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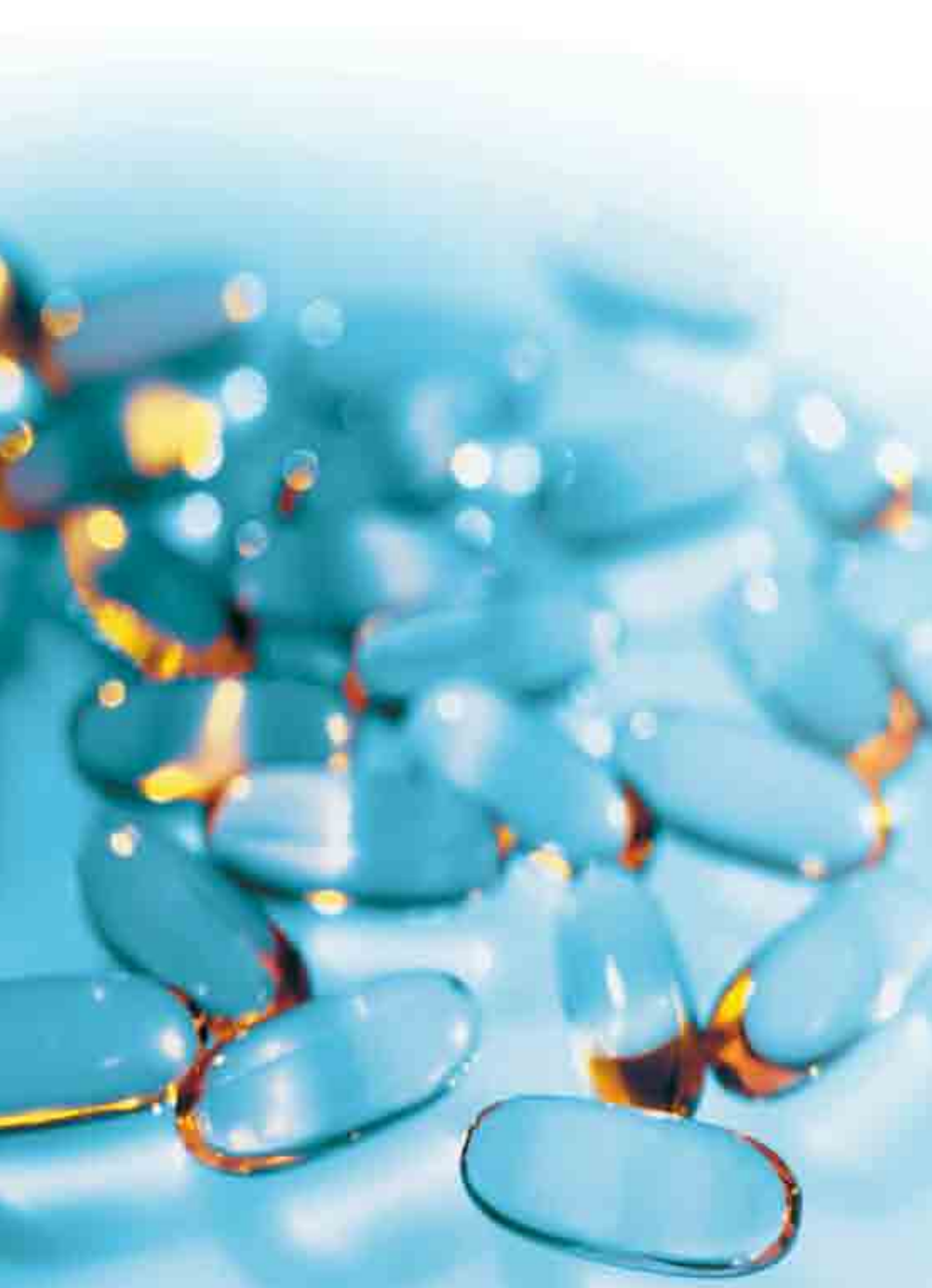

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# Editorial

# Gentamicin: a great way to start

***Robert FW Moulds**, Medical Advisor, and **Melanie S Jeyasingham**, Editor, Therapeutic Guidelines Limited, Melbourne; on behalf of the Expert Writing Group, Therapeutic Guidelines: Antibiotic (Version 14)*

Key words: adverse effects, aminoglycosides, drug monitoring.

*(Aust Prescr 2010;33:134–5)*

For many years, Therapeutic Guidelines: Antibiotic has recommended the use of gentamicin for therapy of serious infections possibly caused by Gram-negative organisms. This is because of its rapid bactericidal activity and comparatively low levels of resistance in most community- and hospital-associated Gram-negative pathogens. These properties make it a very useful empirical drug when rapid control of a serious infection is required.

However, gentamicin is both ototoxic and nephrotoxic. Ototoxicity is less frequently reported but, unlike nephrotoxicity, is much less commonly reversible.[1] Monitoring of plasma concentrations has been recommended to guide safe and effective dosing, but will not prevent the rare occurrence of sudden idiosyncratic deafness. Prolonged therapy is an independent risk factor for nephrotoxicity.[2] Conversely, short-term therapy (three days or less) has a very low incidence of nephrotoxicity.[3]

## In this issue…

Spring is a time of change, so it is appropriate that some of the papers in this issue herald potential changes in practice. Rob Moulds and Melanie Jeyasingham propose abandoning routine monitoring of gentamicin concentrations during short-term use of the drug.

Routine self-monitoring of blood glucose (by some patients with type 2 diabetes) could also be unnecessary according to a Canadian paper reviewed by Julia Lowe. However, according to Peter Davoran and David McIntyre, testing is still recommended in gestational diabetes.

Tests for melanoma are becoming more widespread. Elizabeth Wurm and Peter Soyer review some of the non-invasive diagnostic tools now available.

There have been changes at the National Prescribing Service (NPS), with the closure of the Therapeutic Advice and Information Service, while at *Australian Prescriber* we are mourning the sudden death of Maureen Ryan, our editorial assistant. This issue is dedicated to the memory of Maureen.

Although gentamicin is primarily indicated for empirical therapy, in practice empirical use often continues beyond the time frame originally intended. Despite the best endeavours of all concerned to ensure appropriate monitoring, gentamicin toxicity remains an important clinical problem and many clinicians are reluctant to use it, even for short-term empirical therapy.[4]

This reluctance to use gentamicin has resulted in increasing use of alternative drugs, such as broad-spectrum cephalosporins, for empirical therapy against likely Gram-negative pathogens.[4] Widespread use of broad-spectrum antibiotics has been linked with the increasing prevalence of infections due to methicillin-resistant *Staphylococcus aureus*,[5] vancomycin-resistant enterococci,[6] multiresistant Gram-negative organisms,[7] and *Clostridium difficile*.[8] For empirical use, these drugs should therefore be reserved for situations where gentamicin is specifically contraindicated – previous vestibular or auditory toxicity or serious hypersensitivity reaction to an aminoglycoside.

To resolve the dilemma that concern about long-term toxicity is inhibiting its use as short-term empirical therapy, the expert writing group for version 14 of Therapeutic Guidelines: Antibiotic[9] has recommended some major changes to the way gentamicin is used. There are now clear distinctions between empirical and directed therapy.

These principles apply to use in both adults and children and to other intravenously administered aminoglycosides.

For **empirical therapy**, the recommended treatment duration with gentamicin is now limited to a maximum of 48 hours in all patients. The initial dose is based on the patient's age and weight, then the dose interval for either one or two further doses (or none at all) is determined by the patient's renal function. For example, a patient with normal renal function would receive a maximum of three empirical doses at 0, 24 and 48 hours. As dosing with gentamicin will not continue beyond 48 hours, monitoring of plasma concentrations is not required.

Susceptibility results should be used to guide ongoing therapy. If susceptibility results are not available by 72 hours and empirical intravenous therapy is still required, the gentamicin-containing regimen should be ceased and an alternative regimen used. The recommended alternative depends on the

indication, but broad-spectrum cephalosporins should not automatically replace gentamicin.

If a susceptible Gram-negative organism is identified, gentamicin should only be continued if the patient has one of the following indications for **directed therapy**:

- infections when resistance to other safer antimicrobials has been shown
- combination therapy for serious *Pseudomonas aeruginosa* infections and brucellosis
- low doses as synergistic treatment for streptococcal and enterococcal endocarditis.

The first dose of directed therapy is based on the patient's age and weight, as for empirical therapy. Monitoring of plasma concentrations is essential and should commence with this first dose of directed therapy to guide subsequent dosing.

Computerised methods can be successfully used for gentamicin monitoring. They estimate the 24-hour area under the curve (AUC) of concentration against time and recommend dose adjustment to achieve the target AUC. These methods are the most sophisticated as they automatically adjust for significant individual variation in volume of distribution and elimination. The timing of the blood sample will depend on the specific program used.[1]

The nomograms for plasma concentration monitoring that appeared in previous versions of the guidelines have been deleted. These graphical methods had significant limitations as they were based on population pharmacokinetics and had only been validated in adult patients with normal renal function.[1] They were included in previous versions of the guidelines because it was recognised that not all hospitals had access to the more sophisticated computerised methods.

As there are now only a few specific and uncommon indications where directed therapy with gentamicin is recommended, the expert group decided that the more accurate computerised methods of monitoring should be used. This is to discourage long-term use except in these circumstances, in which case patients should be in a facility that has access to a computerised monitoring program and skilled personnel to interpret the information.

For ongoing directed gentamicin therapy, other monitoring recommendations remain unchanged.

The expert writing group recognises that these changes, and in particular the intentional omission of the monitoring nomograms, might surprise users of the guidelines. However, it is hoped that the changes will lead to better patient care by striking a practical balance between the benefits of the breadth of activity of gentamicin and its rapid bactericidal activity, especially in bloodstream infections, versus the limitations of toxicity with prolonged use.

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*Professor Moulds was chair, and Ms Jeyasingham was editor, of the expert writing group for the Antibiotic Guidelines version 14.*

*Dr John Dowden and Professor John Tiller from the Editorial Executive Committee of Australian Prescriber are directors of Therapeutic Guidelines Limited.*


### RADAR

The latest edition of NPS RADAR reviews sitagliptin and vildagliptin, two drugs from a new class of dipeptidyl peptidase-4 (DPP-4) inhibitors – or 'gliptins' – for type 2 diabetes mellitus. RADAR also reviews an adrenaline autoinjector for acute allergic anaphylaxis.

To read the full reviews go to www.nps.org.au/radar

# Editorial

# Can sunshine cure the unhealthy entanglement of industry and health care?

***Melissa Sweet**, Health Journalist, Moderator of the health blog Croakey, and Adjunct Senior Lecturer, Sydney School of Public Health, University of Sydney*

Key words: advertising, drug regulation, pharmaceutical industry.

*(Aust Prescr 2010;33:136–7)*

Moves are afoot around the world to increase the open disclosure of financial relationships between medical industries and clinicians, researchers and related institutions. This follows widespread concern about the potential for such ties to distort research, clinical practice and policy. In 2009, a report from the Institute of Medicine in the USA called for laws to require pharmaceutical, biotechnology and device companies to report, through a public website, the payments they make to doctors, researchers, academic health centres, professional societies, patient advocacy groups and others involved in medicine.

