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FROM THE EDITOR

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The 2007 edition of the WHO's travel health guide is available on the internet (at no charge) and provides information on the main health risks for travellers, including vaccination advice. International travel can pose various risks to health; changes in altitude, humidity, microbes and temperature can result in ill-health. In addition, serious health risks may arise in areas where hygiene and sanitation are inadequate, medical services are not well developed, and clean water is unavailable.

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- New Zealand Guidelines Group: www.nzgg.org.nz
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Easy-to-read consumer medicine information (CMI) is available on the Medsafe web site (www.medsafe.govt.nz). The CMI can be printed off and given to patients to read, take home and keep for reference. There is a CMI available for most prescription medicines. Health professionals are encouraged to give their patients a CMI, especially when a new medicine is prescribed.

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- Prescribers are entitled to receive a free copy of *Prescriber Update* by post – supply your name and address to the Editor (contact details on page 24). Each pharmacy also receives a copy of *Prescriber Update*.
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Key to *Prescriber Update* articles

To assist readers in knowing the origin of articles published by Medsafe, the symbols below will appear next to the article title, where applicable.

Adverse Drug Reaction Update articles are written in response to adverse reaction reports lodged with the Centre for Adverse Reactions Monitoring (CARM) and material in the international literature. These articles may also be written to alert prescribers and pharmacists to potential problems with medicines.

MARC Prescribing Advice articles are recommendations from the Medicines Adverse Reactions Committee (MARC) in response to medicine safety issues and overseas experiences.

Quinine – not for leg cramps anymore

Local and international reports of thrombocytopenia following quinine use for the relief of nocturnal leg cramps prompted Medsafe and the Medicines Adverse Reactions Committee (MARC) to review the safety of quinine in 2006. In the absence of robust data to support the efficacy of quinine for leg cramps, combined with clear evidence of harm due to unpredictable and potentially life-threatening thrombocytopenia, the MARC concluded that the benefit-risk profile of quinine no longer supported its continued use for nocturnal leg cramps. As a result, Medsafe has required the sponsors of quinine products to remove the indication of leg cramps; this means that quinine should no longer be prescribed for this purpose. The data sheets for quinine products in New Zealand have recently been updated to remove reference to the use of quinine for nocturnal leg cramps.

Background

Despite the use of quinine for leg cramps for many decades, there have been few studies conducted to fully assess the efficacy of quinine, resulting in a paucity of convincing data to support the place of quinine for leg cramps.[1] In contrast, there has been increasing evidence of harm occurring, specifically thrombocytopenia, which is thought to be an idiosyncratic hypersensitivity reaction.[2] A review[3] of published reports of drug-induced thrombocytopenia (excluding heparin) reported quinine to be the second most commonly implicated medicine. In this review of 53 cases of quinine-induced thrombocytopenia, there was a median time-to-onset of seven days. For the 30 cases where it was known how many doses were taken, the median was 3 (range 1-30 doses). The absence of known predisposing factors makes identification of at-risk patients very difficult, and is further complicated by the unpredictable occurrence of thrombocytopenia.[3]

As at 31 July 2007, the Centre for Adverse Reactions Monitoring (CARM) had received 128 reports of adverse reactions to quinine; 45 of these were of thrombocytopenia and included two deaths. In 10 of the 14 most recent CARM reports, onset occurred within seven days; and 10 of the 14 patients were hospitalised.

In both the published[3] and local cases, the short duration to onset and extent of the severity of the reactions suggest that providing patients with advice at the time of prescribing to discontinue the medicine should symptoms of thrombocytopenia occur does not necessarily avoid serious consequences. Therefore, Medsafe is advising prescribers and pharmacists that quinine must no longer be used for the relief of leg cramps. Quinine remains licensed for combination therapy in the treatment of chloroquine-resistant malaria caused by *Plasmodium falciparum*. This is because the benefits of treating malaria outweigh the risks of both thrombocytopenia and dose-related cinchonism.

While Medsafe acknowledges that the removal of quinine as a treatment option in patients with leg cramps may cause adjustment difficulties in general practice, there is no regulatory justification for continuing to approve the indication of leg cramps in the presence of harm and absence of robust efficacy data. This action is consistent with that taken in Australia[4] and the United States.[2]

Prescribers may like to take this opportunity to review their quinine patients to exclude other possible causes of leg cramps. Medical conditions associated with leg cramps include diabetes, Parkinson's disease, hypoglycaemia, anaemia, thyroid and endocrine disorders.[5,6] Medicines such as beta-agonists, cimetidine, diuretics, morphine, nifedipine, statins and steroids have also been implicated.[1,6] Other possible risk factors may include structural disorders (e.g. flat feet), prolonged sitting, awkward leg positions while sedentary, or dehydration.[7,8] It has also been suggested that tight-fitting bed sheets or blankets, particularly when lying supine, may trigger leg cramps by causing the calf muscle to tighten.[8]

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Tendon disorders with quinolone antibiotics

Prescribers are reminded of the risk of tendon disorders, such as tendonitis, tendon rupture and tendinopathy, associated with the use of quinolone antibiotics. The onset of these adverse effects can occur as early as the first few hours after the initial dose and as late as six months after treatment.[1] It is important that patients are asked to inform their prescriber immediately if they experience symptoms suggestive of tendon disorders, such as oedema, erythema, and sharp pain, particularly with walking and palpation.[1]

Of the 104 cases of tendon disorders reported to the Centre for Adverse Reactions Monitoring (CARM) to date, 69% involved quinolones, mainly ciprofloxacin, norfloxacin and enoxacin. Similar figures have been seen in Australia with 75% of reported tendon disorders involving quinolones.[2]

Prescribers should be cautious when prescribing quinolones to patients already receiving steroid therapy, those with renal insufficiency or who are elderly as these risk factors increase the likelihood of quinolone-associated tendon disorders.[1]

It is also recommended that the history of patients presenting with symptoms suggestive of tendon damage be checked for current or previous use of quinolones.

Emerging reports suggest that the newer generation quinolones such as levofloxacin also carry a risk of tendon disorders.[1]

References

1. Gold L, Igra, H. Levofloxacin-induced tendon rupture: A case report and review of the literature. *Journal of the American Board of Family Practice* 2003;16:458-460.
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LABAs – reminder about safe prescribing

Recently published papers[1,2] suggest that long-acting beta agonist (LABA) inhaled bronchodilators might increase the risk of serious asthma exacerbations, including life-threatening episodes, particularly in patients who do not use a concomitant inhaled corticosteroid. LABAs include salmeterol and eformoterol. Medsafe and the Medicines Adverse Reactions Committee would like to remind prescribers of the following key points regarding the use of LABAs:

- LABAs should not be used as monotherapy or first-line treatment for asthma; a LABA should be added to asthma treatment only if an appropriate dose of an inhaled corticosteroid does not provide adequate control.
- Patients should be warned not to stop or reduce corticosteroid therapy without medical advice, even when symptoms improve.
- LABA therapy should not be initiated, or the dose increased, in patients with significantly worsening or acutely deteriorating asthma.
- Patients should be advised to seek medical attention immediately if their asthma deteriorates suddenly.
- A reassessment of therapy should be undertaken if asthma worsens despite regular use of a LABA and an inhaled corticosteroid.

