance with current recommendations; ensure concurrent use of ICS, monitor for adverse reactions (especially early in treatment) and discontinue if there is a lack of or inadequate response.

There is now more choice and wider access for subsidised asthma inhalers

On 1 August 2006 some significant changes occurred to the range of subsidised asthma inhalers. The changes mean that you will be able to prescribe a wider range of asthma inhalers, while there is now also wider access to some existing treatments.

For further details visit http://snipurl.com/12asq or see your latest schedule

Role of combination LABA/ICS inhalers

The combination of a LABA and ICS in one inhaler provides a convenient and effective dose form in a single inhaler and also ensures the concurrent use of an ICS with the LABA. However they do not allow flexibility in adjusting the doses of individual components and their use in asthma exacerbations is unclear. They are most suitable for people who are already established on a moderate dose of ICS and a LABA in separate inhalers.

LABA/ICS combination in asthma exacerbation

There is currently significant controversy and debate on optimal treatment of early asthma exacerbations in those patients who are already taking a combination LABA/ICS preparation.

Budesonide and fluticasone share similar anti-inflammatory characteristics but there are differentiating features between salmeterol and eformoterol which affect how they can be used in worsening asthma. Salmeterol should not be given at doses greater than the maximum maintenance dose, but the dose of eformoterol can be temporarily increased with the potential of quadrupling the lowest recommended dose (Fitzgerald, 2006).

In the management of early exacerbations the patient should follow an individual management plan and for those on combined LABA/ICS options include temporary additional ICS doses provided via a separate inhaler, a short course of oral prednisone or a temporary increase in the dose of eformoterol/budesonide (Symbicort®).

A LABA should not be started during worsening asthma and the dose of either of the LABAs alone or salmeterol/fluticasone combination (Seretide®) should not be increased during exacerbation.

References

Clinical Evidence (BMJ publishing) 2006.

Fitzgerald JM, Gibson PG. Asthma Exacerbations. Thorax 2006;61:992-999.

Lipchik RJ. Addition of salmeterol to usual asthma pharmacotherapy may increase reparatory related deaths or life threatening experiences. Evid Based Med 2006;11:139.

Masoli M, Weatherall M, Holt S, Beasley R. Moderate dose inhaled corticosteroids plus salmeterol versus higher doses of inhaled corticosteroids in symptomatic asthma. Thorax 2005:60:730-34.

Nelson HS, Weiss ST, Bleecker ER et al. The Salmeterol Multicenter Asthma Research Trial; a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. Chest 2006; 129:15-26.

New Zealand Guidelines Group. Diagnosis and trreatment of adult asthma. 2002 available from http://snipurl.com/127p0.

Salpeter SR, Buckley NS, Ormiston TM et al. Meta-analysis: effect of long acting beta agonists on severe asthma exacerbations and asthma related deaths. Ann Intern Med 2006; 144:904-12.

Taylor D R. .Adverse respiratory reactions to long acting beta agonists. Prescriber Update 1999;18;24-28. Available from; http://snipurl.com/120il (Accessed October 2006).

Indications for LABA

The addition of a LABA to inhaled corticosteroids can be considered:

- For younger children (under 12 years) where asthma is poorly controlled despite using ICS for at least three months at total daily doses of 200 micrograms beclomethasone or budesonide or 100 micrograms fluticasone.
- For adults and older children (12 years and over) despite using ICS for at least three months at total daily doses of 400 micrograms beclomethasone or budesonide or 200 micrograms fluticasone.

Source: Current PHARMAC Schedule. This is consistent with current evidence (Masoli, 2005, Fitzgerald, 2006).

Improving the care of children with asthma

The majority of children with asthma, especially Māori children, do not have good control of their asthma

Studies suggest that the majority of children with asthma do not have good control. This appears to be associated with low asthma pharmaceutical use compared to the recommendations of asthma management guidelines.

Asthma has been identified as one of the most heavily under treated diseases. In children there is low usage of long acting beta agonists (LABAs) despite high average daily doses of inhaled corticosteroids.

New Zealand has one of the highest asthma prevalence rates in the world. It affects over 200,000 children, which is approximately one in four. Rates of hospital admissions due to asthma are highest in children, being about double that of adults, with the majority occurring in children under five years.

Although the prevalence of childhood asthma in New Zealand is similar for Māori and non-Māori, Māori children with asthma have more severe symptoms when presenting for routine or acute asthma care, require more time off school because of asthma and require hospitalisation for asthma almost twice as often as non Māori children. While admission rates for childhood asthma have gradually decreased in New Zealand Europeans, rates for Māori and Pacific children have risen.

Despite increased need for good asthma management Māori children are less likely to receive adequate education, have an asthma action plan or be prescribed preventive medication. Other commonly cited barriers for Māori with asthma include cost for consultation, access to transport and telephone and the attitude of the doctor/provider including bias and discrimination.

Implementation of The Paediatric Society of New Zealand evidence based guideline 'Management of Asthma in Children Aged 1-15 Years' should lead to improved asthma outcomes for all children. LABAs do not feature in the management of asthma in children under the age of four years for primary care but its use in children aged 5-15 years is well represented in the following algorithm from the guideline.

The text for this article is adapted from: Asher I, Byrnes C, Editors 'Trying to Catch Our Breath - The Burden of Preventable Breathing Diseases in Children and Young People.' The Asthma and Respiratory Foundation, 2006. Available from: http://snipurl.com/12apl

Summary of Stepwise Pharmacological Management in Children Aged 5-15 Years

Step 1: Mild Intermittent Asthma

Inhaled short acting $ß_2$ agonist as required

Step 2: Regular Preventer Therapy

Add inhaled steroid 200-400 microgram/day beclomethasone dipropionate (BDP) or budesonide (BUD), or 100-200 microgram/day fluticasone

- use the higher dose for greater severity,

(cromoglycate, nedocromil or montelukast[1] if inhaled steroid cannot be used)

Step 3: Add on Therapy

1. Add inhaled long acting $ß_2$ agonist (LABA)[2]
2. Assess response to LABA:
   - good response to LABA - continue LABA
     some beneift from LABA in maximum dose but control still inadequate, increase inhaled steroid to 400 microgram/day BDP or BUD, **or** 200 microgram/day FP (if not already on this dose)
   - no response to LABA - Stop LABA consider trial of montelukast **or** SR theophylline

Step 4: Persistent Poor Control

Increase inhaled steroid to 600-800 microgram/day BDP or BUD, or 300-400 microgram/day fluticasone[3]

Continue to review add on therapy

Refer to paediatrician if not improving

Step 5: Continued Poor Control

Refer to paediatrician

Maintain high dose inhaled steroid

Consider steroid tablet in lowest dose providing adequate control

1. The only NZ Registered Leukotriene Receptor Antagonist, montelukast, is not currently on the Pharmaceutical Schedule.
2. Maximum recommended dose of eformoterol is 12 microgram/bd, and salmeterol 50 microgram/bd.
3. These levels of ICS are greater than usually required to achieve optimal control, do not hesitate to seek advice from a paediatrician.

The algorithm is taken from: 'Management of Asthma in Children Aged 1-15 Years' Paediatric Society of New Zealand Available from: http://snipurl.com/thzj

Tricyclic Antidepressants

Prescribing Points

Recently we have discussed the place of TCAs in the treatment of depression in the elderly. In the treatment of depression, SSRIs are more commonly used, than TCAs as first-line agents in most situations. TCAs may also cause problematic adverse effects especially in the elderly. In this article we point out that TCAs are still valuable in the management of depression and neuropathic pain.

TCAs are effective antidepressants

Tricyclic antidepressants (TCAs) are as effective as selective serotonin reuptake inhibitors (SSRIs) in the treatment of depression and provide an alternative treatment if an SSRI is unsuitable or not tolerated. In general TCAs are less well tolerated than SSRIs, mainly due to anticholinergic effects, and are more toxic in overdose. In some patients low doses of TCAs (75 – 100 mg daily) may be effective with less adverse effects than higher doses (bpac^{nz}, 2004).

Adverse effects less likely with nortriptyline

TCAs vary in their pharmacological properties and this translates mainly to significant differences in the relative intensity of some adverse effects (Table 1). Amitriptyline and nortriptyline are the most commonly prescribed TCAs in New Zealand, and in general nortriptyline is the preferred agent, as it is less likely to cause troublesome adverse effects. Although amitriptyline may be preferred if sedative effects are specifically required, nortriptyline will often give the desired hypnotic effect with less risk of undesirable effects, if given at night time.

TCAs usually first-line agents in the treatment of neuropathic pain

TCAs are effective agents for the treatment of various types of neuropathic pain and are usually considered first-line agents. Amitriptyline and nortriptyline are equally effective (NNT approximately 3). The best evidence for the effectiveness of TCAs in neuropathic pain is in painful diabetic neuropathy and trigeminal neuralgia. SSRIs (NNT 6.7) and venlafaxine (NNT 4.1 – 5.5) do not appear to be as effective as TCAs (Gilron, 2006). The starting dose of TCA is 10 – 25 mg at night or in divided doses every 12 hours. The daily dose can be increased by 10 – 25 mg every week. The usual effective dose is 50 – 150 mg daily (median 50 – 75 mg daily) (Gilron, 2006).