This recommendation has been taken up as part of the health reform agenda in the USA. The proposed Physicians Payment Sunshine Act, which has been incorporated into the healthcare reform bill passed by the House of Representatives in March 2010, requires payments to be reported. Some pharmaceutical and devices companies have endorsed this Act, and a number, including Cephalon, DePuy, Eli Lilly, GlaxoSmithKline and Merck, have begun to release details of their payments to practitioners on their corporate websites. A US company called Obsidian Healthcare Disclosure Services recently launched a searchable online database (PharmaShine) containing all of the publicly available information on such payments. PharmaShine allows users to search for health professionals receiving payments by physician specialty, city, state, and hospital affiliation. By February 2010, it had payment data for over 21 000 physicians, physician assistants, nurse practitioners and other healthcare professionals across the USA. Some institutions, including Harvard University and a related healthcare group called Partners HealthCare, are tightening regulations for doctors and scientists who consult for drug companies and medical device makers.[1]

Relationships between the pharmaceutical industry and patient groups are also coming under increasing scrutiny. Merck notes that while disclosure of grants to patient organisations has been mandatory in Europe since March 2009, it has voluntarily disclosed such payments in Europe, the Middle East and Africa since 2008. It began reporting such payments in Canada last year.[2]

Meanwhile, the Indian Medical Council recently introduced new regulations banning doctors from receiving gifts, travel and hospitality from pharmaceutical or allied healthcare companies. Doctors also must not endorse any drug or product in public. The regulations state, 'Any study conducted on the efficacy or otherwise of such products shall be presented to and/or through appropriate scientific bodies or published in appropriate scientific journals in a proper way'.[3]

In Australia, there is no systematic mechanism for ensuring full and open disclosure of financial ties, despite concern that self-regulation by the profession has been largely ineffective and that 'medicine is facing a credibility problem of unheralded proportions'.[4] The Medicines Australia Code of Conduct requires member companies to reveal some details of sponsored events, but these reporting requirements could be strengthened and extended.[5] I have established the Crikey Register of Influence (www.crikey.com.au/register-of-influence) as a mechanism for identifying some of the associations between key opinion leaders and industry marketing or disease-awareness campaigns. While this is not a systematic effort, it has helped focus some professional and public attention on the issues of industry entanglement and disclosure.

Some medical organisations and medical school deans are moving to address concerns about conflicts of interest. The National Health and Medical Research Council is investigating ways of ensuring that Australian researchers, universities, other research institutions and healthcare practitioners manage conflicts of interest more effectively. A discussion document is expected to be released in the second half of 2010. In the absence of comprehensive public reporting mechanisms, clinicians and health services could consider voluntarily making such declarations. It has also been suggested that patients should consider asking clinicians whether they receive payments or gifts from industry.[6]

Views are mixed, however, about the likely impact of increased disclosure. Some argue that transparency alone is not sufficient in every situation, and that, for example, editorials, reviews and guidelines should be written by experts without any conflicts of interest.[7] In the wake of revelations about commercial ties of experts involved in setting the World Health Organization's

pandemic influenza policies, there have been calls to exclude experts with commercial ties from major public health policy decisions.[8] Cancer Council Australia does not accept funding from the pharmaceutical industry, in part because of the organisation's role in guideline development. The Council also funds the patient group Cancer Voices, which ensures there is a patient advocacy group that is not reliant on industry funding.

Some authors argue that encouraging greater transparency is the wrong solution, and is comparable to asking doctors in the 1800s to declare whether they washed their hands between doing autopsies and delivering babies.[9] They cite the limited evidence[10] that is available, suggesting there is potential for perverse consequences, such as encouraging unwarranted trust in biased advice. A better solution, they argue, is to end the financial entanglements between industry, research and practice.

However, it is likely that such entanglements will continue into the foreseeable future. In the meantime, Australian clinicians, researchers and related organisations and institutions are likely to come under increasing pressure to provide full and open public disclosure of financial and other ties with commercial interests. It would be helpful if efforts to promote open disclosure were carefully evaluated to establish their impact on a range of areas, including the attitudes and behaviours of patients, clinicians, researchers and other relevant parties.

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## Further reading


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*Melissa Sweet has an honorary position as a chief investigator on a National Health and Medical Research Council-funded project 'Calling the tune? Investigating corporate influences on media reporting of health'. She maintains the Crikey Register of Influence.*


# Letters

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 Editorial Executive Committee screens out discourteous, inaccurate or libellous statements and sub-edits letters before publication. The Committee's decision on publication is final.

### Multiresistant organisms at the front line

Editor, – I read the dental note (Aust Prescr 2010;33:71) about not using amoxycillin as the first drug of choice for oral infection to reduce the prevalence of multiresistant bacteria, for example life-threatening *Streptococcus pneumoniae*.

I am a dentist and we have always been told that amoxycillin is the best and safest antimicrobial when encountering oral infection. So what will be the next best thing?

Shahriar Sanati
Dentist, Sydney

*Associate Professor Michael McCullough, Chair, Therapeutics Committee, Australian Dental Association, comments:*

Dentists were once told that amoxycillin was the best and safest antibiotic for most dental infections. However, this idea has been considerably challenged over the past several decades leading to the current concept that penicillin is the best choice as first option. These concepts are clearly outlined in the Therapeutic Guidelines: Oral and Dental. Unfortunately, there is likely not going to be a 'next best thing', so we need to use our currently available antibiotics judiciously.

# Self-monitoring of blood glucose in type 2 diabetes

***Julia Lowe**, Internal Medicine Physician and Associate Professor, Division of Endocrinology, Sunnybrook Health Sciences Centre, Toronto, Canada*

## Summary

**Recent evidence suggests that patients with type 2 diabetes who are not taking insulin may not benefit from self-monitoring of blood glucose. Patients with diabetes who require insulin have to monitor their blood glucose by finger-prick (capillary) testing up to 3–4 times or more a day along with their 1–5 insulin injections. The need for this is widely accepted, but the principle of frequent daily monitoring is also applied to people who are not on insulin.**

Key words: hypoglycaemic drugs, insulin.

*(Aust Prescr 2010;33:138–40)*

## Introduction

A recent systematic review from Canada[1] suggests that patients with type 2 diabetes who are not taking insulin do not require self-monitoring of blood glucose (see box). Type 2 diabetes is increasingly common, so there may be significant costs associated with widespread use of blood glucose testing by these patients. For example, in Ontario blood glucose test strips represented the third largest annual cost to the Ontario Public Drug Program – over CA$107 million, or 3.3% of total drug expenditure in the program.

On 1 January 2010, the Australian Government increased the co-contribution for blood glucose test strips under the National Diabetes Services Scheme from AU$14.10 to AU$14.30 for 100 strips. However, the overall cost is much higher – around $50–60 per box of 100. The National Diabetes Services Scheme supplied nearly three-quarters of a million boxes of varying size to these patients in 2008. If this ceased, significant sums of money could be spent on other areas of diabetes care.

## Current practice in Australia

Many doctors would recommend self-monitoring to people with type 2 diabetes who do not require insulin. Self-monitoring of blood glucose is discussed as part of their diabetes education. The choice of test and timing and frequency of monitoring is negotiated between the patient and their healthcare professionals, taking into account the type of therapy, level of glycaemic control, risk of hypoglycaemia and need for short-term adjustment of treatment. Self-care of diabetes often varies in the course of a person's life, with periods of intense monitoring around medical crises and clinic visits, and little or no monitoring at other times. In theory, patients, doctors and diabetes educators review the results of self-monitoring and together make decisions on actions to be taken to improve diabetes care. In practice this may not occur as often as doctors believe. While Canadian doctors reported that they routinely reviewed monitoring results, patients reported the opposite.[2]

*Box*

**Key messages about self-monitoring of blood glucose in type 2 diabetes** [1]

- People managed by diet alone or who are using metformin alone or in combination with acarbose or DPP-4 inhibitor do not need routine self-monitoring of blood glucose
- People who are on a sulfonylurea either alone or in combination with other oral therapy may need to test their blood glucose periodically because of an increased risk of hypoglycaemia
- Periodic testing may be required in people on oral therapy to monitor blood glucose responses to changes in therapy or when unstable glucose levels are anticipated, e.g. during acute illness or surgery, or when there is a risk of hypoglycaemia (prolonged fasting)
- Testing up to 14 times/week should be sufficient for most people on basal insulin with oral drugs
- To achieve optimal control, people who are using basal-bolus regimens should individualise self-monitoring of blood glucose to guide adjustment of insulin
- Self-monitoring of blood glucose should be used in conjunction with regular HbA1c measurements according to guidelines to assess day-to-day control
- Such testing should be linked to specific patient actions such as insulin dose self-adjustment or detection and treatment of hypoglycaemia

## Is there enough evidence for a change in practice?

Many systematic reviews have looked at this question. However, their conclusions are only as good as the trials available for

analysis. In real life, compliance with self-monitoring of blood glucose may have been poor. There are no studies assessing how well people actually implement the advice they are given on when to test and what to do with their results.

While slight variations in the research question have led to slight differences in the inclusion criteria of the reviews, there is remarkable unanimity in the results, with the size of benefit of self-monitoring ranging from a 0.16% to 0.39% absolute fall in glycated haemoglobin (HbA1c).

At the end of 2009, the Canadian review indicated that self-monitoring was associated with similarly modest improvements in HbA1c (0.25% fall) among patients with non-insulin treated type 2 diabetes.[1] It also concluded that providing education to help patients translate results from self-monitoring tests into appropriate action did not appear to benefit patients, although only one randomised controlled trial[3] assessed this properly. The review found little evidence to suggest that self-monitoring improved health-related quality of life, patient satisfaction, long-term complications or mortality. At the same time a German report also concluded that there is no proof of benefit of blood glucose self-monitoring in patients who are not receiving insulin and that there was no proof of a link between self-monitoring and morbidity and mortality.[3] However in July 2009, using the same evidence, the Australian National Health and Medical Research Council concluded that self-monitoring of blood glucose should be considered in all people with type 2 diabetes but suggested that the decision to do it, and the frequency and timing of testing, should be individualised.[4] Cross-sectional and longitudinal data from participants with type 2 diabetes in an observational, community-based study (Fremantle Diabetes Study) showed neither self-monitoring nor its frequency was associated with glycaemic benefit regardless of treatment.[5]

Most people with medication-treated diabetes, especially insulin users, are encouraged to routinely perform self-monitoring tests 2–4 times a day by diabetes educators and specialists who believe in its value and encourage family doctors to support it. They would argue that special groups such as those newly diagnosed with type 2 diabetes, those who have been doing self-monitoring longer, those who have a high HbA1c or those who have been to an intense education program would benefit from self-monitoring. Unfortunately, the evidence summarised in the Canadian review suggests otherwise.[1] Similarly, a randomised controlled trial from the UK found no statistically significant benefit in people newly diagnosed with type 2 diabetes.[6] Nevertheless, many diabetes specialists and educators believe self-monitoring complements HbA1c testing and may identify problems with management when HbA1c is not in the target range.

The Canadian review of eight randomised controlled studies, including more than 2400 people, showed no effect of self-monitoring regardless of intensity of education. The analysis found a mean change in HbA1c of 0.22% for programs where the intensity of education was less or unspecified, compared to 0.28% when the education was more intense. Six studies of patients with an HbA1c of 8–10.5% showed a mean reduction of only 0.3% in HbA1c.

However, another systematic review published about the same time, which included three studies excluded from the Canadian review, appeared to show a trend for a bigger effect in people with a higher HbA1c.[7] While showing the same overall effect – a reduction in mean HbA1c of 0.24% – this study showed a benefit of 1.23% in mean HbA1c for those with an initial HbA1c over 10%. However, this finding was based on two studies of only 63 people in total.

### *Frequency of testing*

Results of retrospective cohort studies on frequency of glucose self-monitoring were conflicting.[1] However, results from a well-designed randomised controlled trial in people with non-insulin treated diabetes found no statistically significant difference in HbA1c between those who performed self-monitoring of blood glucose once daily and those who performed it four times a day.[8]

### *Other effects of self-monitoring*

The Canadian review also reported that data from randomised controlled trials showed no statistically significant effects of self-monitoring (positive or negative) on body weight, body mass index, hospitalisation, primary care visits, patient satisfaction or patient well-being.[1] While some studies have suggested that increased depression or anxiety may be associated with self-monitoring,[6] these findings have not so far been confirmed in systematic reviews.[1]

### *Special patient groups*

While the overall effect of self-monitoring seems modest, there is a paucity of data on special groups, including heavy goods vehicle drivers for whom hypoglycaemia may pose an unacceptable occupational risk to themselves and the public. Also, people starting or changing their oral diabetes medication may benefit from self-monitoring.