References

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Ototoxicity with aminoglycoside ear drops

A position statement on the use of ototoxic ear drops has recently been released by the New Zealand Society of Otolaryngology Head and Neck Surgery, and published in the *New Zealand Medical Journal*.[1] This is in response to recognition that use of aminoglycoside-containing ear drops when the middle ear is compromised carries a risk of local damage to the cochlea and vestibular labyrinth. Consequently, the Society recommends avoiding, wherever possible, the use of ear drops containing aminoglycosides in patients where there is a direct pathway to the middle ear. This includes conditions such as tympanic membrane perforation and mastoid conditions with open middle ear, and in the presence of ventilation tubes. It is now understood that there is a small risk (1:1,000 to 1:10,000) of damage to the inner ear in circumstances where the ear drops may penetrate into the middle ear. The Society has asked that general practitioners' attention be drawn to the position statement, which includes guidelines for the use of potentially ototoxic agents in patients with ears at risk. There is no risk from the use of these drops where the tympanic membrane is intact. Ear drops containing aminoglycosides currently available in New Zealand are Sofradex®, Soframycin® and Kenacomb Otic®.

Reference

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Warfarin, cranberry and herbs – watch for interactions

It is well recognised that warfarin interacts with many medicines and foods. In the United Kingdom, there have been reports of concurrent consumption of cranberry juice increasing the INR, resulting in an elevated risk of bleeding in patients taking warfarin.[1] In one case, the patient's INR was >50; and he died of gastrointestinal and pericardial haemorrhage.[2] The mechanism may involve inhibition of cytochrome P450 enzymes by the antioxidants contained in cranberries; warfarin is predominantly metabolised by P450 CYP2C9.[2] Due to the potential for serious consequences, patients should be advised to avoid consuming cranberry juice while taking warfarin. It is possible that other cranberry products (e.g. capsules) may also interact with warfarin, therefore should similarly be avoided.[1] Grapefruit juice does not appear to affect the metabolism of warfarin.[3]

Reports of increased INR in warfarin patients who are also taking herbal products or complementary and alternative medicines are becoming more common. Implicated agents in published case reports include German chamomile (*Matricaria recutita*),[4] dong quai (*Angelica sinensis*),[5] fish oil,[6] and royal jelly.[7] Other herbs that may have antiplatelet activity, and thus potentially increase bleeding time, include garlic (*Allium sativum*), ginger (*Zingiber officinale*), ginkgo (*Ginkgo biloba*) and ginseng (*Panax ginseng*). Some herbs such as alfalfa (*Medicago sativa*), celery (*Apium graveolens*) and chamomile (both German – *M. recutita*, and Roman – *Chamaemelum nobile*) may contain coumarins, which could possibly potentiate the effect of warfarin.[3] However, to date, the coumarin compounds detected in herbs such as alfalfa lack the necessary chemical structural requirements for anticoagulant activity.[8] Despite an absence of good evidence of a causal association for all of these interactions, the potential consequences are significant so health professionals and patients should be aware of possible harm.[3] More frequent INR monitoring is warranted in patients who take, stop or start any complementary and alternative medicine while on warfarin. Health professionals are encouraged to report suspected reactions or interactions to the Centre for Adverse Reactions Monitoring (CARM)

so that more information can be gathered about complementary and alternative medicines.

In New Zealand, there have been eight reports received by CARM involving warfarin interactions with complementary and alternative medicines. These included St John's Wort (*Hypericum perforatum*); ginger; aloe vera and manuka honey; creatine; glucosamine with chondroitin; and a product containing *L. acidophilus* and *B. bifidum*. The most common reaction was increased INR (seven cases); but epistaxis occurred in one patient.

To minimise the risk of potential interactions with complementary and alternative medicines, or food products, patients taking warfarin should be advised of the following:[9]

- talk to their health professional before starting any complementary and alternative medicines because the dose of warfarin may require adjustment
- if already taking a complementary or alternative medicine, not to stop taking it unless first discussed with their health professional
- if taking a complementary or alternative medicine, or if regularly consuming food products that can change the effects of warfarin, to keep their usage or intake consistent from day to day
- report any unusual bruising or bleeding to their health care professional right away.

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Patient consent and off-label use of medicines

Medsafe recognises that the unapproved (or 'off-label') use of medicines is sometimes appropriate. In such instances, section 25 of the Medicines Act 1981 allows a registered medical practitioner to "procure the sale or supply of any medicine" (approved or unapproved) for a particular patient in his or her care. "Procure the sale or supply" refers to obtaining the medicine through the usual channels such as a pharmacy or a pharmaceutical company, and it also permits the practitioner to use other means of obtaining a medicine such as importation. Section 25 is intended to allow medical practitioners to either obtain unapproved medicines, or to use medicines for an unapproved indication, for the treatment of a particular patient in the care of that or another practitioner.

There are limitations to this authority embedded in the Code of Health and Disability Services Consumers' Rights 1996. Unapproved use of medicines must comply with this Code, which states that the patient has the right to treatment of an appropriate ethical and professional standard, and the doctor has the responsibility of ensuring that the treatment, whether approved or unapproved, meets this standard. The patient also has the right to be fully informed.

If a prescriber is considering an unapproved medicine (i.e. a medicine that has not been assessed by Medsafe against regulatory standards for safety, efficacy and quality), the onus is on the prescriber to satisfy themself that the medicine is of appropriate safety, quality and efficacy before deciding to prescribe it.

Medsafe considers that, in order for prescribers to comply with the Code, during the consultation the patient should be advised about 1) the unapproved status of the medicine; and 2) the information that led the prescriber to decide why that particular unapproved medicine is the most appropriate treatment for the patient. It is only after this information has been communicated that the patient's informed consent for treatment with an unapproved medicine is considered to have been obtained.

Eltroxin tablets – new formulation so don't halve or crush

Since July 2007, a new formulation of Eltroxin® (levothyroxine; also known as thyroxine) 50mcg and 100mcg tablets has been available. The reformulated tablets are no longer scored and are not intended to be halved, so patients who require a dose of 25mcg daily must instead be prescribed one 50mcg tablet to be taken every second day. It is also recommended by the manufacturer that, due to lack of data on crushing the tablets, Eltroxin tablets should only be prescribed to patients who are able to swallow the tablets whole. Eltroxin tablets should be taken on an empty stomach, preferably before breakfast.[1]

Table: Dosage and administration for new formulation of Eltroxin tablets[1]

Daily dose	Dosing regimen
25 microgram	One 50 microgram tablet on alternate days
50 microgram	One 50 microgram tablet daily
75 microgram	One 50 microgram tablet daily and one 50 microgram tablet on alternate days
100 microgram	One 100 microgram tablet daily
125 microgram	One 100 microgram tablet daily and one 50 microgram tablet on alternate days

Reference

1. GlaxoSmithKline NZ Limited. *Eltroxin (thyroxine sodium) data sheet*. 5 July 2006. www.medsafe.govt.nz/profs/Datasheet/e/Eltroxin(new)tab.htm

Prexige – monthly liver function tests required

Post-marketing events of severe liver dysfunction, including fatal outcome and transplantation, have been observed internationally with Prexige® (lumiracoxib). Consequently, Prexige is now only indicated for the symptomatic treatment of osteoarthritis and limited to a maximum daily dose of 100mg. Patients with severe hepatic disease (Child-Pugh > 9) or with a baseline AST/ALT > 1.5xULN should not be commenced on lumiracoxib.[1]

Liver function monitoring is recommended at baseline and monthly thereafter while on Prexige. The 100mg dose should not be exceeded as higher doses do not provide any additional benefit and may increase the risks of adverse events. Patients using Prexige should be informed about the signs and symptoms of liver dysfunction. Patients who develop signs and/or symptoms suggestive of liver dysfunction should be investigated promptly. Prexige should be discontinued if elevations of AST/ALT > 3xULN occur.[1]

CARM has received three reports of abnormal liver function since August 2007, when the 400mg Prexige tablets were withdrawn from the New Zealand market and restrictions placed on the 100mg tablets.