Table 1: Comparison of Adverse Effects of TCAs

	Anticholinergic	Orthostatic Hypotension	Sedation	Weight Gain	Cardiac Arrhythmias
Amitriptyline	+ + + +	+ + + +	+ + + +	+ + +	+ + +
Nortriptyline	+ +	+	+ +	+	+ +
Doxepin	+ + +	+ +	+ + + +	+ + + +	+ +
Impiramine	+ + +	+ + + +	+ + +	+ + + +	+ + +
***Clomipramine**	+ + + +	+ +	+ + + +	+ + + +	+ + +
****Desipramine**	+	+ +	+ +	+	+ + +
Trimipramine	+ + + +	+ + +	+ + + +	+ + + +	+ + +

From; Drug Information Handbook, 11th Ed. 2003. American Pharmaceutical Association

*Clomipramine has significant serotonergic properties and is usually reserved for specific indications such as Obsessive Compulsive Disorder. Retail Pharmacy Specialist.

** Restricted to Hospital Pharmacy Specialist

Caution with drug interactions

TCAs have numerous clinically significant drug interactions. Some of these involve additive effects when co-prescribed with sedatives, hypnotics and drugs with hypotensive and anticholinergic properties. The metabolising enzyme CYP2D6 is involved in the metabolism of most TCAs and drugs which inhibit this enzyme (e.g. SSRIs, amiodarone, cimetidine, methadone) will increase plasma concentrations of TCAs and dose related adverse effects. TCAs with strong serotonergic properties such as clomipramine have the potential to cause serotonin syndrome with other serotonergic drugs such as tramadol and TCAs. Although controversial, TCAs are sometimes co-prescribed with an SSRI under specialist advice, especially if the patient is having difficulty sleeping. It should be noted that the combination is potentially hazardous due to the increased risk of serotonin syndrome and up to four fold increases in plasma concentrations of the TCA. The smallest possible dose of TCA should be used, usually 10 mg.

Stopping TCAs suddenly can cause withdrawal reactions

If TCAs are stopped suddenly without tapering, patients can experience a withdrawal syndrome characterised by some or all of the following: gastrointestinal disturbances, malaise, chills, anxiety, agitation, sleep disturbances, parkinsonism and mania or hypomania (Dilsaver, 1994).

Most of these symptoms are associated with cholinergic rebound and can be managed by gradual tapering over at least four weeks, or as long as six months in patients who have been receiving long term maintenance therapy.

TCA withdrawal has resulted in cardiac arrhythmias in some patients and seems to be more severe and more common in children.

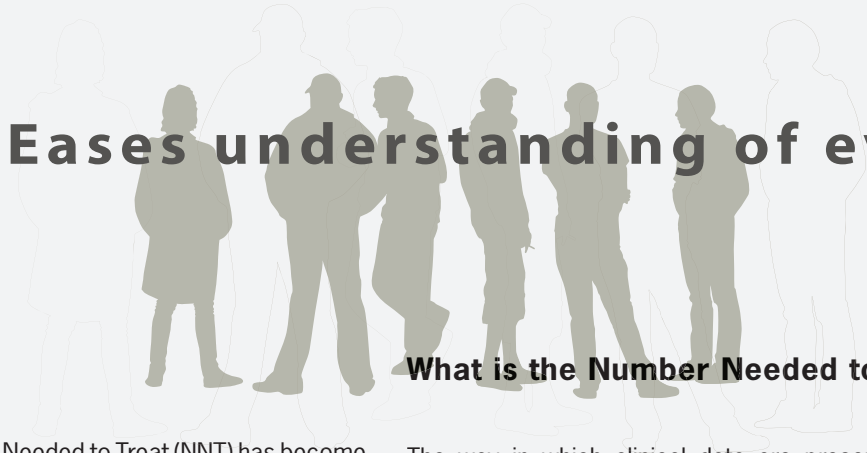
References

bpac[nz]. Depression POEM 2004. Available from www.bpac.org.nz.

Dilsaver SC. Withdrawal phenomena associated with antidepressant and antipsychotic agents. Drug Safety 1994;10:103-14.

Gilron I, Watson PN, Cahill CM, Moulin D. Neuropathic pain; a practical guide for the clinician. CMAJ 2006;175(3):265-75.

NNT – Eases understanding of evidence



Summary

- The use of Number Needed to Treat (NNT) has become popular in evidence based medicine to express the clinical effectiveness of interventions.
- NNT is computed from changes in absolute risk and gives a better indication of effectiveness than relative risk.
- NNTs can be compared for different agents treating the same condition or disease.
- As with other statistical parameters a quoted NNT is a point estimate and 95 % confidence intervals should also be available.
- NNTs calculated from meta-analysis of randomised controlled trials generally provide the highest level of evidence for the effectiveness of an intervention but there are some important limitations.
- When applying population derived NNTs to individual patient care it may be important to consider the patients background level of risk to determine the value of the intervention.
- With every NNT there is a number needed to harm (NNH). Knowledge of the NNH is sometimes important in weighing up the benefits versus risks of treatment.

What is the Number Needed to Treat (NNT)?

The way in which clinical data are presented can have a strong impact on clinical decision making. Relative risk (RR) is often used to summarise treatment comparisons, especially in drug advertising and journal abstracts, but it does not take in to account variation in baseline risk or the absolute size of the treatment effect. Absolute risk reduction (the difference in risk between treatments) gives this information but it can be difficult to interpret in the clinical context.

The NNT is the number of patients who need to be treated in order to prevent one additional bad outcome or to attain one additional benefit. NNT is the reciprocal of the absolute risk reduction associated with an intervention. It may also be calculated as 100 divided by the absolute risk reduction expressed as a percentage (Table 2).

NNTs in context

NNTs can be calculated from any trial data which give dichotomous outcomes, e.g. event or non-event, death or survival or cure from infection/lack or response. The outcomes may be more complex, such as an analgesic effect measured by pre-determined reduction in pain score at a specified time (response) vs failure to reach the target reduction in pain score (non-response). The NNT also needs additional information to indicate how long the treatment needs to be given for likely benefits to be observed. This is particularly the case in prophylaxis or when treatment effects are delayed. Some examples of NNTs are shown in Table 1.

Table 1: Examples of NNTs

Condition	Treatment	Comparator	Duration of Intervention	Outcome	NNT (CI)
Peptic Ulcer	Triple Therapy	H2-antagonist	6 – 10 weeks	*H. pylori* eradication	1.1 (1.08 – 1.15)
Migraine	Oral sumatriptan	Placebo	One Dose	Headache relieved at 2 hr	2.6 (2.3 – 3.2)
Painful Diabetic neuropathy	TCA	Placebo	4 – 12 weeks	At least 50% pain relief	2.9 (2.4 – 4.0)
High 5 year risk of CV mortality	Simvastatin	Placebo	5 years	Prevention of major coronary event	33 (26 – 46)

The acceptability of the NNT depends on whether the intervention is for treatment or prevention. An NNT of over 100 may be acceptable for prevention of death in a common condition such as cardiovascular disease but for the treatment of migraine headache a much smaller value of 4 or 5 would be expected.

Table 2: Relative Risk Reduction, Absolute Risk Reduction and NNT

A new anti-inflammatory drug A reduces the risk of serious GI bleed (event rate) by 50 % compared with a traditional NSAID. This is calculated from:

$$\frac{\textbf{GI bleed rate with drug A}}{\textbf{GI bleed rate with traditional NSAID}}$$

In the trial referred to, the rate was 1% with drug A and 2% with the traditional NSAID.

Relative Risk (RR) = 1/100 divided by 2/100 = 0.5 or 50%. This appears very significant; however the corresponding Absolute Risk Reduction (ARR) is the risk difference which takes in to account the background risk rate and is 0.02 – 0.01 = 0.01 or 1%.

The NNT is 1/0.01 (or 100/1) or 100. Intuitively we can also see that we need to treat 100 patients with drug A to prevent one adverse event (GI Bleed).

The RR can be very misleading. In the above trial if the event rates were 1 in 10,000 and 2 in 10,000 respectively the RR would still be 50% but the ARR is 0.0001 and the NNT is 10,000.

The NNT therefore indicates how many patients we can expect to benefit from treatment. We also need to consider how many patients are likely to be harmed (e.g. from an ADR) from taking the drug or number needed to harm (NNH).

What about Numbers Needed to Harm (NNH)?