## Are there risks to stopping self-monitoring?

While evidence of benefit may be lacking, would abandoning testing in people not on insulin expose them to harm? Overall, there is no evidence that self-monitoring of blood glucose reduces the risk of hypoglycaemia. However, one study[9] showed a significant increase in risk of hypoglycaemia in people on sulfonylurea-type drugs who did not monitor their own blood glucose. As a guide to the proper use of self-monitoring of blood glucose, the prescriber should ask themselves how the results will change the patient's management. From the patient's perspective, if they are not going to make any

change in behaviour or medication, there seems little sense in undertaking the measurement. From the health professional's perspective, if a change in therapy is based on the HbA1c value, there also seems little point in measuring the blood glucose unless it is to reinforce an educational message or demonstrate the benefit of a change in treatment.

## Conclusion

The Canadian review will no doubt generate much discussion. Given the poverty of high quality evidence about how education helps people with diabetes translate results from self-monitoring into effective action to improve their glycaemic control, and the entrenched beliefs of doctors and patient support groups, it will probably require more research in this area before Australian doctors and diabetes educators change their practice.

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*Dr Lowe has conducted a drug review for the Canadian Agency for Drugs and Technologies in Health.*

## Self-test questions

*The following statements are either true or false*
*(answers on page 163)*

1. Evidence suggests that people who control their diabetes by diet alone still benefit from self-monitoring of blood glucose.
2. Blood glucose self-monitoring may be needed during dose adjustment of oral hypoglycaemic drugs.

# Drugs for gestational diabetes

***Peter J Donovan**, Endocrinology Registrar, Royal Brisbane and Women's Hospital, Brisbane; and **H David McIntyre**, Queensland Diabetes Centre, Mater Health Services, South Brisbane*

## Summary

**The prevalence of gestational diabetes is increasing in Australia. Non-pharmacological intervention with dietary measures and exercise is the mainstay of therapy in most cases, but insulin is increasingly necessary to achieve adequate glycaemic control in some women. Basal-bolus insulin is the optimal management strategy, but therapy needs to be individualised. Although there is mounting evidence for the efficacy and safety of metformin, the lack of long-term follow-up data has prevented it from being recommended by most experts in the field. Women with gestational diabetes need long-term follow-up because of their increased risk of type 2 diabetes.**

Key words: hypoglycaemic drugs, insulin, metformin, pregnancy.

*(Aust Prescr 2010;33:141–4)*

## Introduction

Gestational diabetes is defined as an intolerance to glucose that is first diagnosed or has its onset during pregnancy. It is estimated to affect almost 5% of pregnancies in Australia and between 3% and 9% worldwide. Its prevalence increases with age, from 1% in women aged 15–19 years to 13% in those aged 44–49 years.[1] Other risk factors for developing gestational diabetes include being overweight or obese, having a family history of type 2 diabetes or a personal or family history of gestational diabetes or glucose intolerance, being from an Aboriginal or Torres Strait Islander background or belonging to certain ethnic groups (for example Polynesian, Middle Eastern, Indian or other Asian origin).[2] Although gestational diabetes does not affect perinatal mortality, it does increase morbidity, including the risk of shoulder dystocia, nerve palsies and neonatal hypoglycaemia. Maternal outcomes are also affected, with a higher incidence of pre-eclampsia and caesarean section (particularly with poor glycaemic control) in mothers who develop gestational diabetes.[3]

## Diagnosis

Universal screening for gestational diabetes has been recommended in Australia since 1998. A fasting glucose challenge test should be performed at 26–28 weeks gestation. If abnormal, this is followed by a formal two-hour 75 g oral glucose tolerance test. Criteria for diagnosis are presented in Table 1. For women at risk of gestational diabetes, a glucose tolerance test can be performed at any stage during pregnancy. However, as placental production of diabetogenic hormones tends to increase throughout the second and third trimesters, a normal glucose tolerance test in the early part of pregnancy does not exclude the development of gestational diabetes later on. A second oral glucose tolerance test should therefore be performed at the standard 26–28 weeks of gestation even if an earlier test was normal.

New recommendations for screening and diagnosis are currently under consideration, but have yet to be adopted or approved by expert groups in gestational diabetes. It is likely, however, that the glucose challenge test will be removed from the screening process, so that a diagnosis of gestational diabetes will be made if the blood glucose is abnormal when fasting, or one or two hours after a 75 g glucose load (see Table 1).

## Blood glucose targets

Once diagnosed, all women need to be educated about the possible implications of gestational diabetes (both fetal and maternal) and be taught how to perform home blood glucose monitoring. Finger-prick testing should be performed four times

*Table 1*

**Current and possible future diagnostic criteria for gestational diabetes**

| | Test | Venous plasma glucose – for diagnosis |
|---|---|---|
| **Current practices** | screen:<br>non-fasting 50 g glucose challenge | 1 hour ≥ 7.8 mmol/L (requires confirmatory testing) |
| | confirmatory testing:<br>fasting 75 g glucose tolerance | one of either:<br>■ fasting ≥ 5.5 mmol/L<br>or<br>■ 2 hour ≥ 8.0 mmol/L |
| **Potential new criteria**[13] | fasting 75 g oral glucose tolerance | any one of three:<br>■ fasting ≥ 5.1 mmol/L<br>■ 1 hour ≥ 10.0 mmol/L<br>■ 2 hour ≥ 8.5 mmol/L |

a day (before breakfast and two hours after each meal). Target blood glucose concentrations, shown in Table 2, need to be explained.

The results of the Hyperglycemia and Adverse Pregnancy Outcomes trial have demonstrated that the risks associated with maternal hyperglycaemia are on a continuum above the normal blood glucose concentration and treatment targets might be lowered in the future to reflect this.[4] As yet, a consensus on where these targets will be set has not been established.

## Non-pharmacological interventions

All women with gestational diabetes should receive advice from a dietitian with specific knowledge in the area and dietary intervention should be initial therapy for most women. Dietary advice needs to be individualised, taking into account factors such as the patient's body mass index (BMI) and overall nutritional requirements.[2] Care should be taken to avoid excessive caloric restriction, as this can result in ketonuria and adverse pregnancy outcomes.[5] Moderate intensity exercise, such as a brisk walk for 30 minutes each day, can decrease insulin resistance and should be encouraged.[6]

## Insulin

Insulin therapy remains the mainstay of pharmacotherapy and its use is becoming increasingly prevalent. In 2005–06, about 30% of confinements with gestational diabetes were treated with insulin, with women in older age groups requiring it in about 40% of cases.[1] Insulin should be considered when blood glucose concentrations (Table 2) exceed recommended targets on two or more occasions within one week. The indication for starting insulin is stronger if there is evidence of macrosomia or increased fetal abdominal circumference.[2]

All women started on insulin need education regarding storage of insulin, correct injection technique as well as recognition and treatment of hypoglycaemia. The assistance of a diabetes educator with this can be invaluable.

Insulin therapy needs to be individualised and is dependent upon the patient's blood glucose concentrations, her weight and her wishes. The regimen is determined by whether the blood glucose is elevated when fasting, after a meal, or both.

### *Elevated fasting glucose*

If the fasting glucose is elevated, but postprandial levels are within the recommended target range, a single bedtime injection of intermediate-acting insulin (for example insulin isophane) will often suffice. A starting dose of 4–12 units is reasonable. If postprandial hyperglycaemia occurs later in the pregnancy, mealtime injections of rapid-acting insulin may need to be introduced.

### *Postprandial hyperglycaemia*

Occasionally, women may have elevated postprandial blood glucose with normal fasting levels. Dietary intervention can be useful in this situation. However, should this prove inadequate, mealtime injections of rapid-acting insulin (for example insulin aspart, insulin lispro) can be introduced. Starting doses of 4–8 units with each meal are reasonable. Soluble human insulin is an alternative, but has the disadvantage of needing to be injected 30 minutes before eating.

*Table 2*

**Target blood glucose concentrations in gestational diabetes**

| | Blood glucose (mmol/L) |
|---|---|
| Fasting capillary | < 5.5 |
| Postprandial capillary | < 7.0 (2 hours)<br>< 8.0 (1 hour) |

### *Fasting and postprandial hyperglycaemia*

A basal-bolus insulin regimen (mealtime rapid-acting insulin and bedtime intermediate-acting insulin) is generally preferred as it provides the patient with greater flexibility in diet and exercise. Twice-daily mixed insulin (for example insulin aspart/protamine or lispro/protamine) is an alternative, particularly if the patient is reluctant to inject four times per day or might find it too difficult.

### *Dosing*

Larger doses of insulin are reserved for those with higher BMI or blood glucose readings significantly above target. Smaller doses might be appropriate for women with a slighter build. The dose can be titrated every two to three days as required, with increments of 2–4 units (no greater than 20% dose increase) until targets are met or the patient develops excessive hypoglycaemia (more than two to three times per week or any episode of severe hypoglycaemia).

It remains unclear if maternal hypoglycaemia adversely affects the fetus. If there are concerns, it tends to be in women with pre-existing diabetes in the first trimester of pregnancy (during organogenesis)[7] and not in those with gestational diabetes.

Insulin doses may be anticipated to rise throughout the third trimester as a result of increasing maternal insulin resistance. This tends to reach a plateau at 36–38 weeks.

### *Insulin analogues*

There is currently little evidence to support the use of other insulin analogues (for example insulin glargine, insulin detemir) in pregnancy, although their use is increasing.

## Metformin

There is increasing evidence for the use of metformin in pregnancy. The Metformin in Gestational Diabetes (MiG) trial, an open-label randomised controlled trial comparing metformin with insulin, was conducted throughout Australia and New Zealand.[8] It showed the efficacy and safety of metformin in the second and third trimesters with no difference in perinatal complications between treatments. Not surprisingly, patients

preferred oral metformin to insulin injections. Almost half of the patients taking metformin also required insulin to achieve treatment targets. There does not appear to be an increase in the risk of congenital malformations, even when the fetus is exposed to metformin in the first trimester.

Although this is promising, there is no long-term follow-up of children born to mothers who took metformin during pregnancy. The use of metformin in pregnancy is therefore not currently endorsed by regulatory authorities or professional bodies, including the Australian Diabetes in Pregnancy Society. Although no adverse effects have been demonstrated, metformin does cross the placenta, leading authorities to be very cautious in their recommendations. Nonetheless, metformin is used for the treatment of gestational diabetes in many centres around Australia and New Zealand, but has found much less favour in Europe and the USA.

Metformin could be considered for use in patients who have failed non-drug therapies and who either refuse or are unable to take insulin. The mother should be educated about the potential risks, benefits and areas of uncertainty so that an informed decision can be made.

## Sulfonylureas

Glibenclamide has the most evidence for use in pregnancy. Unlike the older sulfonylureas, glibenclamide does not appear to cross the placenta to a significant degree. There does not appear to be an increase in fetal complications, but, like metformin, it is currently not recommended for widespread use in pregnancy because of a lack of long-term follow-up of children exposed to glibenclamide *in utero*.

There is little evidence for the safety or efficacy of other sulfonylureas in pregnancy and their use is not recommended.

## Other drugs

There are few data about the safety or efficacy of acarbose, thiazolidinediones or incretin mimetics and enhancers in pregnancy. Currently these drugs are not recommended and their use in pregnancy should be considered experimental.

## Follow-up and prognosis

Gestational diabetes resolves postpartum in more than 90% of women. In general, all insulin and oral hypoglycaemic drugs are ceased immediately postpartum with ongoing blood glucose monitoring until discharge from hospital. If concentrations return to normal, which occurs in the overwhelming majority of cases, a repeat glucose tolerance test should be performed 6–8 weeks postpartum to ensure that the patient does not have overt type 2 diabetes.

The long-term risk for developing type 2 diabetes is increased over sevenfold in women who develop gestational diabetes compared with those who have a normoglycaemic pregnancy.[9] Women with a pre-pregnancy BMI of more than 27 kg/m$^2$, those of advancing maternal age and those who required insulin for glycaemic control in pregnancy are at particularly increased risk.[10] It is important to counsel women about these issues and the need to continue with dietary measures, regular exercise and attempts at achieving and maintaining a normal body weight long into the future. Both intensive lifestyle intervention and drug therapy (metformin) may be useful to decrease the risk of these patients developing type 2 diabetes.[11]

There are no evidence-based guidelines for long-term follow-up of mothers with gestational diabetes. Australian guidelines recommend a glucose tolerance test at least every two years,[2] while others believe that a fasting glucose test one to two yearly is sufficient. A more intensive follow-up regimen would be rational if the patient has evidence of impaired glucose tolerance or impaired fasting glucose on early postnatal testing, a strong family history of type 2 diabetes, or if there are other major risk factors such as marked obesity or polycystic ovary syndrome.