Reference

1. Novartis New Zealand Limited. *Prexige (lumiracoxib) data sheet*. 20 August 2007. www.medsafe.govt.nz/profs/Datasheet/p/Prexigetab.htm

CLOZAPINE: FATAL 'CONSTIPATION' MORE COMMON THAN FATAL AGRANULOCYTOSIS

ADR UPDATE

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This article was published on the Medsafe web site and e-mailed to electronic *Prescriber Update* subscribers in March 2007.

Clozapine (Clozaril®, Clopine®) is an atypical antipsychotic that is effective for treatment-resistant schizophrenia. It causes agranulocytosis in up to 1% of patients[1] and regular monitoring of neutrophil counts is mandatory throughout treatment. In New Zealand one death from agranulocytosis has been reported to the IMMP. In contrast, four deaths from complications of severe constipation have been reported. This article reminds health professionals that the gastrointestinal effects of clozapine are potentially serious. Awareness of this issue may prevent life-threatening complications.

Clozapine-induced constipation may be fatal

Constipation is often regarded as a frequent, minor side effect of clozapine. However, review of New Zealand reports received by the IMMP shows that clozapine-induced constipation may be associated with serious effects such as intestinal obstruction, bowel perforation and toxic megacolon. The four deaths reported to IMMP demonstrate that these effects can be fatal.

Clozapine affects motility throughout the gut

In addition to reports of constipation associated with clozapine, IMMP has received three reports of paralytic ileus and a further three reports of oesophageal dysmotility. These case reports suggest that clozapine may reduce gastrointestinal (GI) motility throughout the gut, resulting in complications higher in the GI tract.

Mechanism – anticholinergic, serotonergic and more

Many anticholinergic drugs can cause GI dysmotility, but clozapine has a much more potent effect through its interaction with multiple receptors, (including anticholinergic and serotonergic receptors) affecting GI activity. This action is exacerbated by co-prescription of anticholinergic agents such as benztropine and tricyclic antidepressants.

Take-home messages

- Ask clozapine patients about bowel function. This can avert needless discomfort from constipation and may prevent life-threatening complications.
- Dietary advice should be routine.
- Prescribe appropriate laxatives if indicated.
- Clozapine can impair motility of the entire GI tract.

Competing interests (authors):
** None declared.*
***IMMP has in the past received unconditional grants from several pharmaceutical companies, including Novartis who are one of the sponsors of clozapine in NZ. However, pharmaceutical companies have no role in the design, analysis or interpretation of IMMP studies.*

Reference

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GLITAZONES: FLUID RETENTION, CARDIAC FAILURE AND MACULAR OEDEMA

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Glitazones (thiazolidinediones) can cause fluid retention, which is dose related and more likely to occur when they are used in combination with insulin or sulphonylureas. Consequences include new or worsening cardiac failure and macular oedema. Pioglitazone and rosiglitazone are contraindicated in patients with NYHA Class III and IV heart failure, and not recommended in patients with symptomatic heart failure. All patients taking glitazones need to be informed of possible symptoms, and monitored for fluid retention and associated complications. If signs or symptoms develop, prescribers should stop or reduce the dose of glitazone.

The glitazones (also known as thiazolidinediones or TZDs) are used in the treatment of Type 2 diabetes mellitus. They are the first class of medicines to primarily target insulin resistance. Rosiglitazone and pioglitazone are the two glitazones currently available in New Zealand; only pioglitazone is funded (under Special Authority).

Fluid retention and oedema reported locally and internationally

The Centre for Adverse Reactions Monitoring (CARM) has received reports of peripheral oedema, pulmonary oedema, pleural effusion and exacerbation of cardiac failure with pioglitazone and rosiglitazone. A review of the WHO International Drug Monitoring database in December 2006 revealed that reports of fluid retention leading to oedema and related conditions made up the greatest proportion of adverse reactions to glitazones. In clinical trials, fluid retention was commonly reported by patients taking these medicines; oedema was reported more often when insulin or a sulphonylurea was also prescribed.[1,2]

Development of oedema is dose-related and, in most patients, is mild to moderate.[2] However, it can be severe as illustrated in reports to CARM. One patient was admitted to hospital with oedema extending from the legs to the chest while taking pioglitazone 15mg daily. Another developed oedema of the legs and abdomen, and shortness of breath on exertion three weeks after starting rosiglitazone 4mg daily. There was no evidence of cardiac failure. He recovered with frusemide treatment and discontinuation of rosiglitazone.

Fluid retention may lead to pulmonary oedema and cardiac failure

Fluid retention due to glitazones may lead to, or exacerbate, cardiac failure in some patients.[1] Patients with ischaemic heart disease, valvular heart disease or hypertension are already at risk of developing cardiac failure and it is thought that glitazones may increase the likelihood of this occurring.

Risk higher with combined insulin and glitazones

In clinical trials, heart failure and pulmonary oedema occurred commonly in patients taking rosiglitazone and insulin; this was more frequent than in those taking insulin alone. Patients with heart failure were, on average, older, had a longer duration of diabetes and were mostly taking the higher 8mg dose.[2]

Pre-existing heart failure may worsen

In a trial comparing pioglitazone and glibenclamide in patients with moderate to severe heart failure and uncontrolled Type 2 diabetes, 9.9% of patients taking pioglitazone, compared with 4.7% taking glibenclamide, were admitted to hospital because of heart failure. As with rosiglitazone, this was more likely to occur in older patients and those using insulin.[1]

Heart failure precipitated in macrovascular disease

The Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) study[3] examined the incidence of heart failure in patients taking pioglitazone compared with placebo. Patients enrolled had Type 2 diabetes with macrovascular disease. Heart failure, and heart failure leading to hospital admission, occurred significantly more often in patients taking pioglitazone compared with placebo (11% v 8% and 6% v 4%) but there was no difference in the incidence of fatal heart failure.

Mechanism likely to be fluid retention rather than left ventricular dysfunction

Some patients have developed pulmonary oedema without evidence of ischaemic heart disease, or systolic or diastolic dysfunction. Marked peripheral oedema has been a feature in some case reports.[4,5] Studies of rosiglitazone indicate that a dose-related effect on pulmonary endothelial permeability, rather than alterations in left ventricular mass or ejection fraction, is probably responsible for the development of pulmonary oedema and, in susceptible patients, cardiac failure.[6]

Consider background risk, use low doses and monitor patients closely

Use of rosiglitazone or pioglitazone is contraindicated in patients with NYHA Class III and IV heart failure, and not recommended in patients with symptomatic heart failure.[1,2] It would be prudent to use the lowest possible doses of glitazones in patients with oedema and breathlessness without confirmed clinical evidence of cardiac insufficiency.

