EDITORIAL

Data informs debate

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When a new medicine enters the market, medical practitioners are faced with questions on whether it is appropriate for their patients, particularly patients with multiple chronic illnesses taking multiple treatments. When the product is first marketed there may be limited information about it. However, regulatory agencies, such as the Therapeutic Goods Administration in Australia, hold a lot of data from clinical trials. If this data were publicly available it could inform clinical practice. Up until now, the publication of information by regulatory agencies has been limited to product assessment reports or summaries.

One of the particular challenges for assessing the place of a new drug in practice is its efficacy or safety compared to other therapies. Despite the fact that we already have drugs for the majority of chronic diseases, we still do not usually test if a new drug is better than current therapy. Of the medicines approved in the European Union in 2009–10, only 28% were tested to determine if they were better.[1]

While we are now undertaking more medical research than ever before, gaps in the evidence base are still common. Only 30% of the 84 medicines for chronic conditions approved in Europe between 2000 and 2010 were tested for safety and efficacy in more than 1000 patients for at least 12 months.[2] In some specialty areas, trials are even smaller and open-label designs are also problematic. Of the oncology trials registered in the ClinicalTrials.gov database between 2007 and 2010, 72% had 100 participants or less and 88% were open label.[3] Limited evidence translates into uncertainty for both regulators and funders when it comes to decisions to register and subsidise new medicines. A European study of 68 applications for marketing in 2009–10 found that for 11 drugs there were major objections about whether a clinically relevant primary endpoint had been used. Despite this, 5 of these 11 were still approved.[4] Of the 22 medicines where there was doubt or uncertainty about safety issues, 17 were still approved.[4]

Independent re-analysis of the data drug companies submit to regulatory agencies may facilitate a better understanding of the strengths and limitations of the available data for informing clinical practice. The information has often been treated as 'commercial in confidence', but access is improving. In May 2014, European Union Regulation 536/2014 was adopted. This states that 'in general the data included in a clinical study report should not be considered commercially confidential once a marketing authorisation has been granted'. Consequently the European Medicines Agency (EMA) agreed to publish clinical trial reports for products that have been authorised from January 2015.[5] The trial data will be available for non-commercial purposes for researchers, health professionals and the public, providing an opportunity for reassessment of the data. This is likely to lead to significantly increased debate about the place and safety of new drugs in practice.

There have been a number of examples where access to, and analysis of, regulatory data has created controversy or revised opinion about the place of a therapy in practice. Muraglitazar, the first dual peroxisome proliferator-activated receptor agonist for diabetes, was reviewed for market registration in the USA, and in September 2005 the Endocrinologic and Metabolic Drugs Advisory Committee of the US Food and Drug Administration (FDA) voted in favour of approving the drug. However, a concurrent independent analysis of the publicly available data submitted to the FDA found muraglitazar was associated with an increased risk of adverse cardiovascular outcomes.[6] Subsequently, market authorisation has not progressed.

Re-analysis of publicly available FDA data also featured in the controversy concerning the cardiovascular safety of rofecoxib.[7] This contributed to the drug's withdrawal.

From the Editor

Compared to when the ANZACs landed at Gallipoli 100 years ago this month, there is now a greater understanding of post-traumatic stress disorder. Duncan Wallace and John Cooper update us on how to manage this condition.

Patients with post-traumatic stress disorder may also have problems related to alcohol abuse. Philip Crowley explains how drug treatment can help the management of alcohol dependence.

Heavy drinking can interfere with anticoagulant treatment. Philip Tideman, Rosy Tirimacco, Andrew St John and Gregory Roberts include alcohol consumption as one of the factors to consider when optimising warfarin therapy.

Patients drinking heavily may develop abdominal symptoms. Richard Mendelson provides advice on how to use imaging to investigate abdominal pain.

While there have been improvements in imaging techniques, the drug treatment of dementia has not advanced. Louise Waite discusses the direction of research in Alzheimer's disease. When this research is complete, it will be important to have access to the trial data, as Libby Roughead points out that greater scrutiny will help to ensure that new drugs are safe and effective.

Most recently, publicly available data from both the EMA and the FDA has created debate about both the appropriate dose of the oral anticoagulant dabigatran and the need to monitor its concentration.[8] Review of the FDA's reports revealed that an advisory committee had voted six to four in favour of a 110 mg formulation. However, despite this advice only a 150 mg dabigatran product was approved in the USA. The material also revealed at least one committee member raised concern about whether dabigatran required laboratory monitoring, given that the data showed variability in plasma concentrations. Review of information from the EMA also revealed individual committee members had concerns about the large variability in plasma concentrations. Appraisal of the materials from both regulatory agencies also highlighted their different responses to the same evidence. The Europeans approved the 110 mg dose to reduce the risk of bleeding, while the FDA was concerned about the efficacy of this dose and therefore approved the 150 mg dose.[8]

These examples demonstrate the challenges for regulatory agencies in assessing evidence. However, this challenge is not limited to regulatory agencies – even re-analysis of trial results by the original study investigators has resulted in changes in interpretation. There has been a study of 37 re-analyses of randomised controlled trials, 86% of which were undertaken by the same research group that published the original trial. Most commonly, the re-analyses used a different method of analysis or used a different definition of the outcome. In 35% of cases, the re-analysis led to different interpretations as to which patients should be treated.[9]

The release of trial data by the EMA in 2015 increases the transparency of the data on which regulatory decisions are made. Future planned developments include the release of individual patient level data, which may further assist in decision making, and potentially enable additional analyses.

Given that there is often uncertainty about either the safety or efficacy of drugs when they first come to market, the provision of trial data in the public domain will spark much more robust debate about the place of medicines in practice. This will allow us to make more informed decisions that meet patients' needs. ◀

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Letters to the Editor

Pharmaceuticals, pharmacists and profits

Editor, – In his article, 'Pharmaceuticals, pharmacists and profits: a health policy perspective' (Aust Prescr 2014;37:148-9), Professor Philip Clarke highlights the importance of the price disclosure policy in reducing government spending on pharmaceuticals. However, Professor Clarke blatantly disregards the important role that community pharmacists play by comparing pharmacies to 'firms that sell computers or mobile phones'. He asks why community pharmacy should have the support of taxpayer funds in order to remain viable while electronics stores do not. What a ridiculous comparison!

Community pharmacies are staffed by highly trained health professionals and are essential in providing timely access to prescription medicines. This is an essential service that must remain a viable business for those involved. In addition to this, community pharmacists also provide a range of

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