Children and adolescents whose mothers had gestational diabetes seem to be at higher risk of developing features of metabolic syndrome compared with mothers who do not have diabetes. Although unproven, it is likely that these children will also have a higher risk of developing type 2 diabetes as adults.[12]

## Conclusion

Gestational diabetes is increasing in Australia. Appropriate screening, diagnosis and management is important, not only to improve perinatal and maternal outcomes, but also because it may help to decrease the incidence of type 2 diabetes in the future. Insulin remains the mainstay of pharmacotherapy, but there is increasing use of oral hypoglycaemic drugs (particularly metformin) in Australia and New Zealand.

*Acknowledgement: Dr Paul Kubler, Director of Clinical Pharmacology, Royal Brisbane and Women's Hospital, Brisbane*

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*Conflict of interest: none declared*

# Your questions to the PBAC

## Avoiding wastage with insulin prescribing

The Pharmaceutical Benefits Scheme (PBS) provides affordable medicines to all Australians. However, increasing costs of medications are threatening it.

New means of cost-effective and cost-minimising interventions are always needed to ensure sustainability and viability of the scheme.[1] A practical and simple approach of saving is to change the PBS listing of insulin prescribed for gestational diabetes and users of low-dose insulin who will not necessarily go through the normal quantity of insulin provided to them. The standard quantity of insulin supplied by the PBS is five boxes of five individually packed units. This amount is usually excessive for patients using small doses of insulin who are prescribed other antidiabetic medicines.

A new listing of a single box of five individually packed units made available to these groups of patients will significantly save costs to the PBS and promote the quality use of medicines to the consumer as well as the prescribers.

By avoiding wastage of medications and educating prescribers about the need to restrict supply of excess unnecessary medications, resources could be freed up for other government-funded health expenditures.[2]

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### *PBAC response:*

Thank you to Dr Khalil for the suggestion to add a differential PBS listing for insulin. The maximum quantity and number of repeats allowed for items subsidised on the PBS are recommended by the Pharmaceutical Benefits Advisory Committee (PBAC). In general, for drugs which are usually taken on a long-term basis – such as for the management of diabetes – the PBAC recommends a maximum quantity sufficing for about one month's therapy at average doses. The PBAC believes that this requirement is equitable since it is applied across most therapeutic classes of drugs intended for long-term use.

Although a maximum quantity is set out in the PBS listing, there is flexibility to vary the quantity prescribed for patients taking doses that are higher or lower than usual. It is the responsibility of the doctor to ensure that individual patients are prescribed the appropriate quantity. If a prescriber feels the maximum quantity (or number of repeats) should be increased for a particular patient, he or she has the option of completing an Authority PBS Prescription Form with Medicare Australia either by telephone or in writing. This situation usually arises where higher than normal dosages are required. If, as in the case raised by Dr Khalil, a lesser quantity is sufficient for the patient's needs, then this lower quantity may be prescribed. It is not necessary to prescribe the stated maximum quantity as PBS prescriptions and repeats can be for any amount up to the maximum quantity.

## Rifampicin for MRSA

While reviewing an article on bacteria with resistance to multiple antibiotics (Aust Prescr 2010;33:68–71), the Editorial Executive Committee found an anomaly in the availability of rifampicin on the Pharmaceutical Benefits Scheme (PBS). The restrictions for rifampicin do not include the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA). For infections which can be managed with oral antibiotics, rifampicin is often given with fusidic acid. The PBS restrictions for fusidic acid require it to be used with another antibiotic in the treatment of proven serious staphylococcal infections. The other antibiotic is likely to be rifampicin, but this cannot be prescribed as a pharmaceutical benefit.

The purpose of using two antibiotics is to try to prevent further resistance. The Editorial Executive Committee therefore asked for the advice of the Pharmaceutical Benefits Advisory Committee on how to resolve the apparent anomaly in the PBS restrictions.

### *PBAC response:*

The PBAC has to consider the terms of marketing approval of a product. This approval is granted by the Therapeutic Goods Administration (TGA) and specifies the conditions in which the drug has shown acceptable safety and efficacy. The PBAC is not in a position to recommend that a drug be listed outside the terms of marketing approval specified by the TGA.

Currently, rifampicin is approved by the TGA for the treatment of tuberculosis, leprosy, prophylaxis of meningococcal disease and prophylaxis of household contacts of patients with *Haemophilus influenzae* type B. Under the *National Health Act 1953* there is no provision for the subsidised supply of an item listed as a restricted benefit for use in a condition which lies outside the terms of the restriction specified in the Schedule of Pharmaceutical Benefits. The current PBS listing for rifampicin reflects the TGA registration and so rifampicin cannot be prescribed for MRSA under the PBS.

The PBAC is concerned that rifampicin is not available as a pharmaceutical benefit for treating MRSA and has previously asked the drug's sponsor to seek marketing approval for this indication. However, neither the PBAC nor the government can compel a manufacturer to apply for registration of a drug for a particular indication.

### *Industry response:*

The Editorial Executive Committee sought responses from the manufacturers of rifampicin in Australia.

### *Dr Alex Condoleon, Medical Director Australia & New Zealand, Sanofi-aventis, comments:*

The availability of rifampicin as a pharmaceutical benefit in combination with fusidic acid for methicillin-resistant *Staphylococcus aureus* (MRSA) would require supporting evidence to achieve registration with the TGA and subsequently reimbursement through the PBS. Sanofi-aventis has therefore searched the literature about this combination, to determine the feasability of increasing access to this regimen for patients.

### *Treatment guidelines*

The Therapeutic Guidelines: Antibiotic[1] lists the combination of rifampicin and fusidic acid as a treatment option for recurrent staphylococcal skin infections (including MRSA-positive infections), and MRSA osteomyelitis involving the bone or joint prostheses, in both adult and paediatric patients. Similarly, the Australian Medicines Handbook[2] lists combination treatment of MRSA infection as an indication under both the monographs for rifampicin and fusidic acid.

Contrary to the Australian guidelines, the combination is not included in DrugDex Evaluations,[3] the American Hospital Formulary Service (AHFS) Drug Information,[4] the Centers for Disease Control and Prevention (CDC),[5] the World Health Organization (WHO),[6] and the European Centre for Disease Prevention and Control.[7]

### *Published clinical studies and reviews*

A search of the medical literature retrieved a small number of studies evaluating the combination for the management of MRSA infections and a large number of review articles on the management of MRSA infections. This search is subject to the limitations inherent in these databases and cannot be considered exhaustive.

#### Studies in adults

Two small (n=<12) Australian trials[8,9] studied the combination of rifampicin and fusidic acid for the treatment of MRSA infections in orthopaedic patients and patients with cystic fibrosis respectively. Both studies found this combination to be effective at eradicating MRSA infection.

#### Studies in children

None of the small number of studies[10–13] of MRSA infections evaluated the combination of rifampicin and fusidic acid.

#### Review articles

Two of four review articles[14–17] on the management of MRSA infections specifically listed the combination of rifampicin and fusidic acid as a treatment option for MRSA infections.[16,17]

None of six paediatric review articles[18–23] specifically listed the

combination of rifampicin and fusidic acid as a recommended treatment option. However, five of these reviews[18–22] listed rifampicin as a treatment option, stating that it must be used in combination with other antibiotics.

### *Conclusion*

Upon current assessment of available data there appear to be inconsistencies in treatment guidelines and only a small number of studies evaluating the combination of rifampicin and fusidic acid for the treatment of MRSA infections. Sanofi-aventis therefore does not believe that the evidence base exists to satisfy regulatory requirements to support this additional indication. However, we are open to reassessing options should further evidence emerge, or be brought to our attention, that could support a formal regulatory submission.

Note: References are available online with this article in Vol. 33 No. 5 at www.australianprescriber.com.

### *Dr Greg Pearce, Director, Medical Affairs, Alphapharm, comments:*

Most parties with an interest in making older medicines more freely available, at an affordable cost, for unapproved indications agree that this is an important issue. Unfortunately, no-one has been able to devise a satisfactory process for registering the indication and listing the product on the PBS. At a minimum, this process needs to balance evidence requirements, commercial considerations and regulatory scrutiny to a point where the documentation expectations are consistent with the commercial objectives of a potential supplier.

This impasse remains, despite meetings between the Royal Australasian College of Physicians, the TGA and industry representatives, a consultancy commissioned by the Department of Health and Ageing on behalf of the Paediatric Medicines Advisory Group, and direct representation by Alphapharm to the TGA.

Alphapharm is sympathetic to addressing this gap in our ability to deliver quality use of medicines but cannot move forward under the current regulatory and reimbursement framework. Recent PBS reforms have shifted the sponsor's fulcrum even further away for supporting these requests.

The company would support any further discussions aimed at developing innovative approaches to improve access to treatment. These would need to match the costs and evidence requirements for registration against the needs of a manufacturer to achieve a financial return which at least covers the resource and financial costs associated with applying for approval of a new indication.

## In memoriam

### **Maureen Ryan** Editorial Assistant *Australian Prescriber* 2003–10

The Editorial Executive Committee and staff of *Australian Prescriber* are deeply saddened by the sudden death of Maureen Ryan. Maureen was an essential member of the small team which produces *Australian Prescriber*, having worked as the Editorial Assistant for almost seven years.

The Editorial Assistant has a variety of duties and Maureen's many talents and diverse career path suited the role. Maureen had previously been the Business Manager of the Canterbury Division of General Practice. She was therefore able to implement some new procedures to enhance the efficiency of the journal's editorial processes. These procedures streamlined communications with authors, referees and pharmaceutical companies. Maureen also improved the formatting of the articles and became an expert in deciphering the Editor's handwriting.

An important part of Maureen's work was acting as the Secretary of the Editorial Executive Committee. She organised meetings efficiently ensuring that the large agendas were always prepared on time and that the minutes of the meetings were accurately recorded.

Maureen was a very patient person. This attribute was of great assistance when pursuing contributors who had missed their deadlines.

In July Maureen won an EPIC award from the NPS. This reflected her excellence, passion, integrity and commitment. Maureen truly believed that supporting health professionals with independent information would improve people's health through the quality use of medicines. She made a great contribution to *Australian Prescriber* and the NPS and will be sorely missed.

# Goodbye TAIS and thanks for all the information!

***Treasure M McGuire**, Assistant Director of Pharmacy, Mater Health Services, and Conjoint Senior Lecturer, School of Pharmacy, University of Queensland, Brisbane, and Associate Professor of Pharmacology, Faculty of Health Sciences and Medicine, Bond University, Queensland; **Marea Patounas**, Team Leader, Medicines Contact Centre, Mater Pharmacy Services, Mater Health Services, Brisbane*

## Summary

**The Therapeutic Advice and Information Service was funded by the National Prescribing Service to provide a national drug information service for health professionals working in the community. For ten years the service achieved high levels of client satisfaction, and reached its contracted target of 6000 enquiries about medicines per year, however the service ceased on 30 June 2010.**

Key words: drug information, National Prescribing Service.

*(Aust Prescr 2010;33:147–9)*

## Introduction

The National Medicines Policy states that

> … consumers and health practitioners should have timely access to accurate information and education about medicines and their use.[1]

The National Prescribing Service (NPS) launched the Therapeutic Advice and Information Service (TAIS) for health professionals in June 2000. This was a telephone service with an email and online enquiry facility, which aimed to give health professionals working in the community access to therapeutic information and advice.

The nationwide service was provided by a consortium of six hospital-based drug information centres under a single contract with the NPS. These centres offered specialised resources and access to clinical consultants. Their different locations provided extended coverage across Australia's time zones. Service provision automatically switched between participating centres for two-hour blocks across five states. The model gave callers nationwide access to a single pharmacist operator, Monday to Friday between 9 am and 7 pm AEST*, via a 1300 number and online.

