This is not to say that the situation in other countries is optimal; a lot remains to be done. There are also valid exceptions to transparency such as manufacturing information that needs to be protected. However, the current Australian situation, in which the data used to make decisions and the reasons behind these decisions remain secret, is no longer tenable. Full transparency is required at all steps in the marketing of medicines, from publication of the trial protocols to assessment of the data by the TGA. It includes public disclosure of the potential conflicts of interest of all external experts involved in the TGA advisory committees. It concerns not only positive decisions, but also negative decisions, for example when a marketing application for a drug has been refused.

Transparency requires political will and leadership. This is an active process that needs to be adequately resourced. While drug companies spend millions of dollars on promotion of medicines each year, it seems paradoxical that limited funding and cost recovery could prevent the TGA from appropriately informing the Australian public. The TGA urgently needs to take steps to improve its transparency if it wants to retain its credibility not only with the Australian public and health professionals but also on the international scene.

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Conflict of interest: none declared

Letters

Letters, which may not necessarily be published in full, should be restricted to not more than 250 words. When relevant, comment on the letter is sought from the author. Due to production schedules, it is normally not possible to publish letters received in response to material appearing in a particular issue earlier than the second or third subsequent issue.

Varenicline and quitting

Editor, – While Mark Ragg (Aust Prescr 2008;31:60–2) is technically correct in saying that most people quit by themselves[1], he overlooks the more important point that the unaided quit rate is around 5–7%.[2] It is not surprising that quitting is so difficult. Nicotine addiction is a chronic relapsing condition with a relapse curve that resembles that for heroin addiction.[3] Popularity of strategy should not be confused with likelihood of success.

Most smokers find it very difficult to quit and are reluctant to seek help.[4] It is difficult to capture the true natural history of smoking cessation in a study.[1] Studies that have done so show that less than 2% of smokers quit per year.[5] On average, smokers make between five and eight attempts before they are successful despite expressing strong interest in quitting.[6]

In a survey, 92% of smokers used only one strategy to quit.[1] The majority of published evidence recommends the use of a combination of strategies that include some form of pharmacotherapy if nicotine dependent, referral to a proactive callback program like the Quitline, enlisting support, and addressing motivation and confidence.[7,8,9,10] This is reflected in a reduction in the numbers needed to treat as selected strategies are combined. For example, eight smokers need to be treated with varenicline and supportive counselling to get one long-term quitter. Smokers shouldn't have to 'go it alone'. Health professionals should help them to increase their chance of success.

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Therapeutic range for digoxin

Editor, – I read with great interest the target ranges for digoxin interactions in Table 1 of the article on therapeutic drug monitoring (Aust Prescr 2008;31:42–4). The issue of the therapeutic range for digoxin is perhaps a controversial one these days, but the author should certainly be given an opportunity to explain the 'range', particularly because of recent analyses of mortality data in trials of digoxin.

Perhaps a suitable correction as well as clarification would be in order?

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Dr Ghiculescu, author of the article, comments:

The Digitalis Investigation Group found that digoxin reduced hospitalisations, but did not reduce overall mortality in heart failure when the target for the therapeutic range was 0.5–2 nanogram/mL.[1] *Post hoc* analysis of this trial found that mortality and hospitalisations were reduced if the serum digoxin was 0.5–0.9 nanogram/mL. Concentrations greater than 1 nanogram/mL were associated with higher mortality.[2] A concentration less than 1 nanogram/mL equates to less than 1 microgram/L. The currently recommended therapeutic range is therefore 0.5–0.9 nanogram/mL.

It has been suggested that an even lower concentration, less than 1 nanogram/dL, be used in patients with symptomatic systolic left ventricular failure.[3] That equates to 10 nanogram/L which is 0.01 microgram/L. This is significantly lower than the range used in the digoxin trial. However, this low concentration cannot easily be measured.

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Bronchiectasis

Editor, – May I congratulate Amy McLean on her article regarding bronchiectasis (Aust Prescr 2008;31:77–9). She gave a concise and practical approach to strategies often employed in treatment. May I also support the Editor in publishing this article, considering many of the drugs listed and regimens suggested were 'off label' and certainly not supported as subsidised medicines for these indications on the Pharmaceutical Benefits Schedule.

Unfortunately, many such prescriptions are unavailable to doctors who practise outside of major metropolitan teaching hospitals, although the novel approaches with nebulised aminoglycosides and longer term use of macrolides are certainly used by us, the 'respiratory colleagues'. There was also no mention made of colistin, which from experience is expensive to source, and intravenous gammaglobulin used monthly that has proven effective, particularly in those with subclass immunoglobulin deficiency.

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Bipolar disorders

Editor, – There are significant problems with the use of literature to support the statements in the article by Dr Singh and Professor Berk on acute management of bipolar disorders (Aust Prescr 2008;31:73–6). The authors have generalised from bipolar I disorder to bipolar II disorder and from severely ill tertiary-treated bipolar I patients to the broader population of patients with bipolar disorder. They have also misrepresented the risk of suicide and the relationship between medication status and relapse risk.