Due to an increased risk of heart failure and myocardial ischaemia when rosiglitazone is added to insulin therapy, rosiglitazone must not be initiated in patients already using insulin.[2]

For all patients, initiation of the glitazone should be at the lowest recommended dose with cautious increases only after appropriate clinical evaluation of the patient's risk of fluid retention and cardiovascular events.[1,2]

All patients (especially those with cardiac disease putting them at risk of heart failure) taking glitazones should be monitored for signs and symptoms of fluid retention and heart failure following initiation of the glitazone and again following any subsequent dose increases. If signs and symptoms suggestive of heart failure develop, prescribers should either stop or reduce the dose of glitazone. Patients and their carers should also be informed of the symptoms of fluid retention and heart failure.[1,2]

Macular oedema can be exacerbated by glitazone use

Among patients with Type 2 diabetes, the prevalence of macular oedema is 15% in those who use insulin and 4% in those who do not.[7] Post-marketing reports have been received of worsening diabetic macular oedema in association with glitazone use, probably because of fluid retention.[1,2] These reports led to a review of 30 patients who had macular oedema while taking pioglitazone or rosiglitazone.[8] It was observed that these patients also had lower limb oedema. Eleven of these patients were observed for three months after glitazones were discontinued. Mean weight gain after commencing a glitazone in these patients was 13.5 kg and mean weight loss after discontinuation was 8.5 kg. Rapid reduction in macular oedema occurred in four of the eleven patients when glitazones were discontinued.

Disturbances in visual acuity may indicate macular oedema. If macular oedema occurs or worsens during treatment with glitazones, this may be due to disease progression, but also consider whether the glitazone could be implicated. Patients should be advised to seek medical advice if they develop symptoms of visual impairment, and prescribers should give consideration to stopping the glitazone.

Caution and vigilance warranted

In summary, prescribers need to be aware that glitazones commonly cause oedema and related conditions. Pioglitazone and rosiglitazone are contraindicated in patients with NYHA Class III and IV heart failure, and not recommended in patients with symptomatic heart failure. Initiation of glitazone therapy should be at the lowest recommended dose; subsequent dose increases should only occur following evaluation of the patient's risk of fluid retention and cardiovascular events. It is recommended that patients be informed of the symptoms and be monitored, particularly for cardiovascular decompensation.

Competing interests (author): none declared.

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SERIOUS REACTIONS WITH TRAMADOL: SEIZURES AND SEROTONIN SYNDROME

ADR UPDATE

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Seizures can occur with tramadol, particularly if high doses are used or there is concomitant use of medicines that lower the seizure threshold. The use of tramadol with serotonergic medicines can increase the risk of serotonin syndrome. To reduce the likelihood of these serious reactions occurring, prescribe the lowest effective dose of tramadol and avoid its use in patients with a history of seizure disorders. In patients with risk factors for seizures or serotonin syndrome, it may be prudent to consider other analgesics instead of tramadol.

Tramadol is a centrally-acting analgesic indicated for moderate to severe pain.[1] It stimulates opioid receptors, and inhibits noradrenaline and serotonin reuptake. Seizures and serotonin syndrome are amongst the more commonly reported serious adverse reactions attributed to tramadol in the CARM and the WHO International Drug Monitoring databases.

Clinical features of serotonin syndrome

Symptoms and signs of serotonin syndrome include at least three of the following: agitation, ataxia, increased sweating, diarrhoea, fever, hyperreflexia, myoclonus, or shivering. The syndrome usually occurs after initiating or increasing the dose of a serotonergic medicine.

Local reports of serotonin syndrome with tramadol

The CARM database holds three reports of serotonin syndrome occurring in patients taking tramadol. In each case serotonin syndrome occurred after extra serotonergic medicine was taken, as follows: tramadol dose increased in a patient taking tramadol, paroxetine and thioridazine; tramadol added to long-term treatment with amitriptyline and high-dose fluoxetine (60mg daily); citalopram recommenced after patient started tramadol. In the latter case, the tramadol was commenced in hospital where the patient's history of citalopram use was not recorded.

Medicines known to cause serotonin syndrome

Table 1: Agents causing serotonin syndrome[2]

Antidepressants	mirtazapine, monoamine oxidase inhibitors (including moclobemide), SSRIs, tricyclics, venlafaxine
Antiparkinson agents	amantadine, bromocriptine, carbergoline, levodopa, pergolide, selegiline
Illicit drugs	cocaine, hallucinogenic amphetamines such as MDMA (ecstasy), LSD, etc.
Migraine therapy	dihydroergotamine, naratriptan, sumatriptan, zolmitriptan
Other agents	bupropion, carbamazepine, lithium, morphine, pethidine, reserpine, sibutramine, St. John's wort, Tramadol

Tramadol can induce seizures especially at high doses

In the last five years, tramadol has been the most commonly implicated medicine in reports of seizures to CARM. A total of ten reports were received to December 2006, involving eight females and two males with an age range of 15 to 49 years. Ten patients were given tramadol orally and five intravenously. Seizures have been reported in patients receiving tramadol at recommended dose levels. However, reports to CARM indicate that high doses, co-prescribed medicines and a history of epilepsy may increase the likelihood of seizures with tramadol.

Three patients who had seizures were given greater than the maximum recommended dose. One took 600mg orally over 12 hours; another, following a general anaesthetic and cyclizine, was given 50mg intravenously, followed five minutes later by 250mg intravenously as a single dose. The third received an intravenous dose of 300mg; this patient had renal failure. The box on the following page shows recommended doses for tramadol and dose adjustments for patients with renal impairment.

Other medicines or history of seizures may further increase seizure risk

In the CARM reports, three patients were taking a tricyclic antidepressant (TCA) as well as tramadol. One was also taking an antipsychotic medicine, and one an SSRI. Two of these patients experienced seizures when the dose of tramadol was increased. One of these took tramadol daily but had seizures on four occasions when the dose was increased. The third patient developed seizures after tramadol was given following a general anaesthetic.

Three other patients developed seizures when tramadol was given intravenously following, or with, pethidine and/or cyclizine. One other patient with a history of seizures experienced a marked increase in seizure frequency within 24 hours of starting oral tramadol 400mg daily. He was not taking potentially interacting medicines.

Reducing the risk of serotonin syndrome and seizures with tramadol

The dose of tramadol should not exceed the recommended maximum daily dose or the recommended dose for a single administration – see box on next page.

To reduce the likelihood of serotonin syndrome occurring, avoid co-prescribing tramadol with the medicines listed in Table 1, if possible. Tramadol is contraindicated in patients who are taking **monoamine oxidase inhibitors** or who have taken them within the last 14 days.[1] Prescribers also need to be aware that co-prescription of tramadol with **tricyclic antidepressants, selective serotonin re-uptake inhibitors** and **antipsychotics** can lower the seizure threshold.[1] Prescribers should bear in mind the potential risks of serotonin syndrome and seizures when making a clinical decision to use tramadol.

Seizures have been reported with high doses of **pethidine**,[3] **morphine**,[4] **cyclizine**,[5] and **ondansetron**.[6] **Metoclopramide** may lower the seizure threshold in patients with epilepsy.[7] Therefore, if it is necessary for tramadol to be administered with or immediately after these medicines, the lowest effective dose of tramadol should be used. Tramadol should be avoided in all patients who have epilepsy or are susceptible to seizures unless there are compelling circumstances.[1]

TRAMADOL DOSING GUIDELINES[1] *

The dose of tramadol should be titrated to the severity of the pain and the clinical response of the individual patient, after taking into account patient-specific factors such as renal function, concomitant medicines and co-morbidities such as seizures.