* Australian Eastern Standard Time

## TAIS activity

TAIS could handle complex clinical questions through access to specialist drug information expertise and additional resources not readily available outside of hospitals. The service provided timely and tailored responses to questions such as those about comparisons within and across therapeutic classes, non-approved indications, complementary medicines, drugs marketed overseas, the likely outcomes of polypharmacy, and prescribing in pregnancy and children.

TAIS handled over 56 000 enquiries about medicines. Most were from community pharmacists and general practitioners (see Table 1). Approximately a third of enquiries were from practitioners in rural or remote parts of Australia. More than 85% of enquiries were about an individual patient. The average enquiry was 31 minutes (range 15 minutes to 16 hours). This included phone time, literature review, collation, data entry and provision of a response.

Calls most frequently involved drugs used in psychiatry (15%), cardiovascular medicine (11%), infection (10%) and neurology (10%). Complementary medicines accounted for 8% of calls. These enquiries were commonly related to medication safety issues, such as drug interactions (19%), adverse drug reactions (18%), dosing or administration (11%), and pregnancy or lactation (8%). Enquiries about optimising therapeutic strategies

*Table 1*

**Callers seeking therapeutic advice, June 2000–June 2009**

| | |
|---|---|
| Community pharmacists | 38% |
| General practitioners | 33% |
| Specialists | 11% |
| Consultant pharmacists | 5% |
| NPS facilitators and staff | 4% |
| Hospital pharmacists | 4% |
| Nurses | 3% |
| Allied health professionals | 2% |

*Table 2*

**Typical enquiries for therapeutic advice**

| | |
|---|---|
| Adverse reactions | ■ Which antidepressant causes least weight gain? (GP)<br>■ Which selective serotonin reuptake inhibitor or serotonin noradrenaline reuptake inhibitor causes the least amount of sexual dysfunction? (Specialist) |
| Interactions | ■ How clinically significant is the interaction between clopidogrel and proton pump inhibitors? Should all patients avoid this combination? (Hospital pharmacist)<br>■ What is the interaction between methotrexate and amoxycillin (flagged in dispensing software)? (Pharmacist) |
| Optimising therapeutic strategy | ■ Is a wash-out period required when switching from St John's wort to venlafaxine, if the patient has only been on St John's wort for five days? (GP)<br>■ Which antimalarial(s) are recommended as prophylaxis in Papua New Guinea? Patient is trekking Kokoda track for 15 days (GP) |
| Pregnancy/lactation | ■ Patient is six weeks pregnant taking venlafaxine, valaciclovir, sumatriptan and temazepam. Should she be screened for malformations? (GP)<br>■ Could desvenlafaxine reduce fertility if taken by the male partner? (Specialist)<br>■ Is an extract of marshmallow, garlic and echinacea safe when breastfeeding a six-week-old infant? (Nurse) |
| Complementary and alternative medicines | ■ What dose of melatonin is recommended to treat insomnia in a visually impaired three year old? (Specialist)<br>■ Is glucosamine safe for a patient with diabetes? (NPS Facilitator)<br>■ Can 'Cordyceps', a Chinese herb, be used to prevent colds? (GP) |
| Illicit drugs | ■ Patient uses ecstasy and cocaine. What is the safety if citalopram is also used? (GP) |
| Foreign trade names | ■ What is the equivalent to thiamazole (Chinese female taking 10 mg daily for hyperthyroidism)? (GP)<br>■ What is the equivalent brand of Belara oral contraceptive pill (South American patient)? (GP) |
| New drugs | ■ Can H1N1 vaccine be given if there is history of a severe reaction to tetanus vaccine? (Nurse)<br>■ Is H1N1 vaccine live? Patient takes methotrexate (Specialist) |

constituted 16% of calls. Table 2 shows examples of typical questions answered by TAIS.

TAIS adopted a quality management approach and adhered to professional[2] and contact centre standards.[3] Every two months a peer review committee audited a random 2% sample of enquiries. Between 2004 and 2009, 315 callers, of 633 surveyed, gave feedback. Of these, 97% reported that 'overall the information provided met my needs' and 40% stated a change in therapy had occurred as a consequence of advice from TAIS.

## TAIS closure

The service could answer approximately 6000 calls annually, and operated at maximum capacity for a number of years. Over the life of the service, the funding provided amounted to a cost per call of $52, however this did not cover all costs of service provision. TAIS was able to capitalise on shared use of existing infrastructure, training and resources at individual sites. Although the service was of high quality and valued by its users, the NPS concluded that the model was no longer sustainable, and discontinued funding on 30 June 2010.

While there will be no telephone service to replace TAIS, the NPS has provided a 'Guide to medicines information resources' for health professionals. This is available on the NPS website at www.nps.org.au/health_professionals/guide_to_medicines_information_resources.

## Lessons learned

For a decade, TAIS supported health professionals across Australia by providing timely access to quality therapeutic information and advice to support the quality use of medicines. Over this time, delivery of healthcare in the primary-care sector has become more demanding, with patients of greater complexity with multiple morbidities and medications. This trend is likely to continue and any future therapeutic advice and information service should be designed to be able to meet these changing complex needs. If a national drug information service is available in the future, it must be part of a coordinated effort to support the quality use of medicines in this dynamic environment.

Access to a drug information pharmacist, with expertise in retrieval and interpretation of therapeutic evidence, presents an opportunity to assist health professionals make timely and appropriate decisions about medicines for the individual patient and avoid harm from medicines. While a national service can provide access to this expertise for health professionals working outside hospitals, and enhance collegial relationships between health professionals, it requires significant resources to establish and maintain. A key challenge is to develop a service model that provides for long-term viability and achieves maximum value for the investment required.

Achieving the cost-effective delivery of therapeutic information and advice requires careful consideration of the processes and systems used for responding to individual enquiries. The relative merits of a multi-site versus single-site service model were considered. The TAIS multi-site experience demonstrated that the advantages of sharing workload, resources, leave cover, and providing extended service hours across time zones exceeded any duplication disadvantages at a comparable cost. While documentation of enquiries and responses is important for quality assurance and evaluation, it is time-consuming and therefore costly. Sophisticated technological solutions are likely to improve efficiency, but must be sufficiently flexible to adapt to changing needs. The service model must also have capacity to allow for fluctuations in demand.

Systems should be in place to allow timely sharing and analysis of enquiry and response data. This can inform other quality use of medicines activities by identifying medicines information needs and emerging areas of controversy or uncertainty.

While TAIS did use a database to record and report questions and answers, its construction did not allow for straightforward analysis on demand. Any future services should consider potential uses for information captured when designing or adapting a database. Answers to frequently asked questions should be made available to health professionals – for example, as decision support in clinical software – as a means of managing enquiry demand, allowing the service to focus on responding to complex or unusual requests. Information should also be shared more broadly between centres to improve efficiency and provide for a more consistent national approach.

Measuring the value and utility of a service for clinicians, and its impact on patient outcomes, may be difficult and expensive, yet it is important for ongoing service improvement and, possibly, for funding. Evaluation methods need to be planned during service model development, adequately resourced and focused on the service's aims to improve health outcomes.

## Conclusion

TAIS expertly responded to health professional enquiries over the past 10 years and provided many lessons for any future national therapeutic advice and information service.

A service such as TAIS presents an opportunity to support health professionals to provide high quality information and advice to individual patients and to inform other quality use of medicines activities through collection and analysis of enquiry data. However, any such service must be carefully designed and evaluated to ensure the most efficient use of funding to improve patient outcomes.

*Acknowledgements for contribution to TAIS:*

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Diagnostic tests

# Scanning for melanoma

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## Summary

**Non-invasive diagnostic tools aim at increasing accuracy of melanoma diagnosis. Clinical naked eye observation in combination with dermoscopy can be regarded as the practical reference standard to identify lesions for histopathological evaluation. Pigmented lesions need to be evaluated in the context of patient history to identify risk factors for melanoma, followed by a dermoscopically-aided entire skin examination. Patients with identified risk factors should be further examined. Total body photography is widely used in the follow-up of high-risk patients (particularly those with numerous and dysplastic naevi) and can be coupled with digital dermoscopy or videodermoscopy. New non-invasive diagnostic aids comprise multispectral image analysis, reflectance confocal microscopy and computer assisted diagnostic systems. Also, molecular profiling of lesions is an emerging technique under investigation for melanoma diagnosis.**

Key words: dermoscopy, total body photography, reflectance confocal microscopy.

*(Aust Prescr 2010;33:150–5)*

## Introduction

Early detection of melanoma remains a significant challenge for clinicians. The critical issue is to remove all lesions that may be malignant while minimising the excision rate of harmless benign lesions. Since naked eye examination has a comparatively low sensitivity in melanoma detection, additional non-invasive diagnostic tools such as dermoscopy are being used in daily practice and have improved the sensitivity of diagnosis when applied by experts.[1–3] The current diagnostic gold standard is visual inspection with dermoscopy followed by histopathological examination as required. A high number of unnecessary surgical procedures are still performed. A recent report dealing with primary skin cancer care in Queensland showed that 19.6 pigmented lesions are excised per melanoma.[4]

Several new non-invasive diagnostic tools aimed at increasing the accuracy of skin cancer diagnosis and thereby minimising unnecessary surgical procedures have emerged in recent years (Table 1). This expanding choice of diagnostic tools may cause confusion among doctors about what they are and how they can be used. Most systems offer a combination of diagnostic methods which may add to the uncertainty.

## Clinical examination with visual inspection

A patient history to identify risk factors for melanoma as well as a full body examination aided by dermoscopy should be performed for every new patient. Since further evaluation is time-consuming, those individuals at risk, as well as lesions that are considered as atypical or suspicious, should be identified. A detailed history should include:

- age and sex
- personal history of melanoma or non-melanoma skin cancer
- family history of melanoma
- number of naevi
- presence of atypical or dysplastic naevi
- skin type
- tanning habits
- response to sun exposure and evidence of skin damage from the sun.[5,6]

An inspection of the entire cutaneous surface should include the axillae, groin, the interdigital webs of the hands and feet, the nail apparatus and the scalp.

The ABCD acronym – Asymmetry, Border irregularity, Colour variegation, and large Diameter – supplemented with an E for Evolution, represents the clinical guideline for melanoma diagnosis. In contrast, the EFG acronym – Elevated, Firm and Growing progressively – is more appropriate for nodular melanomas that often have a more subtle clinical appearance.[7] On physical examination, new and changing naevi should be detected as well as any 'ugly ducklings', that is, lesions that are

*Table 1*

**Comparison of mole scanning methods**

| Method | Facts | Advantages | Main disadvantages |
|---|---|---|---|
| Visual inspection | ABCDE* rule is the usual clinical guide for most lesions, but EFG† is more appropriate for nodular lesions | Easy to perform | Limited sensitivity in melanoma diagnosis |
| Total baseline photography | Digital imaging in standardised positions<br>Nearly whole skin surface visualised | Identification of 'ugly ducklings'<br>Identification of new or evolving lesions | Only gives macroscopic information |
| Handheld dermoscopy | Visualisation of subsurface anatomic structures of epidermis and upper dermis<br>Dermoscopes with polarised and non-polarised light are available | Well-established criteria<br>Increases diagnostic sensitivity without diminishing specificity, when performed by specialists | Requires specialised training |
| Sequential dermoscopic follow-up | | Automated diagnosis/ teledermoscopy and combination with total baseline photography possible | Only preselected lesions can be compared dermoscopically<br>Not suitable for nodular lesions |
| Multispectral image analysis | Light reflected in different skin depths is collected and analysed | Visual information of deeper skin layer compared with dermoscopy<br>Automated diagnosis possible | Needs further evaluation in clinical trials |
| High-frequency ultrasound and optical coherence tomography | Vertical imaging of the skin | Monitoring of topical treatment possible | To date, not diagnostic aids |
| Reflectance confocal microscopy | Horizontal imaging of the skin with laser light that causes no tissue damage<br>Melanin/melanocytes are a strong source of contrast | Quasi-histological resolution offers *in vivo* biopsy, monitoring of treatment, pre-surgical margin assessment | Requires specialised training<br>Limited imaging depth<br>To date, mainly used for research |
| Multiphoton laser scanning microscopy | | Visualisation of cellular and subcellular structures | To date, mainly used for research |

* Asymmetry, Border irregularity, Colour variegation, and large Diameter, supplemented with an E for Evolution
† Elevated, Firm and Growing progressively

dissimilar to the rest.

