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Randomized Controlled Trials and Assessment of Drug Safety

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"It is simply not possible to identify all the side-effects of drugs before they are monitored. The difficulty is not a failure of the drug-development process or of the drug-approval process; it is the expected consequence of the biological diversity of humans and the fact that low-frequency adverse effects are unlikely to be detected in the few hundred or thousand patients studied in trials before a drug is approved."

— Wood et al.[1]

We were surprised to read the statement that "The randomised clinical trial is considered to be the most reliable tool to assess the efficacy and safety of new drugs" in a recent editorial by Drazen et al.[2] in the *New England Journal of Medicine*. Although such a statement may be correct with regard to efficacy in the treatment of a particular disease in a defined population, it is certainly not correct with regard to the safety of drugs in the general population. As pointed out in the recent *Drug Safety* editorial from Professor I. Ralph Edwards,[3] the information available from clinical trials on potential harms, and therefore of safety of a medicine under trial, is limited. Randomized clinical trials (RCTs) are normally designed to provide evidence of efficacy in a specific disease and population, compared with placebo or occasionally a comparable medicine. Thus, although RCTs are usually able to provide comparisons of the incidence of relatively common adverse reactions, their limitations result in not being able to identify less common but potentially serious adverse reactions that occur in the real world of medical practice (see table I). As a result, many important safety issues arise only after marketing and general use.

In August 1993, the antiepileptic drug felbamate was approved in the US for the treatment of adults with partial seizures and children with the Lennox-Gastaut syndrome, a severe form of childhood epilepsy. Reports to MedWatch, the voluntary medical products adverse event reporting programme of the US FDA, led to the FDA recommendation to withdraw patients from felbamate treatment only a year after approval.[4] Both aplastic anaemia and hepatotoxicity were identified as serious, potentially fatal, adverse effects of this drug through such voluntary reports long after RCT data had incorrectly suggested that felbamate was a very safe drug. As a result, the estimated number of patients taking felbamate in the US fell from 126 000, who had initially been prescribed the drug in the first year, to 12 000 remaining on the drug.[5]

It should also be noted that RCTs have failed to identify even common reactions on a number of occasions. Some early RCTs on captopril and enalapril did not identify coughing as a reaction despite coughing being common with ACE inhibitors.[6] RCTs on practolol did not identify the common precursors of the serious oculomucocutaneous syndrome (rash, dry eyes, popping ears).[7] Visual field defects, a common and significant adverse effect of the antiepileptic drug vigabatrin, were reported 8 years after vigabatrin was licensed in the UK.[8] Wild et al.[9] estimated the frequency of this

Table I. Types of reactions unlikely to be identified in randomized clinical trials (RCTs)

1.	Dose-related reactions: RCTs have fixed-dose regimens. Therefore, there are no data on harm related to doses outside the trial doses. Dose variations are common in clinical practice
2.	Reactions where young or old age is a risk factor: RCTs normally have a limited age range excluding the elderly and the young
3.	Interactions with concomitant medicines, prescribed or self-administered: patients in RCTs are usually restricted to taking the trial drug only. Self medication excluded
4.	The effect of the trial medicine on other diseases, or the effect of other diseases on the action of or response to the trial medicine: RCTs usually involve a single disease
5.	The effect of the trial medicine on the course of pregnancy and/or the fetus/newborn: pregnant women are excluded from clinical trials
6.	Reactions related to the female sex: women are frequently under-represented or excluded from clinical trials
7.	Reactions due to genetic variations in different ethnic groups: RCTs are often limited to a single ethnic group or patients with a very limited range of ethnicity
8.	Reactions associated with unlabelled use: in real-life clinical practice medicines are frequently used outside the recommended guidelines under which they have been tested in the RCTs
9.	Delayed reactions: the duration of RCTs is often too short to identify reactions with a time to onset of months or years
10.	Withdrawal effects: the duration of treatment or of observation is often too short to identify withdrawal effects
11.	Uncommon or rare reactions: the numbers of patients in clinical trials are usually too small to identify any but common reactions
12.	Unfavourable changes in death rates: a significant measure of changes in death rates is usually impossible because of low numbers and/or an inadequate observation period and/or the exclusion of seriously ill patients (e.g. fenoterol)

adverse effect as being 29% (95% CI 21, 39), although it is often asymptomatic, detected only through visual field testing. The reports of this adverse effect in 1997 had a profound influence on prescribing trends, as clearly demonstrated in children by Ackers et al.[10] using the General Practice Research Database in the UK (figure 1).