Trials may show negative or harmful effects instead of anticipated benefits and drugs may also cause minor or major adverse reactions. In systematic reviews it is becoming the usual practice to present NNH for major and minor events along with the NNT for benefits to assist in clinical decision making. The balance of the NNT versus NNH indicates the risks versus benefits of treatment. For example, consider if the NNT for a statin to prevent a major coronary event is 50 given for five years and the NNH for rhamdomyolysis (a major harm) is 10,000. In this case we can expect one case of rhabdomyolysis for every 200 patients who will benefit from treatment.

Confidence is required in our NNTs!

Any NNT is just a point estimate and as such has some uncertainty around it. By convention, a 95% Confidence Interval (95% CI) is used to indicate the upper and lower limits of the actual NNT so we can say that there is a 95% probability that the true value lies within this range. To look at this another way, if we have an NNT of 4 (95% CI 3.2 – 6.1) this means that if the studies were repeated, 95 times out of 100 the result would fall in the range 3.2 – 6.1. It also means that we may need to treat as few as three patients or as many as six to get an extra response. Narrow confidence intervals are obviously preferable as they indicate a consistent treatment effect and give assurance that the NNT is close to the point estimate. The upper limit of the 95% CI may cast considerable doubt on the benefits of an intervention, and wide confidence intervals are usually due to variable treatment effects or small numbers of subjects, in the trials analysed.

Caution is required when interpreting NNTs derived from meta-analysis.

Since the introduction of NNTs some 15 years ago a debate has raged about whether NNTs derived from meta-analysis are misleading. It is relatively simple to calculate NNTs from a single randomised controlled trial but pooling of data from multiple RCTs is often employed to give the highest level of evidence. Applying NNTs derived from meta-analysis presents two main problems. Firstly, NNTs from a meta-analysis are subject to variation in risk differences among the studies included in the meta-analysis, as well as in baseline risks. Secondly, applying NNTs to an individual requires adjustment for their baseline risk. In practical terms, meta-analysis should always state variation in baseline risk, and if this is significant the NNT calculation should be based on pooled estimates of relative rather than absolute risk. When appropriate, in future articles in BPJ we will give guidance on the application of NNTs in practice.

Further Reading

Marx A, Bucher HC. Numbers needed to treat derived from meta-analysis: a word of caution. ACP Journal Club 2003;138(2):11.

Schechtman E. Odds ratio, Relative Risk, Absolute Risk Reduction, and Number Needed to Treat - Which of these should we use ? Value in Health 2002;5(5):431-36.

Bandolier

Independent evidence-based thinking about health care

PPIs for reflux oesophagitis

When estimating relative efficacy of different treatments in meta-analyses of randomised trials, the usual situation is that we have many comparisons with, typically, placebo, but few direct comparisons between treatments. As a consequence of this we resort to indirect efficacy. It is a bit like testing every athlete for how long it takes them to run 100 metres individually (indirect comparison = world record) as opposed to who is fastest in a single race (direct comparison = Olympic champion).

It is unusual to have a feast of large, good quality, direct comparisons, but that is the situation in a meta-analysis of proton pump inhibitors (PPI) for healing of reflux oesophagitis [1]. This sort of data can help us generate information on relative efficacy in order to help formulate cost-effective strategies.

Systematic review

The systematic review built on an earlier one, with wide searching up to early 2005 for randomised trials comparing PPIs with esomeprazole. Trials chosen were those of European licensed standard doses of a PPI with esomeprazole 40 mg.

The outcome of interest was endoscopic healing data at four and eight weeks, in patients with comparable grades of oesophagitis (Los Angeles A-D or equivalent). Where necessary data from trials was recalculated with the number of patients randomised, to ensure a consistent intention to treat approach.

Results

Eight trials were identified, with 14,800 patients. Of these about 7,400 used esomeprazole 40 mg, 3,300 lanzoprazole 30 mg, 2,400 omeprazole 20 mg, and 1,700 pantoprazole 40 mg. No trials were identified with rabeprazole. Trials generally examined patients with grades A-D oesophagitis, though two limited patients to grades B and C or C and D.

The main results calculated from data in the paper are shown in Table 1. Esomeprazole 40 mg was significantly better than other PPIs used in these trials, with higher healing rates at four and eight weeks (Figure 1).

Analysis by baseline Los Angeles classification showed that, at eight and four weeks, healing rates tended to be lower at higher initial grade. Thus four week healing rates for esomeprazole 40 mg ranged from about 82% for grade A to about 50% for grade D. Eight week healing rates for esomeprazole 40 mg ranged from about 92% for grade A to about 77% for grade D. Similar but lower results were reported for the other PPIs combined.

Comment

The first thing to bear in mind is that two of the three authors of the meta-analysis were employees of the manufacturers of esomeprazole. That is not necessarily a bad thing, but the thrust of the analysis, with esomeprazole 40 mg as the common comparator which had to be in an included trial, would tend to exclude other trials and limit the evidence we have to look at.

A different approach, which might be interesting, would be to compare relative efficacy using placebo, and using esomeprazole or other common comparators to see if they give the same order of efficacy. Such an approach might also include non-standard or non-licensed doses, further broadening the available evidence if there were sufficiently large amounts of data in properly conducted trials with the same outcomes and conducted in patients with similar initial disease severity. A case for an extended systematic review, probably.

A second observation from looking at the individual trials is how consistent the results were. Figure 2 shows the eight week healing rates in the esomeprazole arms of the eight trials. With high event rates and large numbers of patients, the result of each trial is close to the overall average of 88%. This is quite unlike the situation of small numbers and low event rates.

A third moment for reflection is for the economic consequences of small differences between healing rates. The immediate thought on costs would be to leap to the lowest acquisition cost, in this case generic omeprazole 20 mg, at about £13 for four weeks treatment, rather than somewhat more effective, but expensive, branded PPIs that cost up to twice as much.

It all depends on the cost of someone not healed. As that increases, the economics change, so a good health economic analysis would help in decision-making.

Figure 1: Percentage of patients with endoscopic healing of reflux oesophagitis for four common PPI doses

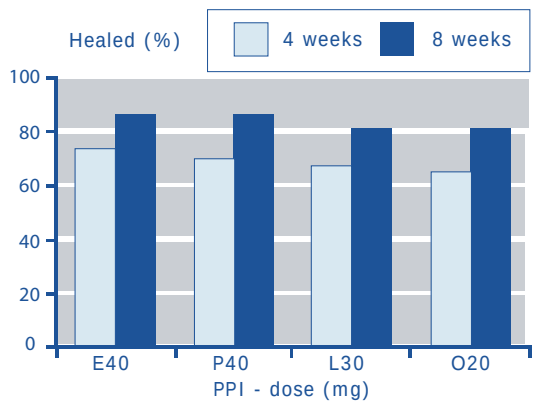
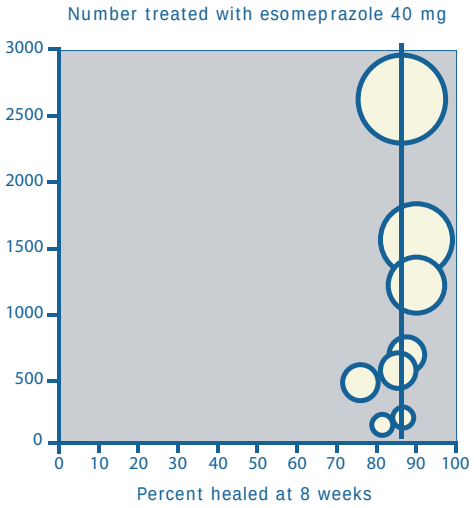


Table 1: Comparison of esomeprazole 40 mg daily with other PPIs in endoscopic healing of reflux oesophagitis after four and eight weeks of treatment

Comparator	Number of		Percent healed with		Relative benefit (95% CI)	NNT (95% CI)
	Trials	Patients	Esomeprazole 40 mg	Comparator		
At 4 weeks						
Lanzoprazole 30 mg	3	6526	73	68	1.07 (1.04 to 1.10)	22 (15 to 42)
Omeprazole 20 mg	3	4877	74	65	1.14 (1.10 to 1.18)	11 (8.6 to 15)
Pantoprazole 40 mg	2	3397	77	71	1.09 (1.04 to 1.13)	16 (11 to 32)
At 8 weeks						
Lanzoprazole 30 mg	3	6526	86	83	1.04 (1.02 to 1.06)	30 (20 to 65)
Omeprazole 20 mg	3	4877	89	82	1.08 (1.06 to 1.11)	16 (12 to 23)
Pantoprazole 40 mg	2	3397	90	88	1.02 (1.00 to 1.04)	49 (24 to infinity)

Figure 2: Eight week healing rates for esomeprazole 40 mg in individual trials



Reference:

1 SJ Edwards et al. Systematic review: proton pump inhibitors (PPIs) for the healing of reflux oesophagitis – a comparisons of esomeprazole and other PPIs. Alimentary Pharmacology & Therapeutics 2006 24: 743-750.