According to the article, 'sufferers spend 32–50% of follow-up in depressive states and only 1–9% in elevated states'. However, the source cited focused on bipolar I disorder and cautioned that 'Generalization to other samples of BP-I may be limited because the CDS cohort consisted of severely ill, tertiary care, white patients'.[1] Inappropriately generalising biased samples contributes to the clinician's illusion[2], which distorts perceptions of chronicity and severity.

The article claimed that over 90% of patients with bipolar disorders relapse without medications. However, in the source cited the relapse rate applied specifically to bipolar I disorder.[3] The implication that relapse occurs only **without** medication ignores a large body of evidence that it frequently occurs **with** medication.[4,5,6,7] The use of psychotropic drugs between episodes is not associated with time to relapse or recurrence.[8]

The statement that 15% of people with bipolar disorders die by suicide is based on pharmaceutical industry funded grey literature.[9] Australian empirical evidence was lacking in this citation and relied on an article by Goodwin and Jamison.[10] Later, Jamison acknowledged that the quoted risk of 15% may have been too high.[11] The inflated risk was based largely on inpatient samples, inappropriately generalised to the broader population.

The article largely ignored the value of psychological interventions. There is strong evidence that these are effective in the prevention of relapse. Despite emphasising the destabilisation potential of antidepressants, the authors do not mention the potential adverse effects of antipsychotics and other drugs for bipolar episodes. These include obesity, diabetes, metabolic syndrome and dyslipidaemia.[12]

These problems with the article exaggerate both the severity of bipolar disorders and the value of medications, while devaluing psychological treatments.

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Dr Ajeet Singh and Professor Michael Berk, authors of the article, comment:

Several issues are raised by the reader's correspondence. It needs to be stressed that the paper is based on the available, if imperfect, evidence base. Firstly, the validity of suicide risk estimates in bipolar disorders has been raised. A meta-analysis of studies on suicide risk in all psychiatric disorders found that the risk of suicide was about 15-fold for patients with index diagnosis bipolar disorder.[1] In a 1–9 year follow-up study, 6% of bipolar I and 18% of bipolar II patients died by suicide.[2] Based on six independent studies, the rate of suicide attempts is reported as 17% for bipolar I disorder and 24% for bipolar II disorder.[3] Despite varying rates in the literature, the risk of suicide and self-harm in bipolar disorders is the major driver of mortality in the disorder, and needs to be one of the critical foci of treatment.

Secondly, while psychoeducation and cognitive behavioural therapy have an important place in relapse prevention in the maintenance phase, they have not been studied in the acute treatment of either mania or depression, and while we agree that they are of potential value, the absence of an evidence base precludes their inclusion in an evidence-based summary. Clinical trials of psychosocial treatments in the acute phase of the disorder, particularly in depression, are clearly a priority, given the limitations of available treatments.[4,5] While healthy skepticism has an important role in evidence-based medicine, it is still necessary to be guided by the available data.

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Compounding in community pharmacy

Editor, –The editorial 'Compounding in community pharmacy' (Aust Prescr 2008;31:30–1) outlines concerns that regulators have with the activities of some 'compounding' pharmacists. Regulators are concerned with high-volume (bulk) compounding and the promotion of formulations that are not subject to the same regulations as are applied to the pharmaceutical industry. They do not appear to be concerned with single-unit extemporaneous dispensing of low-risk products.

While we agree that compounding practice standards are in need of review, we believe a risk-management approach should be followed. Uniform adoption of standards that may, for example, demand end-product testing would not seem practical, or necessary, for low-risk extemporaneously prepared products such as creams or lotions.

The prescribing of many compounded medicines is regarded as 'off label'. Consequently, prescribers and dispensers should be guided by contemporary standards for evaluating off-label prescribing.[1] We believe the guidance for off-label prescribing should be extended for compounded medicines to include the risk-based evaluation and classification of the factors outlined in Table 1.

We suggest a code of practice in compounding which would include:

- establishing, assuring and maintaining quality through appropriate processes and documentation
- a risk-management approach (Table 1) to the evaluation of compounded medicines
- ensuring that prescribers and consumers have current, evidence-based information to support the quality use of compounded medicines
- complying with therapeutic goods advertising codes and legislation.

These risk-management approaches would support the role of pharmacists in compounding medicines to contemporary standards of quality, safety and efficacy within the spirit of Australia's National Medicines Policy.

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Table 1

A risk-based evaluation of compounded medicines

Factors	Risk criteria
Patient population	Is the medicine to be used in a high-risk population (e.g. children, the frail elderly)?
Site of action	Is the medicine intended to have a local or systemic effect?
Indication	Does the indication require acute or chronic therapy?
Route of administration	Is the medicine intended for topical, enteral or parenteral administration?
Pharmacodynamics	Is there a wide or narrow safety margin (therapeutic index)? Is the dose-response relationship steep or shallow?
Biopharmaceutics	Do formulation factors affect the bioavailability or stability of the medicine? Is the bioavailability highly variable? Is the complexity of the formulation appropriate for a compounded medicine and is dose-uniformity guaranteed (e.g. in sustained release, transdermal or inhaled formulations)? Is quality-assurance testing required and can it be performed?
Regulatory	Are the active and inactive ingredients approved for use in Australia? Have any of the ingredients been withdrawn or rejected from registration because of safety concerns?