In addition to phase III pre-marketing trials, RCTs may be designed as post-marketing trials to examine specific safety issues that arise following the marketing of new medicines (phase IV clinical trials). In these, the endpoint is the occurrence of specified adverse effects. Although such trials may help validate suspected ADRs, they suffer the same limitations as pre-marketing clinical trials, in that the populations studied are carefully selected, with patient characteristics and doses used being carefully defined. They are not equivalent to medicine use in the 'real world'.

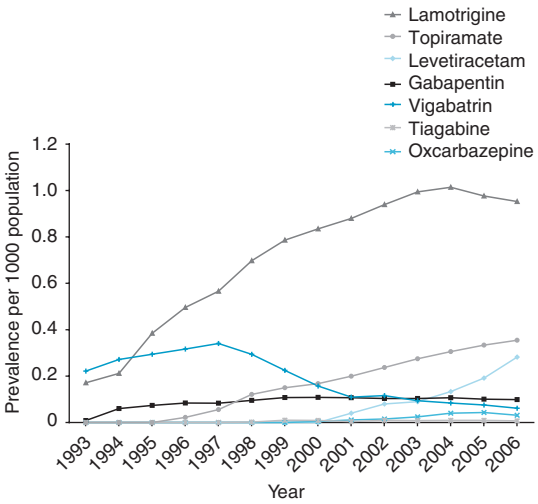

Fig. 1. Prevalence of newer antiepileptic drug use in children aged 0–18 years showing the fall in vigabatrin prescribing after 1997.

Stricker and Psaty[11] made the following statements in an article published in the *British Medical Journal*: "The widespread marketing of a new drug is in fact a large experiment on a population. This is especially the case when it concerns a novel molecular entity with potentially a new set of clinical experiences. As the marketing of new drugs includes the discovery of adverse effects, the public's health would be best protected by a complementary set of techniques for the detection, verification and quantification of safety issues." This emphasizes the important point that in the real-world population, as distinct from the selected, standardized, relatively small and artificial population of a clinical trial, people requiring drug treatment may be very different from each other (and the trial patients): they may be from different ethnic groups, have different ge-

netic make-up and are likely to be exposed to widely different environmental factors, including the taking of concomitant medicines. In addition, they may take the medicine for a much longer period than that possible in a clinical trial. All of these factors may lead to differences in the ways in which individuals respond to drugs, including their susceptibility to adverse drug reactions (ADRs).

Monitoring by National Pharmacovigilance Centres of individual case safety reports (ICSR; spontaneous reports of possible ADRs) remains the mainstay for the early detection of signals of possible ADRs in the 'real world'. The first indication that an event with a medicine may represent a possible ADR (i.e. an ADR signal) frequently arises from meticulous scrutiny of ICSR data in pharmacovigilance databases. Signals identified may arise from the accumulated data of ICSRs received by individual National Pharmacovigilance Centres. They may also arise from the internationally pooled data in the WHO Collaborating Centre for International Drug Monitoring (the Uppsala Monitoring Centre [UMC]). The UMC database contains ADR reports from more than 80 countries worldwide. This very large database contains information on all drugs and all of the reported events associated with them, many combinations of which are potential ADRs. Although in many instances the quality of data from some centres is insufficient to allow definitive causality assessment, the numbers of reports are large and this has allowed the development of a Bayesian Confidence Propagation Neural Network (BCPNN) programme to indicate combinations of drugs and events that stand out from the background of all reports in the database.[12] The procedure is undertaken routinely and significant drug-event combinations are subject to clinical review. This includes causality assessment, which requires information from national centres on 'time to onset of reaction', the effect of drug withdrawal ('dechallenge') and the effect of re-exposure to the drug ('rechallenge'). Following assessment of a causal relationship between the drug and the adverse event, in those reports that contain sufficient information, a signal of a possible newly recognized ADR may be identified. The signal may require further validation by epidemiological methods, such as prospective cohort studies, case control studies or RCTs, as well as identification of a plausible pharmacological mechanism. ICSRs are a valuable information source that contributes to the evidence of an association between a drug and an adverse reaction that has not been identified by RCTs.