What patients want to know about adverse events

A reader asked the very pertinent question about what information patients wanted about adverse events of treatment. This is one of those perennial questions for which the answer varies from nothing to everything. A quick search indicated an important paper Bandolier had managed to overlook [1]. It is important because it asked a lot of patients, and because the answer is very clear.

Study

The population was a convenience sample of adults aged 18 years or older attending outpatients clinics, accompanying family, medical students or non-professional employees. Over two weeks individuals in these categories were approached in outpatients and asked to participate in completing a questionnaire. The questionnaire had a number of questions, about demographics, about what patients wanted to know about adverse events of treatment, and how they wanted their doctors to behave in terms of informing patients about adverse events (which were always called side effects in the questionnaire).

Results

Of 2,500 individuals approached, 2,348 (94%) agreed to participate. These were mostly women (61%), and the mean age was 47 years, with a good spread between younger and older age groups, though only 17% were aged over 65 years. These participants had a mean of 14 years of education.

Desire for information

Two questions asked patients to select one answer that reflected their opinion about the information they would want about adverse events of medication. The first of these was preceded by a statement that some adverse events were common, and some rare, but a response was required for all adverse events. The second was preceded by a statement that some adverse events were mild, but some were serious (defined as causing prolonged discomfort, disability, or death), but a response was required for serious adverse events.

For both the choices were as follows:

1 I want to hear of any side effects from the doctor no matter how rare.
2 I want to be told if a side effect has occurred in 1 in 100,000 patients.
3 I want to hear if a side effect has occurred in 1 in 100 patients.
4 I am not interested in being informed as to side effects.

The results for this question are shown in Figure 1. Over 90% of patients answered that they wanted to know about adverse events (all or serious) even if they occurred in as few as 1 in 100,000 people.

Doctors' behaviour

Another two questions asked about the behaviour expected of doctors. Overwhelmingly (68%) respondents wanted doctors to give the same information to all their patients

rather than using their judgement by withholding information from some. When asked whether doctors were ever justified in withholding information about adverse events, 73% considered that they were not.

Comment

We might choose to ignore these results because they come from Kansas, but it is worth reflecting that this study is not only large, but is probably the only such study we have. It is absolutely clear, that patients want to know about adverse events, and they expect their doctors to level with them. There is considerable analysis of differences between ages or education levels, but these are small compared with the clarity of the answer.

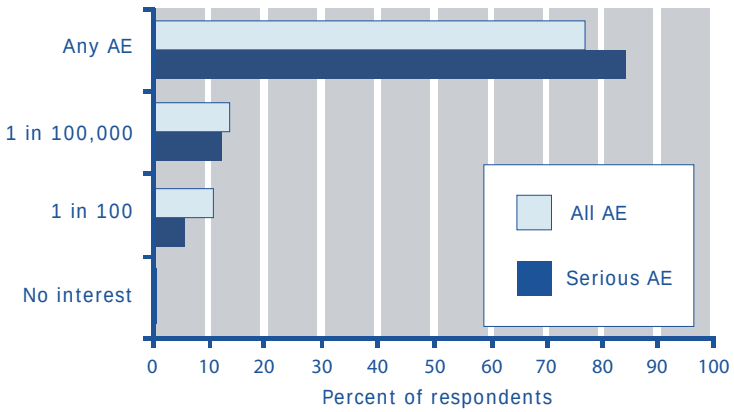
There is a bit of a problem, as most readers will have spotted. First, that adverse event information of the required quantity and quality is simply not available for many medicines. Second, that given the large number of adverse events that occur with any medicines, the average GP consultation will need to be expanded from 10 minutes to an hour or more. Third, as any readers of Bandolier will know, we simply haven't a clue as to how best to convey information about risk in ways that patients will understand.

Ho hum. As Chairman Mao once said (or says he said), the longest journey starts with a single step. And it will be a long journey, because what patients think they know now is miles from reality. A survey of 100 patients admitted on acute medical on call in Dublin [2] indicated that they considered NSAIDs and PPIs to be equally the safest of drugs.

References:

1 DK Ziegler et al. How much information about adverse events of medication do patients want from physicians? Archives of Internal Medicine 2001 161:706-713.
2 G Cullen et al. Patients' knowledge of adverse reactions to current medications. British Journal of Clinical Pharmacology 2006 62:232-236.

Figure 1: What patients want to know about adverse events



Hypnotherapy for IBS?

Irritable bowel syndrome (IBS) is common, with each UK GP seeing an average of about eight patients every week. It is unpleasant for sufferers, negatively affects quality of life, and is expensive for health services. A large proportion of patients do not do well with conventional therapy, and many seek unconventional alternatives.

One of these is a form of hypnotherapy known as gut-directed hypnotherapy. It is based on relaxation to try to normalise gut function. Because there are claims that it works, some purchasers are tempted to provide a service. A systematic review of trials [1] suggests a large degree of caution is warranted.

Systematic review

Authors sought studies, of any design, in nine electronic databases, and even contacted authors for information about any further studies.

Results

Eighteen unique studies were identified and included in the review, four randomised trials, two controlled trials, and 12 uncontrolled studies. All concluded that hypnotherapy had some beneficial effect.

The four randomised trials studied 153 patients. They used five to 12 gut directed hypnotherapy sessions in patients who were mostly refractory to conventional therapy. Controls tended to receive usual monitoring, though one trial used supportive psychotherapy. About half the patients were in trials of 12 weeks, and the remainder in one trial with 12 months follow up.

Three smaller studies indicated some significant statistical improvement, usually in symptom scores at 12 weeks. The largest trial with the highest quality score indicated that differences were not maintained at six months.

Mind over bowel?

It sounds familiar. This is exactly what we find in so many reviews of unconventional therapy. By now we should have learned the lesson, that without good evidence hope is likely to be trumped by later experience.

The authors conclude, rightly, that there is far too little evidence to justify use of hypnotherapy in any circumstance. At least one good quality, large trial, with long follow up should be the absolute minimum requirement for efficacy, but would still be less than what we expect for medicines, where two positive trials are needed. Don't hold your breath.

Reference:

1 S Wilson et al. Systematic review: the effectiveness of hypnotherapy in the management of irritable bowel syndrome. Alimentary Pharmacology and Therapeutics 2006 24: 769-780.

The trouble with aspirin

Bandolier is always interested to revisit a topic when some new evidence, new analysis, or new thoughts make it relevant. Low dose aspirin (LDA) is an important topic, and worth revisiting for a new look at the data.

We know that it does good in people at high cardiovascular risk. We also know that it does some harm in a variety of ways. A new meta-analysis [1] provides a better insight into some of the harm.

Systematic review

This followed a fairly standard path of searching, and was able to draw on many previous meta-analyses in this therapeutic area. Studies for inclusion were those comparing aspirin with placebo for primary or secondary prevention, or prophylaxis of deep venous thrombosis. Aspirin had to be low dose (75 to 325 mg daily).

Studies had to provide information on bleeding events, non-cardiovascular deaths, or discontinuations or symptoms for other than bleeding or cardiovascular events. They had to be randomised, have a duration of two months or longer, and have 100 patients or more in each treatment arm.

A series of outcomes were extracted from the trials, but the outcomes of primary interest were any major bleeding, major gastrointestinal bleeding, and intracranial bleeding. When not otherwise described as major, those needing transfusion were so defined.

Results

The basis of the analysis was 14 randomised trials with 57,000 participants, about 53,000 of whom were in studies lasting 12 months or longer. Annualised event rates for the three primary outcomes, with calculated numbers needed to harm for LDA compared with placebo, are shown in Table 1. Those taking LDA have an additional risk of any major bleed or major gastrointestinal bleed of about one person in 800 every year.

Comment

In longer-term trials in people at high risk of cardiovascular problems (previous heart attack, stroke, or other high risk causes), there are clear benefits from using LDA in reducing fatal or nonfatal heart attacks or strokes, or vascular deaths. Table 2 shows the benefits for LDA and placebo in high risk patients in an annualised form calculated from the Antithrombotic Trialists' Collaboration (Bandolier 108), alongside the annual risks of all major bleeding events.

Benefits outweigh the risks, though there are probably other risks, so this will overstate the benefit:risk balance. It is possible to present the information in a number of ways, both as a percentage rate, or as a risk or odds, and for the actual rates or the difference.

In people who do not have high levels of cardiovascular risk, the benefits will fall, but the potential for gastrointestinal bleeding almost certainly remains the same. And yet our newspapers, and the tone of the media in general, is that taking a small amount of aspirin every day is beneficial for everyone. Not stated, but implied, is that it harms no one. It might be a useful example to use when explaining that all drugs are also poisons, and that safety is relative. For high risk patients the balance is easy to remember: good outcome 1 in 70, bad outcome 1 in 770.

Reference:
1 KR McQuaid, L Laine. Systematic review and meta-analysis of adverse events of low-dose aspirin and clopidogrel in randomized controlled trials. American Journal of Medicine 2006 119: 624-638.