Oral tramadol – immediate release capsules, oral drops, and sustained release tablets

The total daily dose should not exceed 400mg.

Injectable tramadol

Single doses should not exceed 100mg.

For post-operative pain, the total daily dose must not exceed 600mg.

For less severe pain, the maximum daily dose is 400mg.

Renal insufficiency (see Note below)

Tramadol is not recommended in patients with severe renal impairment (creatinine clearance <10 mL/min).

In patients with a creatinine clearance of less than 30 mL/min, the dosage frequency of tramadol (injection, oral drops, and immediate release capsules) should be changed to 12-hourly, and to once every 24 hours for tramadol sustained release tablets.

Note: Clinical evidence is that the thresholds for classifying renal impairment are too generous[8] and, consequently, dose adjustments may be warranted when creatinine clearance is less than 60 mL/min.[9]

* for adults and adolescents over the age of 12 years

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OSTEONECROSIS OF THE JAW AND BISPHOSPHONATES – PUTTING THE RISK IN PERSPECTIVE

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Osteonecrosis of the jaw is a poorly understood condition that has recently been associated with the use of potent bisphosphonate treatment. The prevalence appears to be approximately 1-10% in patients with malignancy treated with very high doses of intravenous bisphosphonates. In Paget's disease and osteoporosis, where the doses of bisphosphonate used are an order of magnitude lower than the oncology dose, the prevalence appears to be much lower – probably less than 1 in 60,000. The aim of this article is to put the risks of osteonecrosis of the jaw into context with the benefits of bisphosphonate treatment in these clinical scenarios.

Osteonecrosis of the jaw (ONJ) is a recently recognised (but poorly understood) dental condition that is associated with use of potent bisphosphonate therapy, usually in the context of malignancy.

Recent publicity about ONJ in the lay media in New Zealand, and cautious recommendations by North American dental authorities,[1] have created uncertainty, and in some cases alarm, amongst patients, doctors, and dentists about the safety of bisphosphonates. Specifically, some dentists are declining to perform dental work in patients who are receiving bisphosphonate therapy for non-malignant skeletal conditions, and some patients are discontinuing or declining effective therapy for osteoporosis because of concern about ONJ.

The aim of this article is to examine the risks and benefits of bisphosphonate treatment in light of the current evidence pertaining to osteonecrosis of the jaw (ONJ).

What is ONJ?

ONJ is characterised by exposed areas of jawbone, more commonly affecting the mandible than the maxilla.[2-5] Most cases are precipitated by tooth extraction or other dental surgery, but 25% occur without obvious preceding oral trauma.[3] The problem may progress to bone necrosis and sinus or fistula formation, but its natural history is not known. While pain is a typical presenting feature, approximately 33% of cases are asymptomatic. Plain X-rays may be normal in the early stages, but later show poorly defined osteolysis with or without sequestrum formation. Histology has been reported as showing necrotic bone, bacterial debris and granulation tissue.[3-5]

The clinical syndrome of ONJ was first described in association with bisphosphonate use by Marx in 2003.[2] The pathophysiology of ONJ is unknown, however, it is important to emphasise that ONJ appears to be unrelated to avascular osteonecrosis of long bones, or to radiation-induced osteonecrosis.

Previously, the bisphosphonate-associated disorder had only been observed in the jaw, however, one patient has been recently reported with ONJ of the jaw and auditory canal.[6] It is hypothesised that high doses of bisphosphonates suppress bone remodelling in the jaw to a degree that impairs the ability to repair microdamage induced by oral trauma and/or infection.

The role of other potential risk factors such as chemotherapeutic agents, corticosteroids, poor oral health, and other dental comorbidities has not been established.[4] The optimal management of established disease is uncertain at present but pain and infection control, conservative debridement of necrotic bone, and bisphosphonate withdrawal are recommended.[5]

Who receives bisphosphonates?

Before considering the incidence of ONJ in bisphosphonate-treated patients, it is important to emphasise that these agents are prescribed to two groups of patients: one with non-malignant skeletal diseases, in particular osteoporosis and Paget's disease of bone; the other with cancer-related skeletal disease, most commonly metastatic breast cancer and multiple myeloma.

Important differences exist between these patient groups in the dose of bisphosphonate prescribed, in concomitant medical therapies, and in the risk of developing ONJ (see below). Thus, patients with malignant skeletal disease typically receive 12-fold higher doses of bisphosphonates (4mg intravenous zoledronate or 90mg intravenous pamidronate monthly, alendronate not used) than patients with non-malignant skeletal disease (osteoporosis, alendronate 70mg weekly, intravenous pamidronate 90mg annually, zoledronate 4-5mg annually; Paget's disease, intermittent courses of treatment every 2-3 years with alendronate 40mg daily for 6 months, intravenous pamidronate 60–180mg, or intravenous zoledronate 4-5mg). In addition, patients with cancer are typically receiving cytotoxic agents that may influence general and oral health.

How common is bisphosphonate-associated ONJ?

A recent review summarised published cases of ONJ.[5] 95% of the reported cases of ONJ occurred in patients with malignant skeletal disease. Of the three cases of ONJ that have occurred in association with bisphosphonate treatment for Paget's disease, 2 were prescribed inappropriately high doses of bisphosphonates (alendronate 40mg/day for 5 years, pamidronate 90mg monthly for 18 months). In this review, 15 cases of ONJ were reported in patients receiving bisphosphonate treatment for osteoporosis.[4]

By March 2006, approximately 170 cases worldwide of ONJ in association with alendronate had been reported to the manufacturer (Merck).[7] There are few clinical details available for the majority of these cases. These cases have occurred on a background of very extensive use of bisphosphonates for osteoporosis and Paget's disease in the past decade.

In 2004, it was estimated that there had been approximately 20 million patient-years of alendronate treatment for these conditions.[8] It is possible that under-reporting of cases has occurred, but this would have to be very substantial to significantly alter the very low incidence.

No cases of ONJ were reported in randomised controlled trials of alendronate, risedronate or ibandronate that collectively included more than 60,000 patients treated for at least 2 years. Therefore, while the incidence of ONJ in patients treated with bisphosphonate for Paget's disease and osteoporosis is difficult to determine, it is very likely to be less than 1/60,000 and is perhaps as low as 1/200,000.

The incidence of ONJ in patients receiving high-dose bisphosphonate treatment for metastatic malignancy is much higher. Estimates range up to 10%,[5] but the best available data, collected retrospectively on 4000 patients from a single institution, suggest that about 0.85% of these patients are affected.[9]

Patients with ONJ in this setting have all had metastatic malignancies, most commonly multiple myeloma or breast cancer, and often have been receiving chemotherapeutic agents, or corticosteroids, or had other dental comorbidities.[4] The roles of these possible predisposing factors have not yet been determined.

Balancing the risks

Osteoporosis – Bisphosphonates are the only available agents of proven effectiveness for the treatment or prevention of osteoporosis in New Zealand (oestrogen replacement therapy is also effective[10] but not widely used).

Alendronate treatment reduces the risk of vertebral and non-vertebral fractures by about 50%.[11] The absolute benefit in fracture prevention from treatment with alendronate depends on the baseline risk of sustaining a fracture. For a 65-year-old woman with a bone density T score of -2.5 and no other clinical risk factors for osteoporotic fracture, the estimated probability of sustaining a hip fracture in the next 10 years is 5.9%.[12] In this situation the number of women that need to be treated (NNT) with a course of alendronate to prevent one hip fracture is 35.