However, any one single visual inspection fails to detect small melanomas and amelanotic melanomas. Thus for high-risk individuals, six-monthly full cutaneous examinations supported by total body photography and dermoscopy as well as patient education for self-examination have been recommended by Australian guidelines.[8]

## Total body photography

Total body photography is widely used in the follow-up of high-risk patients, particularly those with numerous and dysplastic naevi. The technique can be performed with any camera, and a standard digital camera that provides good image quality for digital sectional body images is the most cost-effective option. To document nearly the entire body surface the patient should assume standardised positions under good light conditions. Images should be taken of the face, neck, area behind the ears, scalp (in bald individuals), anterior and posterior trunk, and the extremities (including palms and soles). Subsequent new or changing lesions that may be indicative of melanoma can be

*Table 2*

**Overview of various mole scanning devices**

| Device | Standardised total body photography | Total body photography comparator | Macroscopic lesion images | Non-polarised dermoscopy | Polarised dermoscopy | Sequential dermoscopic imaging | Computer assisted diagnosis | Fully automated diagnosis | Teledermatology | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| EpiScope www.welchallyn.com | | | | • | | | | | | Handheld device |
| Dermatoscope Delta www.heine.com | | | | • | | | | | | Handheld device |
| DermoGenius basic www.biocam.de | | | | • | | | | | | Handheld device |
| DermLite Platinum www.dermlite.com | | | | | • | | | | | Handheld device |
| Molemax www.equipmed.com | | | • | • | • | • | • | | | Imaging system |
| Fotofinder www.fotofinder.de | • | • | • | • | | • | • | | | Imaging system |
| DermoGenius Ultra www.biocam.de | | | • | • | | • | • | | | Imaging system |
| MicroDerm www.visiomedag.com | | | • | • | | • | • | | | Imaging system |
| Dermoscopix www.dermoscopix.com | • | | | • | | • | | | | Imaging software |
| Melanoscan www.melanoscan.com | • | | | | | | | | | Imaging system |
| MoleMap www.molemap.net.au | • | | | • | | • | | | • | Imaging and patient history done by trained nurse |
| Db-Dermo Mips www.skinlesions.net | | | | | • | | | • | | Automated diagnosis based on dermoscopy |
| MelaFind www.eosciences.com | | | | | | | | • | | Automated diagnosis based on multispectral image analysis |

The features of the devices that are, in our estimation, most important are indicated by dots. For further detailed information on the devices and recent developments, follow the web links.

recognised in follow-up examinations by comparing the images with the patient's skin. Specific digital skin photography systems are available which facilitate standardisation of imaging and data storage (Table 2).

Total body photography has been reported to enable melanoma detection at an early stage.[9] However, small changes in naevi will probably be missed when only applying macroscopic imaging. A combined dermoscopic and total body photography approach is therefore recommended for patients who have atypical moles. Whereas digital dermoscopic images can

be obtained with dermoscopic lenses that can be attached easily to most commercially available cameras, various skin imaging devices offer a combination of total body photography and dermoscopy (Table 2). Some devices are also able to automatically compare two overview images and highlight new and changing lesions on the screen, though large-scale clinical studies of a high-risk population are needed to validate these findings.

## Dermoscopy

Dermoscopy, also known as dermatoscopy or epiluminescence microscopy, has been widely adopted into everyday clinical use. It enables visualisation of subsurface anatomic structures of the epidermis and upper dermis. A dermoscope consists of a light source and a magnifying lens. While non-polarised dermoscopes require operation with an immersion medium, such as oil or alcohol, dermoscopes with polarised light do not.

Digital dermoscopy or videodermoscopy is also now widely used. As well as easy storage and retrieval, digital dermoscopic and clinical images can be sent electronically. This is called teledermatology or teledermoscopy (Table 1).

Numerous diagnostic algorithms have been proposed to assess a lesion including pattern analysis, ABCD rule, Menzies method, seven-point checklist and three-point checklist. All these algorithms have been proven to be of high specificity and sensitivity in the diagnosis of melanoma. The choice of which one to use should be made upon personal preferences.*

Dermoscopy, when performed by specialists, increases diagnostic sensitivity without diminishing specificity and has been shown to decrease unnecessary excisions.[1–3,10] Two meta-analyses on studies published before 2000 verified that dermoscopy is superior to naked eye examination when used by experts.[1,2]

Another study reported that even a one-day tutorial on dermoscopy can improve the ability of primary care physicians to correctly refer individuals with suspicious lesions to a skin lesion clinic.[11] A recent meta-analysis focused exclusively on studies that were performed in a clinical setting and found the relative diagnostic odds ratio (a measure for diagnostic accuracy) was 15.6 for dermoscopy compared to naked eye examination.[3] This strong scientific evidence indicates that dermoscopy is presently the practical reference standard for non-invasive diagnosis of melanoma.

### *Follow-up examinations*

Due to the impracticability of removing all lesions, follow-up is crucial so that melanomas which lack atypical features at the first visit are not missed. Suspicious lesions can be monitored by serial dermoscopic and macroscopic imaging. Digital dermoscopic (and clinical) images are taken and linked to the body site via a computer. At the follow-up visit, the same lesion is photographed again for comparison. This is especially useful for patients with multiple lesions, and reportedly improves sensitivity in melanoma diagnosis.[3,12] Re-examination after three months with subsequent follow-up visits every 6–12 months seems to be a useful strategy. For individuals with familial atypical multiple mole and melanoma syndrome, follow-up every three months is recommended.[13]

A major disadvantage of the method is, however, that only preselected lesions are monitored, whereas changes in a previously unsuspicious lesion or a *de novo* lesion might be missed. Follow-up should never be performed in nodular lesions, because if they are malignant they tend to grow faster than other melanoma types. Even short delays in treatment might increase the risk of a poor prognosis.

### *Teledermatology*

Digital dermoscopic imaging enables primary care physicians to forward dermoscopic images (together with clinical information and macroscopic images) to specialists for a second opinion.[14] Studies have shown good agreement between face-to-face diagnosis and diagnosis based on digital images.[15,16] This is especially useful in remote areas, where referral is associated with considerable healthcare costs, and time for the patient.

Modern skin imaging devices combine dermoscopy and total body photography with teledermoscopic networks and computer-assisted automated diagnosis (Table 2). The company MoleMap, established by dermatologists, for example, offers a system in which a detailed examination followed by total body photography and comprehensive dermoscopic image capture is obtained by a specifically trained nurse. This information is then sent electronically to a dermatologist for expert analysis.

## Multispectral image analysis

Multispectral imaging relies on the principle that light of different wavelengths, of the visible and infrared spectrum, penetrates the skin to different depths. When coupled with computer-based analysis, certain features not visible in macroscopic and dermoscopic analysis can be visualised.

## Other non-invasive imaging tools

### *High-frequency ultrasound*

High-frequency ultrasound provides a vertical image of the skin based on its different acoustic properties. However, because of the limited resolution, ultrasound alone is not a reliable diagnostic aid. It is more appropriately used for preoperative management in dermatology, for example, in assessing tumour thickness and vascularity.

* A detailed description of these algorithms can be found at www.dermoscopy.org/consensus/tutorial.asp

### *Optical coherence tomography*

Optical coherence tomography is comparable to ultrasound, however it uses light instead of sound waves. It has better resolution than ultrasound but only penetrates to a depth of up to 1 mm, which approximately corresponds to the reticular dermis.

The resolution of optical coherence tomography does not reach the capabilities of reflectance confocal microscopy or histopathology, however cellular details can be viewed with the more modern devices. Although there are studies regarding the various features of skin cancer, reports of the diagnostic accuracy of optical coherence tomography are lacking. It seems that this technique might also play a role in other skin diseases in the future, such as contact dermatitis, psoriasis and bullous diseases, as well as monitoring of topical treatment.[17]

### *Reflectance confocal microscopy*

Confocal laser scanning microscopy can be operated in fluorescence or reflectance mode, but reflectance confocal microscopy is more suitable for clinical applications. Reflectance confocal microscopy allows visualisation of the epidermis and papillary dermis at a quasi-histological resolution. Horizontal sections of a lesion can be scanned and viewed using a near-infrared laser. This method is ideally suited for melanoma diagnosis as melanin provides strong contrast and is easily visualised. Diagnostic algorithms for melanoma detection have been proposed and show improved diagnostic specificity and sensitivity.[18–20] Furthermore, a glossary of terms commonly used in reflectance confocal microscopy has been published.[21] This type of microscopy has also been used in non-melanoma skin cancer, Mohs surgery, *in vivo* surgical margin assessment and in follow-up of response to topical treatment. However, large-scale clinical studies are needed to assess the method's full clinical potential.

### *Multiphoton laser scanning microscopy*

Multiphoton laser scanning microscopy works with a near-infrared laser beam which excites endogenous fluorophores. Nicotinamide adenosine dinucleotide phosphate (NADPH) is the primary source of autofluorescence. Like reflectance confocal microscopy, the multiphoton laser scanning microscopy provides horizontal sections of the skin allowing visualisation of cellular and subcellular structures. To date, it is mainly used as a research tool, rather than clinically.

## Computer-assisted diagnosis

Automated diagnostic systems extract and analyse features of skin lesions and give a diagnosis. They have been shown to reach comparable levels of diagnostic specificity and sensitivity to that of expert dermatologists.[22] To date, a few fully automated systems are available, some of which are integrated in the software of videodermoscopy devices (Table 2). MelaFind uses multispectral imaging information from dermoscopic images. The MelaFind system is currently in the final stages of being granted US Food and Drug Administration approval and is anticipated to be available in the not too distant future. There is a tendency of these tools to over-diagnose melanoma. Further studies are required to assess the impact of automated instruments against human performance in the clinical field.

## Molecular profiling

Molecular profiling is an emerging technique in melanoma diagnosis. A method that analyses RNA acquired from tape stripping of a suspicious melanocytic lesion is currently under investigation.

## Conclusion

Although newer imaging techniques hold great promise, they cannot replace visual inspection and patient examination. Clinical naked eye observation in combination with dermoscopy can be regarded as the practical reference standard to identify lesions for excision. Histopathological analysis of lesions remains the gold standard in skin cancer diagnosis.

It is important to emphasise that pigmented lesions need to be evaluated in the context of a patient's entire skin examination. Although a general practitioner may easily make the decision to excise a suspicious lesion, there are a few clinical situations where a dermatologist's advice should be sought and further evaluation be performed. These include high-risk patients with multiple (atypical) naevi or naevi on specific anatomical locations such as palms, soles of the feet and under the nails, or on the genitals.

New non-invasive imaging techniques have great potential for monitoring lesion growth and response to treatment, as well as true margin assessment before surgery.

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## Further reading

Selected dermoscopy books and online learning resources are listed with this article online at www.australianprescriber.com

*Professor Soyer is co-founder and shareholder of e-derm-consult GmbH, a spin-off company of the Medical University of Graz, Austria, with emphasis on holistic solutions for teledermatology. He is also shareholder and consultant for MoleMap Australia by Dermatologists Pty Ltd.*

### Self-test questions

*The following statements are either true or false (answers on page 163)*

3. All patients with suspicious skin lesions need a full body examination at their first visit.
4. The ABCD rule is the appropriate clinical guide for assessing nodular lesions.

# Book review

## Dale and Applebe's Pharmacy Law and Ethics. 9th ed. Applebe G, Wingfield J.

London: Pharmaceutical Press; 2009. 553 pages.

***Betty Chaar**, Lecturer, Pharmacy Practice and Professional Ethics in Pharmacy, Faculty of Pharmacy, The University of Sydney*

This very thorough examination of all legal aspects of the practice of pharmacy in the United Kingdom is the ninth edition of a popular text, widely used as a resource for pharmacists and in the training of future pharmacists in the UK. It is perhaps of less relevance to Australia, except that it could serve as a superb model for a similar text prepared in the Australian context of legal and ethical frameworks.