Table 1: Meta-analysis of bleeding events in about 57,000 patients taking low dose aspirin, showing the absolute annual event rates with low dose aspirin (LDA) and placebo, and relative risk and number needed to harm

Bleeding event	Annual event rate (%) with LDA	Annual event rate (%) with Placebo	Relative risk (95% CI)	NNH (95% CI)
Any major bleeding	0.31	0.18	1.7 (1.4 to 2.1)	769 (500 to 1200)
Major gastrointestinal bleeding	0.24	0.12	2.1 (1.6 to 2.7)	833 (530 to 1400)
Intracranial bleeding	0.08	0.05	1.7 (1.1 to 2.4)	3300 (1250 to 10,000)

Table 2: Some calculations on the annual benefits and harms with placebo and low dose aspirin (LDA), and the risk difference to demonstrate additional annual risk

Event	Annual rate with placebo		Annual rate with LDA		Annual rate difference	
	Percent	Risk	Percent	Risk	Percent	Risk
Fatal or non-fatal heart attack or stroke, or vascular death	**6.9**	**1 in 14**	**5.6**	**1 in 18**	**1.4**	**1 in 71 will benefit**
Fatal or non-fatal major bleeding event	0.18	1 in 560	0.31	1 in 320	0.13	1 in 770 harmed

Patients on amiodarone can fall between the cracks...

Contributed by District Health Boards New Zealand Safe and Quality Use of Medicines Group (SQM)
www.safeuseofmedicines.co.nz

All patients recently initiated and discharged on amiodarone from hospital should have their dose reviewed when a prescription is requested in general practice.

Who is taking responsibility for your patients on amiodarone?

Are they on the right dose?

Are they having the recommended monitoring?

Loading v maintenance dose

The problem: Some patients initiated on amiodarone in hospital are discharged on a loading dose and remain on this long term in the community.

What causes the problem?

- The discharge summary sent to general practice is often delayed so that the general practitioner is unaware that the dose needs to be reviewed
- The discharge summary does not make it clear that the patient is on a loading dose and that the dose should be reviewed and changed to a maintenance dose

The possible extent of the problem was identified in two DHBs.

- Approximately a quarter of the patients discharged on amiodarone are discharged on a loading dose

This problem is generated in secondary care and SQM is looking at how the accuracy of discharge summaries and their timely transfer can be improved.

In the meantime, please be aware that patients who have been initiated on amiodarone during a hospital admission and who request a repeat prescription may have been discharged on a loading dose.

Monitoring for adverse effects

Investigating the extent of the initial concern highlighted another safety issue for patients on long term amiodarone therapy. One DHB reviewed all their patients on long term amiodarone therapy following publication of a Medsafe Prescriber Update article in 2006. They found that patients were falling between primary or secondary care in terms of monitoring. Neither was clear about who was doing the monitoring with the result that adverse reactions were only picked up when obvious complications arose.

Amiodarone therapy is associated with a number of adverse reactions including pulmonary toxicity, visual disturbances, hepatotoxicity, cardiac toxicity and both hyper and hypothyroidism. The long half life of amiodarone (approximately 50 days) may contribute to a slow resolution of any adverse reactions once they are recognised. The lead carer needs to be clearly identified for all patients requiring long term amiodarone treatment. Please liaise with the specialist who initiated amiodarone to ensure that all patients on long term therapy are appropriately monitored for adverse reactions.

Monitoring requirements

Baseline assessments:

- Lung function assessment (including chest X ray)
- ECG and serum potassium levels
- LFTs
- TFTs
- Ophthalmological examination if there is pre-existing visual impairment

Re-assessments every 6 months

- Lung function assessment (including 6 monthly chest X ray)
- ECG and serum potassium levels (ideally every 6 -12 months)
- LFTs
- TFTs

Re-assessment every 12 months

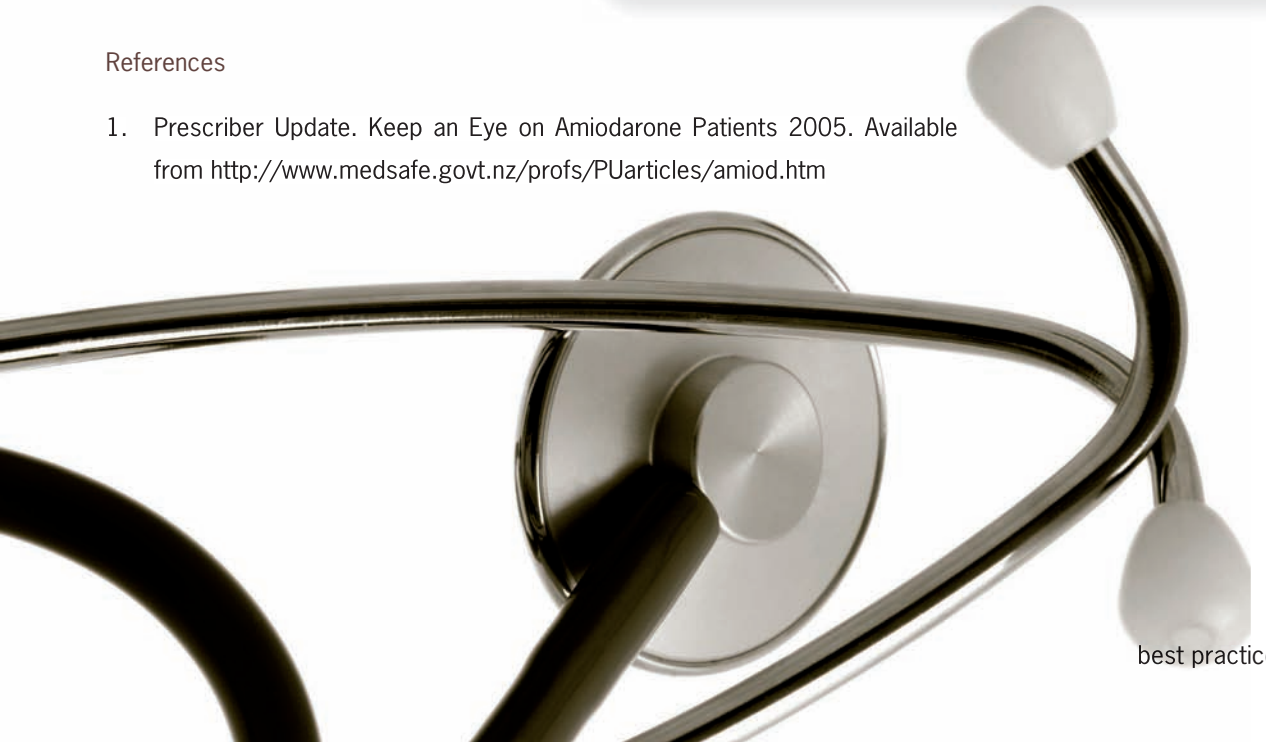
- Eye examinations (e.g. slit lamp biomicroscopy, visual acuity, fundoscopy) but more immediately or frequently if visual changes occur

Editor's note

When reviewing this article concerns were raised over the practicality of the above monitoring requirements. In particular lung function assessment and ophthalmological examination. In the next issue of best practice we will include cardiologist's and ophthalmologist's comments on these recommendations.

References

1. Prescriber Update. Keep an Eye on Amiodarone Patients 2005. Available from http://www.medsafe.govt.nz/profs/PUarticles/amiod.htm



etc

evidence that counts

Antibiotics for acute otitis media – a meta-analysis

National Electronic Library for Medicines - *Peter Golightly*

Bottom line: The group of children most likely to benefit from antibiotics for acute otitis media (OM) is becoming clearer: very young children, young children with bilateral OM, and all children with significant systemic features or otorrhoea. At the other end of the scale older children with mild OM are appropriately managed by watchful waiting. In between there is a group of children calling for careful clinical judgement and possibly judicious use of back pocket prescriptions.

Antibiotics seem to be most beneficial in children younger than 2 years of age with bilateral acute OM, and in children with both acute OM and otorrhoea. For most other children with mild disease, an observational policy seems justified. These are the conclusions of a meta-analysis published in the Lancet in which data from six randomised trials of the effects of antibiotics in children with acute OM were assessed. Individual patient data from 1643 children aged from six months to 12 years were validated and reanalysed. The primary outcome was defined as an extended course of acute OM, consisting of pain, fever or both at 3–7 days.

Significant effect modifications were noted for otorrhoea, and for age and bilateral acute otitis media. In children younger than 2 years of age with bilateral acute OM, 55% of controls and 30% on antibiotics still had pain, fever or both at 3–7 days, with a rate difference between these groups of -25% (95% CI -36% to -14%), resulting in a number needed to treat (NNT) of four children. No significant differences were found for age alone. In children with otorrhoea the rate difference and NNT respectively, were -36% (-53% to -19%) and three, whereas in children without otorrhoea the equivalent values were -14% (-23% to -5%) and eight.

