reduced the risks of myocardial infarction and all-cause mortality. As a result metformin became the first-choice treatment for obese patients with type 2 diabetes. Later subgroup analyses showed that it had similar vascular protective effects in all patients, but it took another decade for these findings to be translated into official recommendations. In 2012 diabetes experts in the USA and Europe[6] declared that metformin is the drug of first choice for all patients with type 2 diabetes. The Australian National Health and Medical Research Council is considering a similar recommendation.

The story is not yet over. Nephrologists believe metformin is underused in kidney disease. Metformin is now also used to treat polycystic ovary syndrome, gestational diabetes and is showing early promise as a treatment for cancer. Recent meta-analyses controversially suggested that metformin may not prevent macrovascular disease[7], however the risk of cardiovascular events with metformin may be less than with sulfonylureas[8].

There are many lessons from this saga:

- it takes a very long time to collect good population efficacy and safety data
- medications can produce more benefits and harms than first claimed
- drugs marketed by large pharmaceutical companies dominate the market[9] and using new drugs with limited, short-term data from restricted trial populations is a risky activity
- wider understanding of pharmacodynamics and pharmacokinetics could prevent the belief that all drugs in a chemical group have the same actions and adverse effects
- the long delay of translating evidence into practice is occurring with other medicines such as aspirin for preventing cardiovascular disease. <

Conflict of interest: none declared

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Letters to the Editor

Complementary medicines

Editor, – I work regularly in a large public hospital anaesthetic preadmission clinic. I am no longer surprised at how many patients take expensive complementary medicines with little or no validation of their efficacy – for example fish oil to improve vision, ginkgo for Alzheimer's disease, coenzyme Q for cardiac failure. Some patients are on over 10 different products! Can someone please explain the lack of government regulation?

My concerns regarding complementary medicines (and I include here all the usual suspects such as herbals, minerals and vitamins) are:

- some are expensive and could exhaust patients' limited budgets
- some, in fact, may do no good at all or at least there is minimal evidence they do good
- some patients maintain adverse lifestyle choices because they felt, or wanted to believe,

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The Editorial Executive Committee welcomes letters, which should be less than 250 words. Before a decision to publish is made, letters which refer to a published article may be sent to the author for a response. Any letter may be sent to an expert for comment. Letters are usually published together with their responses or comments in the same issue. The Committee screens out discourteous, inaccurate or libellous statements and sub-edits letters before publication. The Committee's decision on publication is final.

LETTERS

these medicines would provide protection (for example, thiamine reverses alcohol-induced liver damage or green tea capsules prevent lung cancer in continuing smokers)

- they may do significant harm (for example vitamin E and increased incidence of prostate cancer).

I do believe that there are some good products out there that will eventually be validated – many current drugs started this way, such as aspirin from willow bark.

How can there be minimal or no regulatory oversight of complementary medicines?

The commonest response in the past when I have raised this issue with the industry was, 'Sure they may not do the job as advertised but at least they are harmless'. This is simply not true!

Bruce Burrow
Deputy director
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Osteonecrosis of the jaw

Editor, – I was very interested in the dental note concerning bone turnover markers (Aust Prescr 2012;35:159). The authors state that the incidence of bisphosphonate-related osteonecrosis of the jaw is 1 in 500 to 1 in 1500. Is this related to oral bisphosphonates used to treat osteoporosis, or does it include intravenous bisphosphonates associated with the treatment of various cancers?

I have recently attended a number of meetings with endocrinologists where they consistently state that the incidence of bisphosphonate-related osteonecrosis of the jaw associated with oral bisphosphonate treatment of osteoporosis is about 1 in 100 000.

There is obviously a wide variation of opinion. I would appreciate comments from the authors regarding this discrepancy on the incidence of osteonecrosis of the jaw.

Graham McNally
General practitioner
Brisbane

Michael McCullough and Alastair Goss, authors of the dental note, comment:

Our dental note on bone turnover markers was specifically quoting the incidence of bisphosphonate-related osteonecrosis of the jaw relating to patients with osteoporosis on oral bisphosphonates.

