EDITORIAL

Limitations of randomised controlled trials as evidence of drug safety

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The pinnacle of the hierarchy of evidence is the systematic review and meta-analysis. One step below this is the randomised controlled trial. These are 'gold standard' measures of medical knowledge, assessing outcomes and the efficacy of healthcare interventions. However, they rarely provide 'gold standard' information on adverse drug effects and drug safety.

Randomised controlled trials involve a carefully vetted and selected patient population who are exposed to treatment for a relatively short duration. Drugs are later used in practice in a much wider group of patients, who may have multiple comorbidities, and over a much longer period of time. There are numerous examples of now well-established adverse drug reactions that were not apparent when the drug entered the market. For example, ACE inhibitor-associated angioedema was recognised only after marketing. In the years after ACE inhibitors were marketed, the rates of emergency department presentations with angioedema markedly rose.[1]

Generally, randomised controlled trials are statistically powered to assess efficacy, but usually underpowered to assess harm, especially those events that are infrequent or rare. For drugs that are widely used for common conditions, rare adverse effects can have serious clinical impacts. For example, euglycaemic ketoacidosis with sodium-glucose co-transporter 2 inhibitors is rare, but potentially life-threatening. It was not recognised as a complication in the original cardiovascular outcome trials.[2] Recognition of this adverse drug reaction, and its precipitants, has allowed risk mitigation strategies to be implemented.[3]

Randomised controlled trials, even for common conditions, under-represent many groups in our society. Women remain significantly under-represented in lipid-lowering trials compared to their relative burden of disease.[4] When included, it is often only postmenopausal women or surgically sterile women who meet inclusion criteria. No data are therefore available for menstruating women or those who are pregnant or lactating. Similarly, there is limited inclusion of older adults in clinical trials of drugs to treat ischaemic heart disease, despite the high incidence of disease in older people.[5]

There are large disparities in racial and ethnic representation in randomised controlled trials, despite government regulatory bodies recommending targets to enhance the inclusion of minorities in clinical trials. Without representation, unrecognised harm can occur. African Americans respond poorly to ACE inhibitors,[6] and ACE inhibitor-associated angioedema is more prevalent and possibly more severe in African Americans than Caucasians.[7] Australian pharmacovigilance guidelines do not have special requirements to report adverse effects for specific ethnic or cultural groups. There are very little data from Australian indigenous populations about adverse drug reactions and potential harmful effects. This limits strategies to mitigate future adverse events.

Even the way adverse drug reactions are described can be problematic if racial and ethnic groups are not adequately represented. 'Red man syndrome', an infusion-related reaction to vancomycin, describes the reaction in a Caucasian man. This description does not consider what the infusion reaction appears like on the skin of a different patient population. If the syndrome is misdiagnosed as an 'allergy', this can affect future clinical decision making and limit effective treatment options.[8]

In medicines safety, observational studies, including case reports, clinical trial registries, case series and case-controlled studies, are important sources of information about adverse drug reactions and the risk of harm. For individual patients, temporal relationships of events to drug exposure, and experience with drug challenge and rechallenge (if safe to do), are important to consider when looking at relationships between medicines exposure and outcomes. From a practitioner point of view, keeping an open mind and listening to patients can be key. When using new drugs, remember many patients with comorbidities would never have met the strict inclusion and exclusion criteria of clinical trials. Both the efficacy and adverse effects may differ from those seen in the trials. The importance of adverse drug reaction reporting to the Therapeutic Goods Administration (TGA) cannot be emphasised enough (Box). Pharmaceutical companies are mandated to report adverse drug reaction data, however reporting for health professionals is voluntary. Concerningly, adverse drug reaction reports to the TGA are declining.[9]

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While randomised controlled trials and meta-analyses best provide the answer to whether a drug is effective, they are unlikely to determine whether or not the drug is safe for any individual patient. It is therefore important that practitioners, together with patients, consider whether an event may represent an adverse drug reaction. Reporting adverse drug reactions helps bridge the gap in our knowledge and build a picture of what drug safety looks like for the wider Australian community.

Conflicts of interest: Tilenka Thynne is a member of the Australian Prescriber Editorial Executive Committee.

Box Reporting an adverse drug reaction to the Therapeutic Goods Administration

'You don't need to be certain, just suspicious!'

The Therapeutic Goods Administration particularly needs to know about all suspected adverse drug reactions involving:

- new therapeutic goods
- medicine and vaccine interactions
- unexpected reactions (that is, adverse drug reactions that do not appear in the Product Information, Consumer Medicine Information or product labelling)
- serious reactions, such as:
  - death
  - danger to life
  - admission to hospital
  - prolongation of hospitalisation
  - absence from productive activity
  - increased investigational or treatment costs
  - birth defects.

To report an adverse drug reaction, see Therapeutic Goods Administration Australian Adverse Drug Reaction Reporting System.

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