Reference:

Rovers M, Glasziou P, Burke P, et al. Antibiotics for acute otitis media - a meta-analysis. Lancet 2006;68:1429-35.

Misdiagnosis of Essential Tremor

Journal Watch, Volume 26, Number 19, Oct. 1, 2006 - *Allan S. Brett, MD*

Bottom line: This study suggests that a substantial proportion of patients labelled with essential tremor may have alternative diagnosis. It would also be interesting to know how frequently the reverse is true: For example, how often are patients diagnosed with Parkinson's disease when they really have essential tremor? Readers interested in additional information should consult a review article on essential tremor (N Engl J Med 2001;345:887) written by one of the authors of this study (ED Louis).

Essential tremor (a bilateral, largely postural or kinetic tremor involving the hands and forearms) is not rare and it can be debilitating. This study suggests that the condition is commonly misdiagnosed.

Seventy-one patients, previously diagnosed with essential tremor by a neurologist or generalist physician, were evaluated at a neurology referral centre in New York. According to diagnostic criteria of the Movement Disorder Society, 26 of these patients (37%) had been diagnosed incorrectly. The most frequent correct diagnoses for these patients were Parkinson's disease (11 patients) and focal dystonia with dystonic tremor (6 patients). The mean duration of tremor was 21 years for patients with verified essential tremor and 11 years for those with other diagnoses.

Reference:

Jain S et al. Common misdiagnosis of a common neurological disorder: How are we misdiagnosing essential tremor? Arch Neurol 2006;63:1100-4.

Inhaled corticosteroid use associated with increased fracture risk in the elderly

National Electronic Library for Medicines - *Jim Glare*

Bottom line:
To avoid possible increased risk of fracture, ICS should only be used if clearly indicated in COPD and used at the minimum effective dose in asthma.

A cohort study using data from an ongoing MRC trial of screening methods in older people has found that use of inhaled corticosteroids (ICS) for chronic obstructive pulmonary disease (COPD) or asthma, is associated with an increased risk of fractures. The authors combined data from the MRC study, with data from practice computer systems, to determine the dose-response relationship between use of inhaled corticosteroids and time to first fracture. They included a wide range of potential confounding factors in the analysis, including oral corticosteroid exposure. For the purposes of the study all ICS were considered equipotent. Mean duration of follow-up was 9.4 years.

The cohort included 1,671 people with asthma or COPD, and of these, 982 had a prescription for an inhaled corticosteroid and 187 had a fracture. Their mean age was 80.6 years. After adjustment for age and sex, there was a dose-related increase in fracture risk associated with ICS use (rate ratio for mean daily dose >601 micrograms, 2.53; 95% CI 1.65 - 3.89; overall trend P<0.0001). The increased risk remained, after adjustment for potential confounding factors, and in those who had no recorded exposure to oral corticosteroids. Based on their results, the authors conclude that their findings 'provide further evidence that ICS use is an independent risk factor for fracture.' The study has a number of potential limitations, including limited statistical power, the age of the participants and inability to control for historical (pre-computerisation of practice records) oral corticosteroid use. The assumption that all inhaled corticosteroids are equipotent is incorrect; however the great majority of the participants (824, 84%) were prescribed beclomethasone or budesonide for which this supposition is broadly acceptable.

Reference

Hubbard R, Tattersfield A, Smith C, et al. Use of inhaled corticosteroids and the risk of fracture. Chest 2006;130:1082-8.

Should Women Continue to Have Pap Smears Past 65?

Journal Watch, Volume 26, Number 19, Oct. 1, 2006 - Robert W. Rebar, MD

Bottom line: The authors conclude that sexually active older women who are neither married nor living as married might benefit from continued cervical cancer screening. The conclusion seems warranted and suggests that some professional organisations might want to more clearly state the circumstances in which older women should continue to undergo cervical cancer screening.

New cases of cervical cancer and deaths from the disease are disproportionately common in women aged 65 and older. Yet current recommendations call for an end to screenings at age 65, or longer intervals between screenings in women with histories of normal cervical cytology. This analysis of data from the Women's Health Initiative was conducted, to estimate the incidence of cytologic abnormalities and cervical cancer among postmenopausal women, in order to provide guidance for future recommendations.
Subjects were 15,733 women who had been randomised to either placebo or combined estrogen and progestin and who had had Pap smears within 1 year before entry (at age 50 to 79) and at three and six year follow-ups. Only 318 women (2%) had low-grade abnormalities on cytology at baseline. Women taking estrogen plus progestin had an increased incidence rate for new cytologic abnormalities compared with those taking placebo (hazard ratio, 1.4). However, independent risk factors for high-grade cytologic abnormalities and cervical cancer did not include hormone therapy or age, but did include sexual activity in the past year while not being either married or living as married (HR, 3.5).

Reference

Yasmeen S et al. Incidence of cervical cytological abnormalities with aging in the Women's Health Initiative: A randomised controlled trial. Obstet Gynecol 2006 Aug; 108:410-9.

etc

evidence that counts

Systematic review: Hazards of discontinuing or not adhering to aspirin among patients at risk for coronary artery disease

National Electronic Library for Medicines - *Yuet Wan*

Bottom line: In patients with CAD aspirin should only be stopped if the risk of bleeding clearly outweighs the benefits of treatment. Non-compliance is associated with adverse patient outcomes.

A systematic review published early online in the European Heart Journal has examined the hazards of withdrawing aspirin or non-compliance with aspirin in subjects at risk for or with coronary artery disease (CAD).

From the 612 studies screened, six were selected involving a total of 50,279 patients. They examined the following:

- Adherence to aspirin therapy in the secondary prevention of CAD (1 study, n=31,750)
- Aspirin discontinuation in acute CAD (2 studies, n=2594)
- Adherence to aspirin therapy before or shortly after coronary artery bypass grafting (1 study, n=13,706)
- Aspirin discontinuation among patients undergoing drug-eluting stenting (1 study, n=2229)

The review found that overall, aspirin non-adherence/withdrawal was associated with three-fold higher risk of major adverse cardiac events (OR=3.14; 95% CI, 1.75 to 5.61, p = 0.0001). This risk was magnified in patients with intracoronary stents, as discontinuation of antiplatelet treatment was associated with an even higher risk of adverse events (OR=89.78; 29.90-269.60). It concluded that 'non-compliance or withdrawal of aspirin treatment has ominous prognostic implication in subjects with or at moderate-to-high risk for CAD. Aspirin discontinuation in such patients should be advocated only when bleeding risk clearly overwhelms that of atherothrombotic events.' The authors of this paper also discuss the management of aspirin treatment in patients at risk of or with CAD, undergoing surgical and/or invasive procedures with variable bleeding and thrombotic risks. The methodological limitations of this research that is common to all systematic reviews and meta-analysis are also mentioned.

Reference: *Biondi-Zoccai, G., Lotrionte, M., Agostoni P. et al. Systematic review: Hazards of discontinuining or not adhering to aspirin among patients at risk for coronary artery disease. Eur Heart J 2006, Oct 19th {Epub ahead of print}*

Aggressive Approach to Prostate Cancer Among Older Men

Journal Watch, Volume 26, Number 19, Oct. 1, 2006 - *Allan S. Brett, MD*

Bottom line: These studies confirm what most clinicians would suspect: PSA screening and aggressive treatment of localised prostate cancer are common even among older men for whom the benefits are least clear. Many factors, including media hype, ambiguous messages from professional and advocacy groups and physicians' fear of litigation, undoubtedly contribute to these trends.

This trio of studies will be of interest to those who question whether prostate cancer screening, and aggressive treatment of localised prostate cancer, have become excessive.

- Even authorities who favour PSA screening generally believe that elderly men are unlikely to benefit from PSA screening. In an analysis of 1999-2002 data from the National Ambulatory Medical Care Survey, researchers determined the prevalence of PSA testing during nearly 15,000 office visits (to U.S urologists, internists and family physicians) by men without prostate cancer. Extrapolating from these data, the authors estimate PSA testing rates to be about 28% for men older than 75. *cont...*

- Many authorities believe that watchful waiting is appropriate for older men with low-grade localised prostate cancers. In an analysis of data from the U.S SEER cancer registry, researchers found that among men with localised, well-differentiated prostate cancer, 38% of those aged 70-74 and 19% of those aged 75 and older received aggressive treatment (surgery or radiation) rather than expectant management.

- Researchers interviewed 20 patients with newly diagnosed localised prostate cancer immediately after the patients had discussed treatment options with their urologists. Responses indicated that (1) fear and uncertainty led many patients to want treatment as quickly as possible, with minimal deliberation about options; (2) most patients had misconceptions about prostatectomy, with some exaggerating benefits and some exaggerating risks; (3) many patients relied more on anecdotes (i.e. stories about other people with prostate cancer) than on population-based outcome data.