In some centres, where prescription-event monitoring (better referred to as cohort event monitoring [CEM]) is carried out, such as the UK Drug Safety Research Unit (DSRU)[13] and the New Zealand Intensive Medicines Monitoring Programme[14] (IMMP; part of the National Pharmacovigilance Centre), all unwanted events are monitored whether or not they are thought to be adverse reactions. In CEM methodology, a denominator (the number of patients on a monitored medicine) is available as well as the numerator (the number of adverse events that have been recorded). Thus, in contrast to spontaneous reporting schemes, an incidence of the adverse event can be calculated. Because all events, including recognized ADRs and random clinical incidents, are recorded, there is a better chance of identifying previously unrecognized reactions. During a single 10-year period, the IMMP identified 153 signals in 11 drugs soon after marketing. Of these, 132 (86%) were notified to the regulatory authority prior to any publication found in the international literature.[15] CEM is a powerful tool for signal identification. It also provides valuable data from actual clinical practice. These data include the mean and range of age, dose, duration of therapy and time to onset of an event; the measurement of risk factors; indication for use; relevant past history (if necessary); and, as mentioned earlier, incidence.

CEM also provides information that can seldom be obtained from RCTs, including the presence of concomitant diseases and medicines (including those self-administered), the results of exposure in pregnancy and lactation, use in children and the elderly and, importantly, off-label use. Women are often excluded, or are not adequately represented in RCTs, but all patients treated are included in CEM, as they are with ICSRs. Pharmacovigilance in gen-

eral does suffer from a lack of controls. However, comparator medicines from the same pharmacological/therapeutic class are often available in CEM. In addition, patients can be used as their own controls by recording events prior to prescription of the monitored medicine as well as subsequent to its use. By recording 'lack of' or 'reduced therapeutic effect' as events, CEM can detect inefficacy that might be due to faulty administration, loss of quality due to poor storage conditions, out of date products, poor quality manufacture or counterfeit products, or interactions. These problems leading to inefficacy will not be seen in RCTs but are very important in worldwide pharmacovigilance.

On completion of a CEM programme, the cohort should be retained for further possible investigation. In such databases, exposure data to the monitored medicines or to risk factors, together with outcome (adverse event) data are available. This provides a source of data on individuals taking a specified drug, who have experienced a particular adverse event (cases) as well as for those who have taken the drug and not suffered adverse events (controls). Therefore, information from such databases is suitable for the application of case-control and other epidemiological methodology for further investigation of possible ADRs.

Through the US Congress initiative in establishing the Reagan Udall Foundation to "identify unmet scientific needs in the development, manufacture, and evaluation of the safety and effectiveness of FDA regulated products",[16] the FDA have recently been considering and identifying safety issues that are associated with medicine use. Following an FDA workshop to help develop guidance for drug safety studies, Professors Bruce Psaty and Jan Vandenbroucke[17] published an article that summarizes opportunities for enhancing drug safety through the use of large electronic databases, such as those held in US health maintenance organizations, the Veterans Administration or personalized health records. Large databases have been used by the NZ IMMP for many years through electronic linkage of CEM cohorts with other databases such as hospital discharge records, national morbidity databases such as the National Cancer Register, and the register of deaths.

Medicines, with their increasing capacity to target molecular and biological mechanisms that lead to disease, have important health benefits. However, because they are not completely specific in the processes that they target, there are always unexpected safety issues. These are frequently only recognized following release for use in the general population. The data on drug-harm produced by RCTs is essential, but clearly inadequate and RCTs are not in any way a reliable tool to assess the safety of new drugs. As indicated by Stricker and Psaty,[11] a range of "techniques for the detection, verification and quantification of safety issues" is needed. ICSRs (spontaneous reporting) with the WHO collaborative programme will remain the mainstay of safety monitoring in the foreseeable future. For drugs of a new type that are to be used widely, we would recommend, in addition to ICSR, CEM in the immediate post-marketing phase in order to provide rapid, quality, measurable information on safety. CEM is now promoted by the WHO for this purpose.

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