The studies quoted are international, independent and not funded by pharmaceutical companies. They are primarily conducted by oral and maxillofacial surgeons and other specialist dentists who diagnose and treat bisphosphonate-related osteonecrosis of the jaw. They very consistently show an incidence of 1 in 500 to 1 in 1500.[1-3] In specific patient groups having bone invasive procedures, the incidence is more of the order of 1 in 100.[4,5] It should be noted that Osteoporosis Australia, when they met with the Australian Dental Association to develop an instruction pamphlet, agreed that the incidence was at least in the order of 1 in 1500.[6]

Some endocrinologists seem to wish to continue to quote the American Society of Bone and Mineral Research report of the task force in 2007 that indicated an incidence of 1 in 10 000 to 1 in 100 000.[7] This review was published at a time when the only independent published incidence data was the Australian study.[1] The majority of the authors of that task force reported substantial receipt of pharmaceutical company funds. That paper has not been updated in light of the more extensive independent studies.

Another important aspect that has recently received prominence in the medical literature is the length of time a patient with osteoporosis should continue with oral bisphosphonates. In a recent meta-analysis by the US Food and Drug Administration[8] it was shown that for most patients the maximum benefit was achieved by five years. The benefit of continued use beyond this was low with increasing risk of serious complications including bisphosphonate-related osteonecrosis of the jaw, spontaneous femur fracture and oesophageal squamous cell cancer.[8]

Minimising the risk of bisphosphonate-related osteonecrosis of the jaw is straightforward. Prescribers need to be aware of the true incidence of risk and ensure that their patients are dentally fit before commencing oral bisphosphonates. Patients then need to be carefully monitored.

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The seven-year rule for safer prescribing

Editor, – The editorial by Sidney Wolfe (Aust Prescr 2012;35:138-9) suggested that patients should not take any pharmaceutical drugs that have been released until they have been taken by other patients for seven years. By that time, half of the black box warnings or market withdrawals that would ultimately occur for a drug over its lifespan would have already happened.

The logical corollary of this, if it was adopted by all patients, is that the seven-year rule would immediately become an infinite year rule as no patients would be taking any new drugs. Clearly, widespread adoption of this recommendation would have profound effects on achieving any improvement in disease states, let alone the capacity of pharmaceutical companies to continue to exist. The editorial reports that even 25 years is not long enough to exclude the possibility of a new black box warning or market withdrawal.

Perhaps it would be better to outline to patients that changes to medication recommendations can occur and half of these occur within the first seven years and leave it to a harm–benefit discussion between the patient and their prescriber about whether the new medication should be trialled or not.

I do not think that blanket ban approaches are particularly helpful or necessarily balanced.

Marc Russo
Pain medicine physician and specialist
Newcastle
NSW

Sidney Wolfe, the author of the editorial, comments:

Marc Russo's assertions that the seven-year rule, if adopted by all patients, would result in a situation in which 'no patients would be taking any new drugs' and would 'have profound effects on achieving any improvement in disease state' are both incorrect. The editorial clearly states that the rule would not apply to that small proportion of new drugs that represent therapeutic breakthroughs. Patients are not discouraged from using breakthrough drugs, which are defined as offering 'a documented therapeutic advantage over older, proven drugs'. Furthermore, if more patients and their healthcare providers adhered to the rule, there might actually be more incentives for drug companies to develop true breakthrough drugs to improve treatment of diseases, rather than developing a tenth ACE inhibitor, an eighth angiotensin II receptor antagonist or a seventh statin.

Beyond the absence of a documented therapeutic advantage of many new drugs is the increased likelihood of harm from a drug that is statistically much more likely than established, time-tested drugs to have a new risk discovered after marketing – one serious enough to trigger a new black box warning or even market withdrawal.

Russo's proposed alternative to the not 'necessarily balanced' seven-year rule is to 'leave it to a harm–benefit discussion between the patient and their prescriber' to see if the new medication warrants being used. This risks a decision that will likely be tilted toward use because of massively higher promotion of these new drugs to doctors compared with older ones. This decision is therefore more likely to be necessarily unbalanced.

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