References: *Scales CD Jr et al. Prostate specific antigen testing in men older than 75 years in the United States. J Urol 2006 Aug: 176:511-4.*

Miller DC et al. incidence of initial local therapy among men with lower-risk prostate cancer in the United States. J Natl Cancer Inst 2006 Aug 16; 98:1134-41.

Denberg TD et al. patient treatment preferences in localized prostate carcinoma: The influence of emotion, misconception, and anecdote. Cancer 2006 Aug 1; 107:620-30.

Observational study of GP prescribing of high dose inhaled corticosteroids in childhood asthma

National Electronic Library for Medicines - *Yuet Wan*

Bottom line: Overuse of high dose ICS in childhood asthma is widespread, reinforcing the need to audit use and the need for add-on therapy.

An observational study conducted by researchers from the University of Aberdeen has attempted to quantify the prescribing by GPs of high dose inhaled corticosteroids (ICS) and add-on therapy in children with asthma.

The study conducted in 2003, used information from the Doctors' Independent Network database, on 39,184 patients aged under 5 years and 72,580 aged from 5 to under 12 years: The following findings were reported:

- 'High-dose' prescribing (>400 microgram/day ICS) occurred in 44 of the under-5s (5.6%) and 353 of the 5–11 year olds treated for asthma (10%).
- Of those who were prescribed high dose ICS, 63.6% of the under-5s and 46.7% of the 5–11-year-olds were not co prescribed add-on therapy.
- ICS doses >800 microgram/day (equating to over double the recommended maximum dose) were prescribed to 31 of the 788 under-5s (3.9%), and to 175 of the 3544 patients in the 5–11-year-age group who were treated for asthma (4.9%).
- Although beclomethasone was the most commonly used ICS overall, for those patients prescribed >800 microgram/day, fluticasone was the main one used.

The researchers conclude that their study 'highlights the over-use of high-dose ICS, the under-use and inappropriate use of add-on therapy, and the use of very high and potentially dangerous doses of inhaled corticosteroids in a minority of children.' They add that further research is needed to assess the changes in prescribing patterns over time and in response to new evidence and new guidelines. They recommend that GPs audit high dose ICS and add-on therapy prescribing in children to identify children at risk of adverse outcomes.

Reference: *Turner, S., Leather, D. and Price, D. High-dose inhaled corticosteroid use in childhood asthma: an observational study of GP prescribing. Br J Gen Pract 2006;56:788-790.*

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**

SSRIs and bleeding disorders

SSRIs can cause bleeding disorders

The selective serotonin re-uptake inhibitors (SSRIs) (e.g. fluoxetine, paroxetine, citalopram) have been associated with a variety of bleeding disorders and these started to be reported soon after their introduction. Reported reactions have ranged from mild spontaneous bleeding such as bruising and epistaxis to serious conditions including GI haemorrhage, genitourinary bleeding, intracranial haemorrhage and increased bleeding during surgery.

Proposed mechanisms include decreased platelet serotonin leading to impaired haemostatic function and prolonged bleeding time, and an increased pre-disposition to bleeding in the presence of coagulopathy. The true incidence of such bleeding disorders is unknown as the data are based on spontaneous reports and observational studies. They appear to be quite rare but vigilance and an appreciation of contributory risk factors are important in order to prevent potentially serious events.

SSRIs are associated with increased risk of Upper GI bleeding (UGIB)

The evidence is again conflicting due to the variable objectives and quality of observational studies. There has been wide variance in the significance of the increased risk of UGIB associated with SSRIs reported in the literature. A study based on the UK GP research database suggested a risk similar to that of low dose ibuprofen (de Abajo, 1999) whereas a retrospective cohort study found no evidence of increased risk (Dunn, 2000). A recent case control study (Tata, 2005) found that both SSRIs and NSAIDs were associated with a two fold increase in the risk of UGIB (OR 2.38; 2.08 – 2.72 for SSRIs and 2.15; 2.02 – 2.28 for NSAIDs). The latter results are similar to the findings of earlier studies which also found that SSRIs were associated with a similar or just marginally lower risk of UGIB compared with NSAIDs (Mort, 2006).

Whilst at this stage we can't be sure of the magnitude of the increased risk, the available evidence suggests that SSRI use is associated with an increased risk of UGIB especially in high risk patients such as NSAID/aspirin users, those taking anticoagulants, the elderly and people with a history of GI bleeding (Yuan, 2006; Dall 2006; Weinrieb, 2005).

Increased risk with SSRIs and NSAIDS taken together

Several studies have investigated the risk of UGIB associated with combined use of NSAIDs with SSRIs. Yet again the size of the effect is the subject of much debate, but most studies and reviews have concluded that the risk of UGIB is increased with concurrent use of NSAIDs, including low dose aspirin. (Mort, 2006; Weinrieb, 2005, Dall, 2006). Two studies have in fact reported a multiplicative effect from concomitant NSAID and SSRI use (de Abajo, 1999, Dalton, 2003). For example, in the later study the authors found the risk ratios for SSRIs and NSAIDs were 3.6 and 4.5 respectively but the combination gave a risk ratio of 12.2 (Dalton, 2003: Table 1).

Studies did not include or were not designed to measure any differential effect of Cyclooxygenase-2 inhibitors (Coxibs) so there is no evidence they are safer than NSAIDs in this context.

Table 1. Risks of UGIB associated with SSRIs, NSAIDs alone and in combination (Dalton, 2003)

	Risk Ratio (95% CI)
SSRI only	3.6 (2.7 – 4.7)
NSAID only	4.5 (3.9 – 4.2)
SSRI and low dose aspirin	5.2 (3.2 – 8.0)
SSRI and NSAID	12.2 (7.1 – 19.5)

SSRIs plus low dose aspirin may also pose an increased risk

Although the confidence intervals overlap with SSRI alone and NSAID alone there is an indication (Table 1) that low dose aspirin increases the risk of UGIB when added to an SSRI. Other studies have shown a similar effect (de Abajo, 1999).

What about other antidepressants?

The evidence to date suggests that Tricyclic Antidpressants (TCAs) are not associated with a significant risk of bleeding but they have not been studied to the same extent as the SSRIs. Due to its potent serotonergic properties it has been suggested that clomipramine may be associated with a similar risk to SSRIs. There are some reports of bleeding associated with venlafaxine and it is not known if this drug is safer than SSRIs with respect to bleeding risk.

Caution also advised with SSRIs and warfarin

Bleeding risk may be increased from this combination by two mechanisms.
Firstly, as SSRIs can cause bleeding alone, the anticoagulant (warfarin) may increase the severity of any bleeding disorder due to the SSRI. As SSRIs probably cause bleeding by a direct affect on platelets, signs of increased bleeding may be noticed without a change in the INR.

Secondly, SSRIs have been reported to increase the INR in patients taking warfarin; probably due to inhibition or warfarin metabolism in the liver. Patients should be advised to be extra vigilant for signs of bleeding and have their INR monitored closely after starting this combination (Stockley, 2005).

The risk of a serious bleed in patients on an SSRI, NSAID and warfarin has not been evaluated but the increased risk is likely to be at least additive. Avoid this combination unless absolutely essential.

Dear Dave cont....

Practical Advice

The combination of an SSRI and an NSAID is not contraindicated but awareness and management of the possible increased bleeding risk are important to prevent adverse drug events.

All patients started on an SSRI should be advised to report signs of bleeding such as easier bruising, nose bleeds or gum bleeding. This is particularly important, if the patient is at increased risk of a serious bleeding disorder, including UGIB. If an alternative cause of increased bleeding cannot be identified, consider stopping the SSRI and switching to a non-SSRI antidepressant, such as a TCA.

Patients on an SSRI plus an NSAID (including low dose aspirin) appear to be at increased risk of UGIB, and close monitoring is essential. If possible, avoid the combination in patients at increased baseline risk of UGIB including the elderly and those with a previous history of bleeding disorders. Consider the use of paracetamol instead of an NSAID and gastro protection in high risk patients who need to be on the combination.

The New Zealand Context

From encrypted NHI and Pharmhouse data we identified about 11,000 patients over 50 who were dispensed an SSRI and an NSAID in the period July to December 2005. We can't tell if all patients took both drugs at the same time and we also can't account for over-the-counter use of NSAIDs.

References

Dall M, Hallas J. Is the use of selective reuptake inhibitors associated with an increased risk of bleeding ? Ugeskr Laeger 2006;168(23):2232-6.

Dalton SO, Johansen C, Melemkjaer L, Norgard B, Sorensen HT, Olsen JH. Ue if selective reuptake inhibitors and risk of upper gastrointestinal tract bleeding. Arc Intern Med 2003;163:59-64.

de Abajo FJ, Rodriguez LAG, Montero D. Association between selective serotonin reuptake inhibitors and upper gastrointestinal bleeding; population based case-control study. BMJ 1999;319:1106-9.