For an 80-year-old woman with a previous osteoporotic fracture and a bone density T score of < -2.5, the estimated probability of sustaining a hip fracture in the next 10 years is 45%.[12] In this situation, the NNT is 4.5. In comparison, the number of women that need to be treated with a course of alendronate to cause one case of ONJ – the number needed to harm (NNH) – is very likely to be at least 60,000.

Osteoporotic fractures are not trivial events. Hip fracture is associated with a 25% risk of death within 12 months of the event, and a high risk of decreased independence in those who survive.[13,14] Clearly, the balance of risk and benefit favours alendronate treatment for osteoporotic patients. In addition, the NNH is sufficiently high that any form of screening or preventative dental treatment is highly unlikely to be cost-effective or produce a meaningful reduction in ONJ incidence.

Paget's disease – Bisphosphonates are a highly effective treatment for Paget's disease.[15,16] Patients with Paget's disease typically receive infrequent (every 2-5 years) courses of bisphosphonates, such that the overall drug exposure is less than occurs in patients with osteoporosis. It is therefore very likely that the risk of ONJ in patients with Paget's disease treated with conventional doses of bisphosphonates is even lower than that in patients with osteoporosis.

Metastatic malignancy – Bisphosphonates reduce pain from skeletal metastases (NNT at 4 weeks is 11, NNT at 12 weeks is 4).[17] In multiple myeloma, bisphosphonates reduce pathological vertebral fractures by 41% with a corresponding NNT of 10.[18]

In patients with breast cancer metastatic to bone, bisphosphonates reduce the number of skeletal events by 17%, the rate of skeletal events by 29%, reduce pain, and may increase quality of life. The NNT to prevent one skeletal event is 9.[19] In prostate cancer with bone metastases, zoledronate reduced skeletal events by 25% over 18 months in one trial of men with androgen-insensitive prostate cancer (NNT = 9).[20] No other bisphosphonate has been shown to be effective in metastatic prostate cancer.[20]

Treatment with bisphosphonates has not been demonstrated to prolong survival in any of these malignancies.[18-20] Thus, in the treatment of metastatic malignancy, the absolute benefit from treatment (NNT 4-10 depending on endpoint) is much closer to the absolute harm from treatment (NNH 10-120). In this situation, screening or preventative dental treatment prior to initiation of bisphosphonate treatment may be appropriate and guidelines for dentists seeing such patients have been published.[5] The efficacy of the recommended prevention strategies has not been evaluated.

Currently, it is not known whether lower doses of bisphosphonates than are currently prescribed are effective in reducing cancer-related skeletal morbidity. If, as seems likely, there is a dose-response relationship between bisphosphonate treatment and risk of ONJ, the use of lower doses of bisphosphonates for treatment of skeletal metastases may be associated with a lower risk of ONJ.

How should we approach the problem of ONJ?

Current evidence suggests that the risk of ONJ in patients with cancer in whom high dose bisphosphonate therapy is being commenced is high enough to justify the screening and intervention strategies recommended by various dental authorities.[1,5] It should be acknowledged, however, that at present such strategies have not been demonstrated to influence the incidence of ONJ.

Current evidence suggests that the risk of ONJ in patients with non-malignant skeletal conditions who are receiving conventional doses of bisphosphonates is so low that (a) systematic screening or prevention programmes and (b) withholding dental procedures are not justified in this setting.

Adopting an ultra-conservative approach in these patients runs the risk of denying necessary dental care to patients receiving bisphosphonates, and denying patients with dental disease an effective therapy for osteoporosis or Paget's disease.

Recommendations for dental care in patients receiving bisphosphonates for non-malignant skeletal disease have recently been developed.[21] Routine dental care, in the form of an annual examination, should be encouraged in all patients.

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EVIDENCE, RISK AND THE PATIENT

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Drugs are often assessed by their effect on surrogate outcomes, such as blood pressure or cholesterol, rather than clinical end points such as death. This results in risk factors being treated to prevent possible future events. Patients must be willing to take drugs for many years in the hope that they will obtain the same benefit as the patients in clinical trials. Patients in clinical trials are, however, often different from the patients seen in practice. It is therefore important to consider the whole patient and not just prescribe a drug to treat a risk factor in isolation. When deciding to prescribe, the absolute benefit of treatment should be discussed with the patient.

Introduction

Prescribing drugs to treat risk factors is a daily routine activity for most general practitioners. Underpinning the pharmacotherapy of risk factors is evidence from clinical trials that is widely accepted to validate the merit of this treatment. However, many people may need to have their risk factors treated to prevent an adverse outcome for one person. Considering the whole patient is integral to the art of medicine, so we should consider the individual and not just their risk factors.

Evidence-based medicine is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients.[1] To apply this principle we have to assess what the evidence from clinical trials means.

Assessing evidence – the scientific dimension

The anatomical and pathophysiological mechanisms of disease, though important to understand, are not the evidence that underpins the validity of medical treatment. Medicine is essentially an observational science and clinical trials endeavour to determine significant differences between the natural history of disease and the effect of treatment. Some basic understanding of statistics is needed – especially when assessing risk factor modification.

Significance

A result is statistically significant when the 'p' value is less than 0.05. This arbitrarily chosen value means that there is a 95% likelihood that an observation is not due to chance. The p value is a measure of the reliability of an observation, but it does not quantify any effect. The word 'significant' is frequently used inconsistently. A statistically significant result from a trial is sometimes erroneously interpreted as having a high clinical significance.

Reporting risk reductions

Trials look at the incidence of outcomes with and without intervention. Absolute risk reduction is the difference between the outcome in the control group and the outcome in the intervention group in a specified time period.

The relative risk reduction is the absolute risk reduction as a proportion of the baseline rate. A relative risk reduction often seems impressive, but it may only represent a small difference. For example, if the event rate is 0.2% in the control group and 0.1% in the intervention group the relative risk reduction is 50%, but the absolute risk reduction is only 0.1%.

One must always know whether a quoted risk change is relative or absolute. Benefits of treatment are often presented in relative terms, but harms and adverse effects are usually presented in absolute terms (Table 1).

Table 1 **Absolute and relative risk**

Event rate control	Event rate intervention	Relative risk reduction	Absolute risk reduction	Number needed to treat	p value*
20%	10%	50%	10%	10	< 0.05
4%	2%	50%	2%	50	< 0.05
0.2%	0.1%	50%	0.1%	1000	< 0.05

* The p value measures the reliability of the observation, not the quantum of effect. If the effect is small, a small p value can still be achieved with a large sample size.

Number needed to treat or harm

The number needed to treat is the number of patients who must be treated for a period of time to prevent one having the outcome of interest. It is the inverse of the absolute risk reduction (1/ARR). For example, if the absolute risk reduction after five years is 2%, then the number needed to treat is 50 (1/0.02). Fifty people need to be treated for five years to prevent one adverse outcome. This means that the outcome of interest will be unchanged for the 49 other people who took the treatment for five years. Some of these 49 people may come to harm as a result of adverse effects of treatment.