The book has benefited from years of revision, but also updates the reader about the 'plethora of legal changes that have been promulgated in recent years'. It is thoroughly researched, well indexed and is presented in a user-friendly style of headings and subheadings, with the added convenience of a summary at the end of each chapter, further reading suggestions and websites. The examples given to clarify complex issues are particularly useful to practitioners. Comparative analyses with other professions are also illuminating.

The majority of the 27 chapters are dedicated to explanation and examples of cases relating to various sections of the Medicines Act 1968. There are chapters about miscellaneous legislation relevant to the profession, explanation of the roles of various bodies to which the profession is attached, and rules relating to registration as a pharmacist in the UK.

The chapter dedicated to professional conduct is limited in scope, by the authors' own admission, to the Royal Pharmaceutical Society's Code of Ethics. It does however clarify to the reader the exact status of the code and how pharmacists are bound by criminal, administrative and civil law as well as by the Code. In practical terms, the reader is taken through the principles and short explanations in clear unambiguous language, with references for further reading for those interested in more in-depth analyses of ethical principles underlying the Code.

The chapter on fitness to practise is of particular interest to those following the current roll-out of new legislation regarding pharmacy and other healthcare professions in Australia. The authors explain in detail the role of the various committees set up to address the diverse types and levels of misconduct and impairment, providing examples to elucidate stratification of jurisdiction and powers of these committees.

Although focused on the UK, this book is a valuable resource for those involved or interested in the legal and ethical framework of pharmacy practice outside Australia. It is an illuminating and helpful resource, not only because there are many similarities and universal practices in the pharmacy professions of western countries, but also in light of the current changes in Australian legislation.

Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

# Medicines Safety Update

*Medicines Safety Update No. 5; 2010*

Medicines Safety Update is the drug safety bulletin of the Therapeutic Goods Administration (TGA). It is published in each issue of *Australian Prescriber*. You can also read it and sign up for free Medicines Safety Update email alerts on the TGA website at www.tga.gov.au/adr/msu.htm

**In this issue:**



## Cholinesterase inhibitors and syncope

### Summary

**Cholinesterase inhibitors have been associated with syncope and fall-related injuries, including hip fracture. Caution should be used when patients are started on a cholinesterase inhibitor, and patients should only be maintained on these medicines if there is evidence of continuing benefit.**

The cholinesterase inhibitors, donepezil (Aricept), rivastigmine (Exelon) and galantamine (Galantyl, Reminyl) are available on the Pharmaceutical Benefits Scheme (PBS) as authority items for patients with mild to moderately severe Alzheimer's disease. More than 2.5 million PBS prescriptions for cholinesterase inhibitors have been dispensed since 2001.

A recent Canadian population-based cohort study found that cholinesterase inhibitor use was associated with increased rates of syncope, bradycardia, pacemaker insertion and hip fracture in older adults with dementia.[1] Hospital visits for syncope were more frequent in people receiving cholinesterase inhibitors than in controls (31.5 vs 18.6 events per 1000 person-years; adjusted hazard ratio 1.76; 95% confidence interval 1.57 to 1.98). No comparison of event rates for individual cholinesterase inhibitors was conducted as it was assumed that donepezil, galantamine and rivastigmine have similar adverse-effect profiles. The authors noted that cholinesterase inhibitors generally augment vagal influences on the heart and promote bradycardia, which may result in neurocardiogenic syncope.

To June 2010, the TGA had received a total of 623 reports of suspected adverse reactions to cholinesterase inhibitors. Eighty-four (14%) of these reports describe syncope, syncope-related events or bradycardia.

While syncope and bradycardia are listed in the product information for each cholinesterase inhibitor as 'common' to 'very rare' adverse effects, the TGA reminds prescribers to use caution when starting patients on cholinesterase inhibitors, and that patients should only be maintained on these medicines if there is evidence of continuing benefit.

### Reference

1. Gill SS, Anderson GM, Fischer HD, Bell CM, Li P, Normand SL, et al. Syncope and its consequences in patients with dementia receiving cholinesterase inhibitors: a population-based cohort study. Arch Intern Med 2009;169:867-73.

## Statins, macrolides and rhabdomyolysis

### Summary

**The combination of a macrolide antibiotic and a statin can increase the risk of myopathy and rhabdomyolysis. If a patient taking a statin is to be prescribed a macrolide, consider temporarily stopping the statin or choosing a different antibiotic.**

Combining clarithromycin or erythromycin with simvastatin or atorvastatin increases the risk of statin-induced myopathy and rhabdomyolysis. The TGA receives several reports of rhabdomyolysis in patients taking an HMG-CoA reductase inhibitor (statin) and a macrolide antibiotic almost every year. We remind health professionals to use caution with this combination.

If a patient taking a statin is to be prescribed a macrolide

antibiotic, consider temporarily stopping the statin or choosing a different antibiotic, if appropriate. Use particular caution in patients who are on higher statin doses, have comorbidities, are older, or are taking other medicines, because they are at higher risk of rhabdomyolysis (see box). Ask patients taking statins to promptly report muscle aches, pain or weakness, particularly if accompanied by malaise, fever or brown urine.

To July 2010, TGA had received 25 reports of rhabdomyolysis in patients prescribed a macrolide antibiotic and a statin. In 80% of cases, patients had at least one other risk factor for statin-induced myopathy before they were prescribed clarithromycin or erythromycin. In almost 50% of cases, patients had two or more other risk factors. The most common risk factors were older age; high statin dose; concomitant diltiazem, cyclosporin or gemfibrozil; and hypothyroidism or diabetes. This is consistent with an earlier analysis of reports to the TGA.[1]

Either simvastatin or atorvastatin was involved in each case reported to the TGA. Both of these statins are metabolised by cytochrome P450 3A4, which is inhibited by clarithromycin and erythromycin. Interactions with other statins or other macrolides are less likely: CYP3A4 has little or no involvement in the metabolism of pravastatin, fluvastatin and rosuvastatin, and the macrolides azithromycin and roxithromycin are not inhibitors of CYP3A4.[2]

*Box*

**Factors that may increase the risk of rhabdomyolysis with statins** [2,3]

**Concomitant medicines***

| | |
|---|---|
| Amiodarone | Grapefruit juice |
| Azole antifungals | Imatinib |
| Cyclosporin | Macrolide antibiotics |
| Diltiazem | Nicotinic acid |
| Delavirdine | Protease inhibitors |
| Efavirenz | Tacrolimus |
| Fibrates | Verapamil |

**Comorbidity**

| | |
|---|---|
| Diabetes | Severe intercurrent illness (infection, trauma, metabolic disorder) |
| Hepatic impairment | |
| Hypothyroidism | Surgery |
| Renal impairment | |

**Age**

> 70 years

**Statin dose**

Higher doses, e.g. ≥ simvastatin 40 mg/day

* Interaction potential may differ between different statins and members of other drug classes. Refer to the product information or to texts such as the Australian Medicines Handbook for advice about interactions with specific drugs.

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# Uterine perforation with levonorgestrel-releasing intrauterine system (Mirena)

## Summary


**Uterine perforation is a known but rare complication associated with the levonorgestrel-releasing intrauterine system (Mirena). Observing correct insertion technique is important to minimise the risk of perforation.**


Mirena is an intrauterine delivery system that releases levonorgestrel 20 microgram/day. It is approved for use as a contraceptive for up to five years, for the treatment of idiopathic menorrhagia, and for the prevention of endometrial hyperplasia during oestrogen replacement therapy. As with copper intrauterine devices, Mirena is associated with uterine perforation at an incidence of less than 0.1%.[1]

In June 2010 in Canada, a reminder was issued to health professionals about the possibility of uterine perforation with Mirena, after it was noted that the number of perforations reported was rising alongside increased use of Mirena.[2]

In Australia, a total of 161 adverse reactions to Mirena had been reported to the TGA to June 2010. Of these, 22 were reports of uterine perforation. In at least seven cases, patients had known risk factors for uterine perforation. Perforation was reported to have occurred during insertion in three cases.

The presentation of uterine perforation may be subtle. Patients should regularly check for the threads attached to Mirena to ensure that the device has remained in the uterus. Health professionals should instruct women on how to check for the threads, and inform them of the efficacy, risks and side effects of Mirena.

### *Minimising the risk of uterine perforation*

Correct insertion technique is important for reducing the risk of perforation (see box). Women who are postpartum, lactating or have atypical uterine anatomy (such as a fixed retroverted uterus) are at greatest risk of perforation.

Training in inserting intrauterine devices and Mirena is available through the Royal Australian and New Zealand College of Obstetricians and Gynaecologists and state and territory sexual health and family planning organisations. An education DVD is available from Bayer (ph 1800 673 270) and a leaflet explaining insertion is included in the packaging.

*Box*

**Steps to minimise the risk of uterine perforation** [1]

- Only health professionals who are experienced or have had sufficient training should undertake Mirena insertion
- Perform a physical examination including pelvic examination and a cervical smear to rule out pregnancy, uterine anomalies, sexually transmitted disease and genital infections
- Review insertion instructions included in every Mirena package. It is important not to force the inserter and to dilate the cervical canal if necessary.
- Review the training DVD which shows a Mirena device being fitted
- When insertion is difficult and/or exceptional pain or bleeding occurs during insertion, consider physical examination and performing an ultrasound or X-ray imaging immediately to exclude uterine perforation
- Re-examine the patient 4 to 12 weeks after insertion and once a year thereafter, or more frequently if clinically indicated
- Instruct the patient to consult her doctor if she develops pain and abnormal bleeding and/or if she is unable to locate the threads

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## Rivaroxaban (Xarelto) – an overview of adverse event reports

### Summary


**Most adverse event reports involving rivaroxaban received by the TGA describe thrombotic or haemorrhagic events, consistent with international experience and the known safety profile of rivaroxaban. The TGA will continue to routinely monitor reports of adverse reactions to rivaroxaban. We encourage health professionals to report suspected adverse reactions promptly.**


Rivaroxaban is an oral anticoagulant that acts through direct inhibition of coagulation factor Xa. It was first registered in Australia in November 2008 and is approved for prevention of venous thromboembolism following elective total hip replacement or total knee replacement. Approximately 6800 PBS prescriptions have been dispensed since the drug was listed in August 2009.

At 15 July 2010, the TGA had received 44 adverse event reports involving rivaroxaban. Of these, 22 (50%) described thrombotic events and 17 (39%) haemorrhagic events (see Table). This is consistent with the known adverse effects of rivaroxaban (the Product Information lists haemorrhage, anaemia and deep vein thrombosis as adverse events[1]). It is also similar to reports submitted to the World Health Organization's Programme for International Drug Monitoring,* to which more than 90 countries contribute spontaneous adverse drug reaction reports.[2,3]

*Table*

**Adverse events involving rivaroxaban reported to the TGA to 15 July 2010**

| Adverse event | Number of reported cases |
|---|---|
| Deep vein thrombosis | 10 |
| Pulmonary embolus | 12 |
| Gastrointestinal haemorrhage | 3 |
| Haematuria | 3 |
| Haemarthrosis | 6 |
| Other haemorrhagic | 5 |
| Other | 5 |

* The information in adverse event reports in the WHO database is not homogeneous with respect to the sources of the information or the likelihood that the pharmaceutical product caused the suspected adverse reaction. The information in this article does not represent the opinion of the WHO.

Reports received by the TGA do not indicate any new safety signals for rivaroxaban, but report numbers to date are small. Routine monitoring of adverse events with rivaroxaban will continue and as with all new drugs, health professionals are encouraged to report adverse events to the TGA (see *What to report* below).