Dunn NR, Pearce GL, Shakir SA. Association between SSRIs and upper gastrointestinal bleeding. SSRIs are no more likely than other drugs to cause such bleeding. BMJ 2000;320:1405-1406.

Mort JR, Aparasu RR, Baer RK. Interaction between selective serotonin reuptake inhibitors and nonsteroidal antiinflammaory drugs: Review of the literature. Pharmacotherapy 2006;26(9):1307-1313.

Stockley's Drug Interactions, 7th Ed., 2005. Pharmaceutical Press (UK).

Tata LJ, Fortun PJ, Hubbard RB, Smeeth L, Hawkey CJ, Smith CJ, Whitaker HJ, Farrington CP, Card TR, West J. Does concurrent prescription of selective serotonin reuptake inhibitors and non-steroidal anti-inflammatory drugs substantially increase the risk of upper gastrointestinal bleeding? Aliment Pharmacol Ther. 2005 Aug 1;22(3):175-81.

Weinrieb RM, Auriacombe M ,Lynch KG, Lewis JD. Selective serotonin re-uptake inhibitors and the risk of bleeding. Expert Opin Drug Saf 2005;2:337-44.

Yuan Y, Tsoi K, Hunt RH. Selective serotonin reuptake inhibitors and risk of upper GI bleeding: Confusion or Confounding? Am J Med 2006;119:719-727.

Who is Dave?

Pharmaceutical Programme Manager Dave Woods is a graduate of Manchester University (B.Sc. [Hons]) and the University of Otago (MPharm). Dave has extensive experience in hospital pharmacy, drug information, rational use of drugs and quality assurance. He has published on a range of subjects and holds editorial positions for several international journals.

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

Correspondence

Send your letters to 'Correspondence' PO Box 6032 Dunedin, or email editor@bpac.org.nz

Dear Sir

I read with interest the article on polypharmacy in your first issue of Best Practice Journal.
The suggestion of sending medication lists to and from hospitals is good but it does create paperwork for people at each end. Confusion about which is the 'latest' script will naturally arise.
We have the technology to create a universal electronic script.

This would be the only legitimate drug list and dispensing would take place from this list.
Multiple drugs from one class or drugs that have dangerous interactions could easily be identified.
Mistakes in prescribing could be minimised.

Use of a miniature storage medium such as a smart card or a memory stick would be one alternative. Another possibility is storage of patient data in cyberspace. Both have the problem of who has access and who gets to update the data. Other problems would centre around getting different computer software systems to operate together. Loss of the data may also occur if the storage medium is damaged or lost so a valid copy would need to exist.

In the banking world we can obtain updated financial data virtually anywhere where internet access exists. This data is secure and accurate. Why can't medicine emulate such a system? Cost would be an issue. There are no doubt many other blocks in the way. The question is whether it is worth seeking ways to overcome the barriers, or whether it is better to continue as we are, using paper lists of medicines between the various health care providers?

Jonathan Morton
Radius Medical
445 Ferguson Street
Palmerston North

Dear Editor

Thank you for the report/audit re: oral penicillin use. It is interesting and the audit looks like a major bonus which I will look at using - seeing as you have kindly done the data collection, saving me a lot of time.
I have a clinical comment about the use of oral flucloxacillin in young children. The problem is that it tastes bad - it has a bitter taste to it - as anyone who has ever tasted it or tried to administer a course of it to their own children will confirm. I seriously question the likelihood of compliance with a prescribed course of oral flucloxacillin for young children. If they aren't going to take it, what is the point in prescribing it? Therefore I usually prescribe Augmentin® for young children with impetigo or cellulitis.

Ideally, if the taste is improved that could solve the problem and contribute to the main goal of this particular exercise - to reduce rate of Augmentin® prescribing in favour of narrower spectrum alternatives.

I would be interested in your comments and/or others opinions on this matter.
Cheers

Dr Franz Hubmann
Upper Hutt

Thanks for your comments Franz. We would be interested to hear if other GPs have found ways of overcoming this problem.

Editor

Ten Minute Audit

Identifying your patients on LABAs

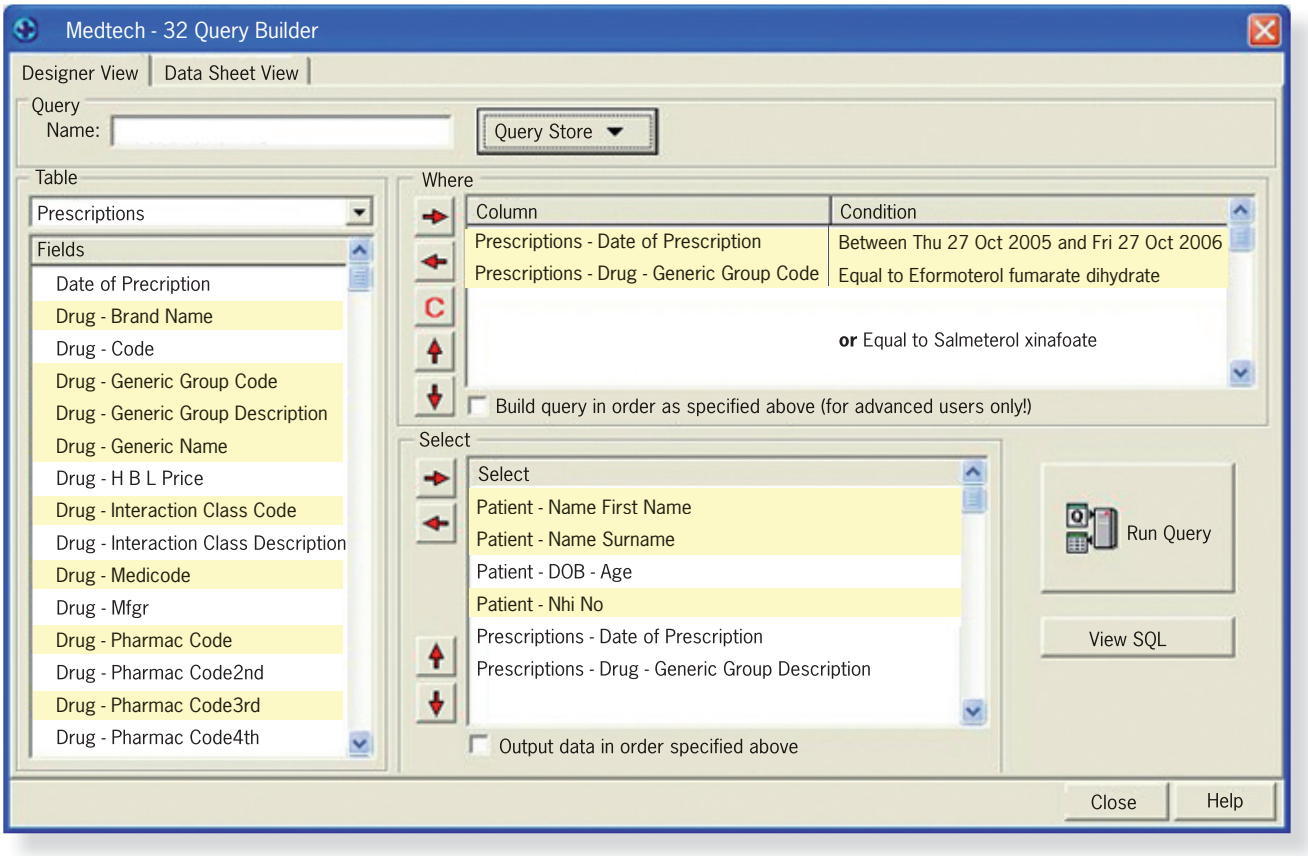
This audit is designed to identify people in your practice on LABAs in order to discuss their Asthma Management Plans and ICS use at their next visit.

People identified in this audit should be queried about ICS use and have their asthma management plans updated to incorporate current thinking on the use of LABAs in worsening asthma.

If you are using MedTech you simply complete the query builder form as below.

Select items from the box on the left and transfer them to the appropriate box on the right of the screen. You will need to run separate queries for eformoterol and salmeterol if you prescribe both.

Once patients are identified, we suggest you flag these patients' notes for a discussion at their next visit.



Decision Support is more than CVD

bestpractice is the exciting new electronic Decision Support from BPAC Inc. It provides up to date clinical support for patient management, with a wide range of clinical modules based on current New Zealand guidelines and best practice.

It is designed to integrate with your PMS system, incorporating both extraction and write-back functions, including prescriptions, laboratory tests and referral letters.

***watch for regular updates and information about* bestpractice**

bestpractice
DECISION SUPPORT FOR HEALTH PROFESSIONALS

Contact:
Murray Tilyard *or* Sarah Kennedy, bestpractice Decision Support, Level 7, 10 George Street, PO Box 6032, Dunedin
ph: 03 479 2816 email: sarah@bpac.org.nz *or* murray@bpac.org.nz

bpac nz
better medicine