The number needed to harm is a less frequently published number. It is essentially the inverse of the absolute rate of adverse effects. Over 10 years, if 4% of women suffer venous thromboembolism while on hormone replacement therapy and 2% without hormone replacement therapy, the absolute harm rate of the therapy is 2% and the number needed to harm is 50. That is, for every 50 women treated one will develop a thrombosis that would not have otherwise occurred.[2]

Outcome

Trial end points are varied and one must have a clear understanding of the outcomes measured. Death, disability and morbidity are clinical end points, while others such as blood pressure, cholesterol or bone density are surrogate or intermediate markers. Surrogate end points may have merit as indicators of potential benefit, but they rely on other evidence providing a causal link to clinical outcomes. In the end all interventions must be justifiable by an improvement in patient well-being, that is, by clinical end points.

Assessing evidence – patient factors

Many trials exclude pregnant women, children, older people and patients with significant comorbidity. The benefit or harm in 'real world' patients may not be equivalent. Similarly, some treatments have only been studied in particular groups or after patients intolerant to test doses have been excluded (for example, the HOPE trial where 10% of the initial cohort were excluded after the run-in phase).[3]

Health professionals interact with individuals, not trial cohorts or populations. The characteristics of the individual patient are therefore an important consideration when deciding whether to treat a risk factor.

Patient attitude

Everyone has a different attitude to risk. The sedentary smoker who drinks a bottle of wine per day clearly has a different life attitude to a teetotal non-smoker who walks for an hour every day.

Patient anxiety

The label of 'risk' can cause some patients to become significantly anxious. The effect of labelling has been well documented to impair quality of life. This is particularly pertinent in the context of a symptomless risk factor and should be considered before introducing the issue of risk with patients.

Patient effort

Harm from treatment includes more than potential drug adverse effects. Treatment involves visits to the doctor, prescriptions, blood tests, possibly

diagnostic imaging, cost and the daily consumption of drugs. When the benefit of treatment is a trust that the odds of some future event are reduced rather than an immediately experienced improvement in well-being, the effort to adhere to treatment can be significant.

Comorbidity

The outcome being prevented must be relevant to the patient. A critical phenomenon here is significant other disease. The quality of life gained is more important than the raw quantum. In patients with significant comorbidity, a physician needs to consider and discuss whether the benefit gained is worth the additional intervention. An example here is hypercholesterolaemia in a patient with advancing dementia. One may be able to reduce the risk of a cardiovascular event, but is this relevant to this patient?

Risky realities

The association of an observation with a negative outcome does not necessarily mean treating the observation improves the outcome. The transverse ear lobe crease has been associated with a higher risk of coronary artery disease.[4] Excision of the ear lobe is unlikely to change things. For many years it was stated that hormone replacement therapy reduced the risk of heart disease on the basis of plausible pathophysiological models. The Women's Health Initiative trial suggests the actual outcome was different.[2]

Risk is never zero and is never reduced to zero. At any age there is a risk of disease and even death. Drug therapy for cardiovascular risk reduces a baseline level of risk at best by a relative 50%. For example, in a person with known ischaemic heart disease whose absolute risk of another event may be 30% in five years, maximal risk factor reduction reduces that to 15% in five years. It is not reduced to zero, and in that time that individual still has various risks for injury or other illness. Prevention by drug therapy of risk factors is never absolute, contrary to prevention in other contexts such as immunisation, where a serious infectious disease prevented is one that will probably never occur.

There are quite distinct principles underlying treatment and prevention. All interventions have a risk of harm, but a person's willingness to accept the risk will depend on their situation. The rate of adverse reactions to chemotherapy may be acceptable to a cancer patient with a poor prognosis. However, a similar rate of adverse effects would not be acceptable for a vaccine given to many healthy individuals to prevent disease in a few. Similarly, the effort of treatment for symptomatic disease can be readily justified by the improvement in the symptoms, whereas in risk factor modification the effort is now, for all, but the benefit is later, for some.

Who to treat?

Drugs are approved by the Therapeutic Goods Administration (TGA) if they are relatively safe and have reasonable evidence of efficacy. If the drug is cost-effective in a particular condition it will be listed on the Pharmaceutical Benefits Scheme (PBS). Similarly, treatment guidelines are expert interpretations of the evidence on how to achieve the best outcomes for a particular disease. However, the health professional's role is a step further beyond the TGA, PBS and guidelines to a focus on the outcome for the whole patient rather than just their disease. Specific consideration must be given to the individual relevance of the outcome being sought, and what information is suitable for a patient to make an informed decision.

Informing patients about risk

Patients should understand the benefits and harm of the treatment being offered, especially when this could be lifelong drug therapy. Relative risk reductions do not really quantify the merit of a treatment. Absolute data can be presented in several ways. Some authors recommend the Visual Rx analogue diagrams with a number of people represented as stick figures and the control and intervention groups marked in different colours or shades.[5] Other authors have shown that patients and physicians more readily understand outcomes by using natural frequencies[6] (such as, for 100 similar persons an event will occur in 10 without treatment and 7 with treatment) rather than percentages or odds ratios. Another technique is to ask the patient to imagine a room full of 100 similar people and compare the various outcomes for a number of those in that room.

Using natural frequencies and absolute risk data, a patient can be in a better position to assess the merit of a treatment in the context of their own attitudes, preferences, expectations and other morbidity. Absolute outcome data and number needed to treat have been published for many drugs.

Here are two examples of using absolute outcome data to assist with decision-making about preventive pharmacotherapy.

Sixty-year-old female with hypercholesterolaemia

The readily available New Zealand cardiovascular risk calculator[7] can quantify absolute risk. With a blood pressure of 130/80, total cholesterol of 7.5 mmol/L, and an HDL cholesterol of 1.1 mmol/L, a non-smoking non-diabetic female has a five-year cardiovascular event risk of 7%. It is generally agreed that statins will reduce risk by a third. With treatment the five-year risk is thus about 5%.

When discussing the merit of treatment against the effort and potential adverse effects, consider the absolute risk reduction. About seven in 100 people will have an event in five years with no treatment, but if 100 take the statin for five years, five will have an event.

Overweight patient taking metformin for type 2 diabetes

The United Kingdom Prospective Diabetes Study (UKPDS)[8] showed a difference in diabetic end points over 10 years between 'conventional' treatment (fasting glucose <15 mmol/L, and no hyperglycaemic symptoms) and 'intensive' treatment (glucose <6 mmol/L). With conventional treatment macrovascular complications occurred in 31% of patients and microvascular in 9.2%. With intensive treatment including metformin, the rates were 23% and 6.7%.[3] The prescriber and patient should discuss the downside of intensive treatment with respect to hypoglycaemia, metformin adverse effects such as diarrhoea, and the patient effort required to achieve a fasting glucose <6 mmol/L.

Conclusion

Risk factor pharmacotherapy is underpinned by population-based research. In contrast, the primary care physician has to decide what to recommend or do with each individual patient. An understanding of the limitations of epidemiological evidence, a familiarity with using absolute outcome data, an acknowledgement of the ethical perspectives and a focus on the whole patient should ensure that pharmacotherapy for risk factors is useful and relevant to the patient.

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Further reading

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Conflict of interest: none declared

ADVERSE REACTIONS OF CURRENT CONCERN

MARC Rx ADVICE

The Medicines Adverse Reactions Committee (MARC) initiated the list of *adverse reactions of current concern* to bring particular medicine adverse reactions to the attention of prescribers. The intention is to encourage prescribers to report these reactions to the Centre for Adverse Reactions Monitoring (CARM) so that more information can be gathered, and further action taken if necessary. The reports provide a New Zealand perspective on emerging medicine safety issues.

