which bias might creep in – say, in assigning a cause of death, or judging an X-ray – this can be avoided by arranging for these outcomes to be assessed independently by people who do not know which treatments individual patients have received.

Generating and investigating hunches about unanticipated adverse effects of treatments

Generating hunches about unanticipated effects of treatments

Unanticipated effects of treatments, whether bad or good, are often first suspected by health professionals or patients. Because the treatment tests needed to get marketing licences include only a few hundred or a few thousand people treated over a few months, only relatively short-term and frequent side-effects are likely to be picked up at this stage. Rare effects and those that take some time to develop will not be discovered until the treatments have been in more widespread use, over a longer time period, and in a wider range of patients than those who participated in the pre-licensing tests.

In an increasing number of countries – including the UK, the Netherlands, Sweden, Denmark, and the USA – there are facilities for clinicians and patients to report suspected adverse drug reactions, which can then be investigated formally. Although none of these reporting schemes has been especially successful in identifying important adverse reactions to drugs, there are instances where they have been. For example, when the cholesterol-lowering drug rosuvastatin was launched in the UK in 2003, reports soon began to identify a serious, rare, unanticipated adverse effect on muscles called rhabdomyolysis. In this condition, muscles break down rapidly and the breakdown products can cause serious kidney damage. Further investigation helped to show that the patients most at risk of this complication were those taking high doses of the drug.

Investigating hunches about unanticipated effects of treatments

Hunches about adverse effects often turn out to be false alarms. So how should hunches about unanticipated effects of treatments be investigated to find out whether the suspected effects are real? Tests to confirm or dismiss suspected unanticipated effects
must observe the same principles as studies to identify hoped-for, anticipated effects of treatments. And that means avoiding biased comparisons, ensuring that ‘like is compared with like’, and studying adequate numbers of instances.

As with hoped-for effects of treatments, unanticipated dramatic effects are easier to spot and confirm than less dramatic treatment effects. If the suspected, unanticipated treatment outcome is normally very unusual but occurs quite often after a treatment has been used, it will generally strike both clinicians and patients that something is wrong. In the late 19th century, a Swiss surgeon, Théodor Kocher, learned through a general practitioner
that one of the girls whose thyroid goitre Kocher had removed some years previously had become dull and lethargic. When he looked into this and other former goitre patients on whom he had operated, he discovered that complete removal of the enlarged thyroid gland had resulted in cretinism and myxoedema – rare, serious problems resulting from lack of the hormone produced by the gland, as we now know. The unanticipated effects of thalidomide (see Chapter 1, p4-5) were suspected and confirmed because the association between use of the drug in pregnancy and the birth of babies born without limbs was dramatic. Such abnormalities were previously almost unheard of.

Less dramatic unanticipated effects of treatments sometimes come to light in randomized trials designed to assess the relative merits of alternative treatments. A randomized comparison of two antibiotics given to newborn infants to prevent infection revealed that one of the drugs interfered with the body’s processing of bilirubin, a waste product from the liver. The build up of the waste product in the blood led to brain damage in babies who had received one of the antibiotics being compared.

Sometimes further analyses of randomized trials done in the past can help to identify less dramatic adverse effects. After it had been shown that the drug diethylstilboestrol (DES) given to women during pregnancy had caused cancer in the daughters of some of them, there was speculation about other possible adverse effects. These were detected by contacting the sons and daughters of the women who had participated in controlled trials. These follow-up studies revealed genital abnormalities and infertility in men as well as in women. More recently, when rofecoxib (Vioxx), a new drug for arthritis, was suspected of causing heart attacks, more detailed examination of the results of the relevant randomized trials showed that the drug did indeed have this adverse effect (see Chapter 1, p5-7).

Follow-up of patients who have participated in randomized trials is obviously a very desirable way of ensuring that like will be compared with like when hunches about unanticipated effects of treatment are being investigated. Unfortunately, unless advance provision has been made for it, this is seldom an option. Investigating hunches about possible adverse effects of treatments
would present less of a challenge if contact details of people who have been participants in randomized trials were collected routinely. They could then be re-contacted and asked for further information about their health.

Investigation of suspected adverse effects of treatments is made easier if the suspected adverse effects concern a totally different health problem from the one for which the treatment has been prescribed.\textsuperscript{15} For example, when Dr Spock recommended that babies should be put to sleep on their tummies, his prescription was for all babies, not those believed to be at above average risk of cot death (see Chapter 2, p13-14). The lack of any link between the prescribed advice (‘put babies to sleep on their tummies’) and the suspected consequence of the advice (cot death) helped to strengthen the conclusion that the observed association between the prescribed advice and cot death reflected cause and effect.

By contrast, investigating hunches that drugs prescribed for depression lead to an increase in the suicidal thoughts that sometimes accompany depression presents far more of a challenge. Unless there are randomized comparisons of the suspect drugs with other treatments for depression, it is difficult to assume that people who have and have not taken the drugs are sufficiently alike to provide a reliable comparison.\textsuperscript{16}

\textbf{KEY POINTS}

\begin{itemize}
  \item Fair tests of treatments are needed because we will otherwise sometimes conclude that treatments are useful when they are not, and vice versa
  \item Comparisons are fundamental to all fair tests of treatments
  \item When treatments are compared (or a treatment is compared with no treatment) the principle of comparing ‘like with like’ is essential
  \item Attempts must be made to limit bias in assessing treatment outcomes
\end{itemize}