There were several reports to the TGA in which rivaroxaban was apparently not used according to the dosing and administration instructions. These involved use of rivaroxaban sequentially with postoperative enoxaparin (3 cases: one haemarthrosis, two thrombotic events); double dosing with rivaroxaban for 3 days (one case: haemarthrosis); and starting rivaroxaban therapy one day after surgery (one case: thrombotic event). A causal link between these administration errors and the adverse events reported has not been established. Nevertheless, note that rivaroxaban should be started 6–10 hours after surgery, providing that haemostasis has been established, and a single 10 mg tablet taken daily for up to 14 days (knee replacement) or 35 days (hip replacement).[1]

In two cases, haemorrhagic events were associated with concomitant use of meloxicam or clopidogrel. Rivaroxaban should be used with caution in patients taking clopidogrel or non-steroidal anti-inflammatory drugs because of an increased risk of bleeding.[1]

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**What to report? You do not need to be certain, just suspicious!**

The TGA encourages the reporting of all **suspected** adverse reactions to medicines, including vaccines, over-the-counter medicines, herbal, traditional or alternative remedies. We particularly request reports of:

ALL suspected reactions to **new medicines**

ALL suspected medicines interactions

Suspected reactions causing

- death
- admission to hospital or prolongation of hospitalisation
- increased investigations or treatment
- birth defects

Reports may be submitted:

- **using the 'blue card'** available from the TGA website (www.tga.gov.au/adr/bluecard.pdf) and in the April, August and December issues of *Australian Prescriber*
- **online** on the TGA website (go to www.tga.gov.au and click on 'report a problem' on the left)
- **by fax** to (02) 6232 8392
- **by email** to ADR.Reports@tga.gov.au

For further information, please contact the TGA's Office of Product Review on 1800 044 114.

# New drugs

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may be limited published data and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained either from the manufacturer's approved product information, a drug information centre or some other appropriate source.

## Agomelatine

Valdoxan (Servier)

25 mg tablets

Approved indication: major depression

Australian Medicines Handbook section 18.1

Agomelatine is a synthetic analogue of melatonin. The manufacturers claim that as well as agonising melatonin, it also antagonises the serotonin $5HT_{2C}$ receptors.

Numerous placebo-controlled trials have assessed the efficacy of agomelatine for major depression.[1–5] The primary endpoint in these studies was based on the 17-item Hamilton rating scale for depression. At baseline, average scores were around 27 out of a possible 52. After 6–8 weeks, both agomelatine (25 or 50 mg) and placebo had reduced the scores (to between 12.8 and 19.6). Although agomelatine reduced the score significantly more than placebo in most comparisons, the mean difference between agomelatine and the placebo was never more than a few points. For example in a trial of 503 randomised patients, mean scores were reduced to 17.1 with placebo and to 15.0 and 15.9 with agomelatine 25 mg and 50 mg.[5]

Agomelatine has also been compared with other antidepressants. A comparative trial with sertraline favoured agomelatine after six weeks, however, the difference in mean scores (Hamilton rating scale) between treatments was only 1.68.[6] Agomelatine has also been compared to fluoxetine and paroxetine. However, superiority of the active treatments over placebo was not consistently shown and most of these studies have not been published.

The ability of agomelatine to prevent relapse of major depression has also been investigated in a 24-week trial of patients who had already responded to 8–10 weeks of agomelatine treatment. Relapse rates were significantly lower for patients who continued agomelatine (after 8–10 weeks) compared to those who switched to placebo (20.6% vs 41.4%).[7] However in a similar but unpublished study, relapse rates for agomelatine and placebo were not significantly different (25.9% vs 23.5%).

After oral administration, agomelatine is rapidly absorbed with peak plasma concentrations reached within 1–2 hours. Bioavailability is low and varies considerably between individuals. It is increased by oral contraceptives and female gender and decreased by smoking. Agomelatine is rapidly metabolised by the cytochrome P450 isoenzyme CYP1A2, and to a lesser extent by CYP2C9 and CYP2C19. The inactive metabolites are mainly eliminated in the urine. Potent inhibitors of CYP1A2, such as fluvoxamine or ciprofloxacin, are contraindicated with agomelatine and caution is urged if patients are taking a moderate inhibitor such as propranolol.

Over 3900 patients took agomelatine in the depression trials. The most common adverse effects were headache (14.1%), nausea (7.7%), dizziness (5.5%), dry mouth (3.5%), diarrhoea (3.1%), somnolence (2.9%), fatigue (2.6%), abdominal pain (2.4%) and insomnia (2.4%). These were mostly mild to moderate. There were four deaths out of 3956 patients who took agomelatine and one out of 826 patients who took placebo – these were all due to suicide. There were more suicide attempts with agomelatine than with placebo (0.6% vs 0.4%).

Increases in liver enzymes (more than three times the upper limit of normal range) occurred in around 1% of people taking agomelatine. This effect seemed to be dose-related. Serious hepatic reactions included hepatitis and a transaminase elevation more than 10 times the upper limit of the normal range. Agomelatine should not be given to people with cirrhosis or active liver disease. Liver function tests should be performed before a patient starts treatment and at regular intervals during treatment. Consuming alcohol with agomelatine is not advisable.

Caution is urged in patients with impaired renal function and those aged 65 or over. Agomelatine should not be used in elderly patients with Alzheimer's disease.

Although agomelatine reduces symptoms of depression on the Hamilton rating scale, its effect seems to be only marginally better than placebo, if at all. This questionable efficacy coupled with the potential risk of adverse hepatic reactions suggests that doctors are probably better continuing with the more established antidepressants.

T T manufacturer provided additional useful information

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## Indacaterol

Onbrez Breezhaler (Novartis)

capsules containing 150 microgram and 300 microgram as dry powder for inhalation

Approved indication: chronic obstructive pulmonary disease

Australian Medicines Handbook section 19.1.1

Patients with chronic obstructive pulmonary disease (COPD) who have symptoms despite using short-acting bronchodilators may obtain relief by adding a long-acting bronchodilator. The choice of drug includes beta$_2$ agonists such as eformoterol, salmeterol and now indacaterol.

A specific device is used to inhale indacaterol. Bronchodilation begins within five minutes of inhalation, with a peak effect after 2–4 hours. This action is prolonged so indacaterol is suitable for once-daily dosing. Some of the dose is absorbed into the circulation and then metabolised with very little being excreted in the urine.

Indacaterol was compared with placebo in a 28-day study of 163 patients with moderately severe COPD. From the first day the mean improvement in the forced expiratory volume in one second ($FEV_1$) with indacaterol was significantly greater than with placebo. On day 28, $FEV_1$ was 220 mL greater than placebo with 400 microgram indacaterol and 210 mL greater with 800 microgram once-daily.[1]

A lower dose (150 microgram) was used in a 12-week placebo-controlled trial involving 416 patients. $FEV_1$ increased with indacaterol from day 1 and at the end of the study was 160 mL greater than with placebo. The trough $FEV_1$, measured 24 hours after the final dose, was 130 mL higher than with placebo. The patients given indacaterol needed to use sulbutamol less often as a 'rescue' medication for their symptoms.[2]

In the placebo-controlled studies adverse events occurred with a similar frequency in all groups, although inhaling indacaterol was more likely to cause the patients to cough.[1,2] From all the studies of indacaterol, the adverse events which have occurred more frequently than with placebo include upper respiratory tract infections, cough, muscle spasms and headache. At therapeutic doses, indacaterol does not appear to significantly affect the heart rate. There may be small changes in blood glucose and potassium.

Once-daily indacaterol has been studied with twice-daily (e)formoterol in a year-long trial. There were 437 patients randomised to inhale 300 microgram indacaterol, 428 to inhale 600 microgram, 435 to inhale 12 microgram formoterol (twice daily) and 432 to inhale placebo. Both doses of indacaterol had increased the trough $FEV_1$ by 170 mL more than placebo and 100 mL more than formoterol, when assessed after 12 weeks. The differences between the active treatments and placebo remained significant after 12 months. Both drugs improved the control of symptoms and reduced the requirement for rescue doses of salbutamol. However, the study was not primarily powered to detect significant differences between indacaterol and formoterol.[3]

Another option for maintenance treatment of COPD is the long-acting anticholinergic drug tiotropium. This drug is also taken as a once-daily inhalation of dry powder. Tiotropium 18 microgram and indacaterol 150 microgram or 300 microgram were compared with placebo in a study of 1683 patients with moderate to severe COPD. After 12 weeks trough $FEV_1$ had increased by 140 mL with tiotropium and by 180 mL with both strengths of indacaterol compared to placebo. The difference between treatments was still present after 26 weeks. Indacaterol had a greater effect on some symptoms than tiotropium did, but, as tiotropium was given open-label, any differences in efficacy will need confirmation.[4]

Although indacaterol has been studied in asthma, it has not been approved for this indication and it is also not recommended for mixed airways disease. While indacaterol is an efficacious bronchodilator in patients with moderate–severe COPD, the extent of long-term clinical benefit is unknown.

☒ manufacturer declined to supply data

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## Plerixafor

Mozobil (Genzyme)

vials containing 20 mg/mL

Approved indications: lymphoma, multiple myeloma

Australian Medicines Handbook section 14.4

High-dose chemotherapy is used in the treatment of cancers such as non-Hodgkin's lymphoma and multiple myeloma. As this suppresses the bone marrow, the patient may be transfused with stem cells to improve survival. Autologous transplants use the patient's own previously collected stem cells. Normally there are not many stem cells in the peripheral blood, but they can be mobilised from bone marrow by colony stimulating factors such as granulocyte colony stimulating factor (G-CSF).

In some patients, G-CSF does not mobilise enough stem cells. By inhibiting a chemokine receptor, which has a role in holding cells within the bone marrow, plerixafor helps to release stem cells into the blood. Plerixafor was originally studied as a treatment for patients infected with HIV, but was found to cause an increase in white blood cells associated with stem cell mobilisation.

An open-label pilot study gave patients with multiple myeloma and non-Hodgkin's lymphoma different regimens of G-CSF and plerixafor. Most of the 40 patients who were given plerixafor had enough cells mobilised for transplantation.[1]

A phase III trial randomised 298 patients with non-Hodgkin's lymphoma to receive G-CSF with or without plerixafor. G-CSF was given daily for up to eight days, with patients starting plerixafor or a placebo on the fourth day and continuing it for up to four days. The target was the collection of at least $5 \times 10^6$ CD34+ cells per kg body weight within four days. This outcome was achieved by 59.3% of the 150 patients randomised to plerixafor, but by only 19.6% of those who added placebo. The response enabled 90% of the plerixafor group to have transplantation compared to 55.4% of the placebo group.[2]

Another study compared G-CSF with or without plerixafor in 302 patients with multiple myeloma. The target was the collection of $6 \times 10^6$ CD34+ cells per kg within two days. This was achieved by 71.6% of the 148 patients randomised to receive plerixafor and 34.4% of the placebo group. Transplantation took place in 95.9% of the plerixafor group and 88.3% of the placebo group.[3]

The main trials did not give plerixafor alone. It is therefore only approved for use in combination with G-CSF.

There is a concern that plerixafor could mobilise tumour cells as well as stem cells. In a study of seven patients with multiple myeloma, G-CSF alone increased the frequency of tumour cells in five patients. Three patients given plerixafor after G-CSF had an increase in tumour cells in their peripheral blood, so plerixafor appears unlikely to have a significantly greater effect on tumour cell mobilisation.[4]

Plerixafor is given by subcutaneous injection and injection-site reactions are more common than with G-CSF alone. The drug is not metabolised and most of the dose is excreted in the urine. A reduced dose is given if the patient has moderate to severe renal impairment (creatinine clearance 20–50 mL/min). Patients complaining of upper abdominal or scapular pain should be investigated as animal studies show splenic enlargement. Some patients given plerixafor will have excess white cell production, while others will develop thrombocytopenia. Other adverse events which occur more frequently with G-CSF and plerixafor than with G-CSF alone include nausea, vomiting and diarrhoea.

While plerixafor increases the mobilisation of stem cells, it does not have much impact on the patients' survival. After a year, 88% of the patients with non-Hodgkin's lymphoma given plerixafor had survived compared with 87.2% of those given G-CSF alone.[2] In multiple myeloma, 95.3% of the plerixafor group had survived compared with 96.1% of the patients given G-CSF alone.[3]

T T manufacturer provided additional useful information

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The T-score (T) is explained in 'New drugs: transparency', Aust Prescr 2009;32:80–1.

* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov).

† At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Medicines Agency (www.ema.europa.eu).

A At the time the comment was prepared, information about this drug was available on the website of the Therapeutic Goods Administration (www.tga.gov.au/pmeds/auspar.htm)

## Answers to self-test questions

1. False
2. True
3. True
4. False

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