As with any adverse reactions monitoring scheme, analysis can only be based on reports that are received. Prescribers are therefore encouraged to continue reporting adverse reactions to CARM so that the MARC can make the best possible recommendations based on information reflecting the New Zealand situation.

Please report **all cases** of the following adverse reactions to: CARM, NZ Pharmacovigilance Centre, PO Box 913, Dunedin. Use the reporting form inside the back cover of *Prescriber Update*, or download it from either the CARM or Medsafe web sites: http://carm.otago.ac.nz/reporting.asp or www.medsafe.govt.nz/Profs/adverse.htm

Medicine/s	Adverse reactions of current concern	*Prescriber Update* references
Complementary and alternative medicines*	all adverse reactions (including interactions)	This issue (see page 4) & Vol.23(2), July 2002 & No.13, Oct 1996
Leflunomide	all adverse reactions	Vol.27(1), June 2006 & Vol.26(2), December 2005 & Vol.25(1), May 2004
Pioglitazone and Rosiglitazone	all adverse reactions	This issue (see page 8) & Vol.27(1), June 2006

* includes herbal medicines, bee products, homoeopathic products, dietary supplements, minerals, and any other medicines containing animal or plant extracts.

INTENSIVE MEDICINES MONITORING PROGRAMME

About the IMMP

The purpose of the Intensive Medicines Monitoring Programme (IMMP) is to identify previously unrecognised adverse reactions to new medicines or to investigate safety issues with existing medicines. It develops adverse event profiles for these medicines, measures incidence and characterises events of clinical concern. In addition, the IMMP is able to identify any high-risk groups amongst the patients being treated. The medicines currently being monitored are listed in the table below (recent additions are in **bold**).

Medicine	Brand name/s
Clozapine	Clozaril, Clopine
Dextropropoxyphene-paracetamol combination medicines	**Capadex, Paradex**
Levonorgestrel intrauterine system*	Mirena*
Olanzapine	Zyprexa
Quetiapine	Quetapel, Seroquel
Risperidone	Ridal, Risperdal
Varenicline	**Champix**

* New patients are no longer being added to the cohort for Mirena because sufficient numbers of patients have been recruited. However, follow-up of existing patients is continuing, which means that prescribers may receive follow-up questionnaires asking about adverse events experienced by their patients using Mirena. IMMP encourages prescribers to complete the questionnaires because their participation is a valuable contribution to patient safety.

How to report

Use the reporting form inside the back cover of *Prescriber Update*, or download it from either the NZ Pharmacovigilance Centre or Medsafe web sites: http://carm.otago.ac.nz/reporting.asp or www.medsafe.govt.nz/Profs/adverse.htm

Recent additions (effective from July 2007)

- **Champix** (varenicline) has been added to the list of IMMP medicines. It is a selective nicotinic acetylcholine receptor partial agonist, approved as an aid to smoking cessation. It is the first medicine of this new class to be licensed in New Zealand and is therefore subject to monitoring in the IMMP.
- Dextropropoxyphene-paracetamol combination products: **Capadex** and **Paradex** have been included in the IMMP for a short-term monitoring study, following a request from the Medicines Adverse Reactions Committee for more data on the prescribing of these medicines in New Zealand.

What to report

Please report **all clinical events** in patients taking IMMP medicines, including:

- any suspected adverse reaction
- deaths (including cause if known)
- any new clinical events, even if minor or common
- accidents
- change in a pre-existing condition
- abnormal changes in laboratory test results
- possible interactions.

What to tell patients prescribed IMMP medicines

Please remember to tell patients that they have been prescribed a monitored medicine. This means the IMMP receives details of their prescriptions and that their doctor may be asked for clinical information on the patient's experience whilst taking this medicine. If possible, an explanatory IMMP leaflet should be given to the patient (available from the IMMP, NZ Pharmacovigilance Centre, PO Box 913, Dunedin).

Prescriber Update is published and distributed by Medsafe in the interests of safer, more effective use of medicines, medical devices and methods of diagnosis and treatment.

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New Zealand Government

CARM
CENTRE FOR ADVERSE REACTIONS MONITORING

Fax: (03) 479 7150
Phone: (03) 479 7247

Reporting form for Adverse Reactions to Medicines, Vaccines and Devices and all Clinical Events for IMMP

PATIENT DETAILS

HP3442

Surname:	First Name/s:	NHI No:	
Address:		Date of Birth:	Sex:
		Ethnicity:	

ALL MEDICINES IN USE *ASTERISK SUSPECT MEDICINE/S* Include over-the-counter (OTC) and alternative medicines

Medicine or Vaccine+batch no. (and brand name if known)	Daily Dose	Route	Date Started	Date Stopped	Reason for Use

DESCRIPTION OF ADVERSE REACTION OR EVENT

Date of onset: _____

Recovered ☐ Not yet recovered but improved ☐ Not yet recovered ☐ Unknown ☐ Fatal ☐ - Date of Death: _____

Severe? - Yes ☐ No ☐ Rechallenged? - No ☐ Yes ☐ Result: _____

OTHER FACTORS - Please tick or specify as appropriate

Renal disease ☐ Allergy ☐: _____ Other Medical Conditions: _____

Hepatic disease ☐ Nutritional Suppl or OTC use ☐ : _____ Industrial Chemicals ☐ : _____

REPORTER - Please tick as appropriate: Doctor ☐ Pharmacist ☐ Dentist ☐ Nurse ☐ Other ☐ : _____

Name:

Address:

Signature: _____

Phone: _____ Date: _____

Send completed form to CARM

Freepost 112002, CARM, PO Box 913, Dunedin **or** Fax: (03) 479 7150

ADVERSE REACTIONS

What to report

Please report any suspect reaction of clinical concern. This includes adverse reactions involving:

- Prescription medicines
- Over-the-counter medicines (medicines purchased without a prescription)
- Complementary medicines (herbal medicines, naturopathic and/or homoeopathic medicines, and nutritional supplements such as vitamins and minerals)
- Vaccines.

In particular, please report the following:

- All suspected reactions to NEW medicines
- All Adverse Reactions of Current Concern[1]
- All events to IMMP medicines[2]
- All suspected drug INTERACTIONS
- UNEXPECTED or SERIOUS reactions (including those suspected of causing death, admission to hospital, prolongation of hospitalisation, or birth defects)
- Serious ALLERGIC reactions (to enable a danger or warning to be entered in the national health database so re-exposure can be avoided for that individual).

How to report

Fill in the reporting form, which is available:

- overleaf (inside the back cover of *Prescriber Update*)
- from the CARM web site: http://carm.otago.ac.nz/reporting.asp

On-line reporting is also available on the CARM web site.

Where to report

Send all adverse reaction reports to CARM (Centre for Adverse Reactions Monitoring) in Dunedin.

Post to: Freepost 112002
The Medical Assessor
CARM
University of Otago Medical School
PO Box 913
Dunedin

Fax: (03) 479 7150

Phone: (03) 479 7247

E-mail: carmnz@stonebow.otago.ac.nz

1. The list of *Adverse Reactions of Current Concern* is on page 22
2. The list of medicines in the Intensive Medicines Monitoring Programme (IMMP) is on page 23