Editorial

Adverse Effects, Adverse Events and Side-Effects: Does the Terminology Matter?

It could be argued that the primary aim of drug safety investigations is to determine factors related to the frequency and severity of adverse effects so as to minimise them. Second only to efficacy, adverse effects of the drug are of major importance. Both patients and clinicians are keen to know about adverse effects before deciding whether the benefits of taking any drug outweigh the potential risks. However, adverse effects are not always easy to determine. In this context it is very important to distinguish between adverse effects, adverse events and side-effects. Some working in the field of drug safety might consider it quite unnecessary to discuss the difference between these terms but regrettably, many papers offered to scientific journals do not use the terminology in a scientifically correct way.

How are these terms defined? Wikipedia [1] provides the following definitions. "'Side effect' can mean: a 'therapeutic effect', an unintended but desirable consequence of medical treatment or an 'adverse effect', an unintended and undesirable consequence of medical treatment or an adverse drug reaction, such an effect caused by a drug." In relation to adverse effects of drugs, the term "adverse drug reaction" is equivalent to "adverse effect". The broader term "adverse event" is sometimes restricted to clinical trials but there is no reason why this should be the case.

How are adverse effects to be distinguished from adverse events? Consider the following hypothetical situation. After a baseline evaluation period of one month, a new drug is prescribed to a group of patients for a further month. In this trial patients act as their own controls. The drug is, accordingly, withdrawn for one month to determine whether any adverse events during the treatment period were genuinely associated with the drug or simply occurred by chance. The entire group has an adverse event that potentially affects quality of life in a major way and which was not present in the baseline period nor in the subsequent period after the drug had been stopped. Some might argue that there is no doubt whatever that this major adverse event was an adverse effect, since the patients were acting as their own controls and the adverse event was not experienced before or after the drug was taken. However, if the major adverse event was that none of them was able to fly in an aeroplane during the drug treatment, they all resided in the UK and the period during which they were treated happened to coincide with the volcanic eruption in Iceland that grounded all aircraft, it is immediately clear that the major adverse event was certainly not an adverse effect of the drug. This simple hypothetical example is intended to illustrate that adverse events are not necessarily adverse effects, even if there appears to be quite strong evidence suggesting that they might be.

Drug trials can provide good data on adverse events but seldom provide good data on adverse effects. The determination of whether an adverse event is an adverse effect depends on a number of factors. If an adverse event occurs with a statistically significantly higher frequency in the treatment group than in the placebo group in well-designed, randomised, double-blind, placebo-controlled trial on well-matched groups of patients there is a stronger basis for judging it to be an adverse effect rather than a chance association or the result of some confounding issue. However, other factors will also influence the assessment of whether an adverse event is an adverse effect. The time relation to the prescription of the drug may be important, although it should be noted that some adverse effects may not appear until the drug has been taken for several weeks or, indeed, for years [2]. If an adverse event otherwise occurs rarely but is consistently associated with a particular drug, then it becomes much more plausible to consider that it might be an adverse effect of the drug. This introduces the concept of "plausibility" but it would be unwise to over-emphasise the role of plausibility without a strong basis for doing so. For example, if a drug is found to be associated with a higher rate of road traffic accidents in drivers this might not immediately appear to be a plausible association but the possibility that the medication concerned might be affecting judgement or impulsivity would have to be considered. On the other hand, if a particular drug were associated with an increased risk of being killed by lightning, the plausibility of a causal association would be very low and, in that case, the adverse event would be unlikely to be an adverse effect.

Pharmacovigilance provides a very important means of collecting drug safety data, particularly with regard to rarer adverse events. However, it is again important to distinguish between adverse events, which may be associated with taking a drug, from adverse effects that are the result of taking that drug. Patients treated for depression with selective serotonin reuptake inhibitors (SSRIs) are at increased risk of having seizures. If a group of people in the general population, matched for age, sex, educational status and other factors is compared with a group of people taking SSRIs, the second group would have more seizures. This clearly demonstrates that SSRIs are associated with seizures. However, it does not demonstrate that SSRIs cause seizures. One of the commonest indications for SSRIs is depression, which is a major risk factor for seizures. The wrong choice of comparison groups has been made; if a group of depressed people treated with placebo is compared with a group of depressed people treated with SSRIs, the latter group has less not more seizures, suggesting that, far from precipitating seizures, SSRIs may protect against them [3]. Again, very careful evaluation needs to be made before drawing any conclusions with regard to causality.

The term "side effect" can refer to any effect, either beneficial or harmful, of the drug other than on the condition or symptom that is the target indication for that drug. One of the prime examples of a drug that had a notable side effect which was not considered to be an adverse effect is sildenafil citrate (Viagra) [4]. This was initially prescribed to treat angina but was found to have a side effect that some of the patients considered to be beneficial. It has subsequently attracted a major market for what was originally considered to a side effect. Other side-effects are used intentionally by prescribers in certain situations. For example, weight loss, which can occur with the antiepileptic drug topiramate [5], may be considered to be either an adverse effect or a beneficial effect, depending on the patient. The patient who is overweight might choose this drug in preference to

sodium valproate [6], which can be associated with weight gain. Some antiepileptic drugs can also have beneficial or adverse effects on mental state. For example, carbamazepine and valproate are viewed as mood-levelling drugs [7] and, in addition to their use in psychiatric patients who do not have epilepsy, they might be chosen to improve seizure control in a patient with epilepsy who also had a mood disorder, in preference to the drug such as topiramate, which is associated with depression. Should these beneficial effects still be considered as "side effects" or should they be viewed as a secondary indication for prescribing the chosen medication?

Sudden death is clearly an adverse event of major importance. There has been ongoing discussion about the association between sudden cardiac death and the prescription of stimulant medication for treating children with ADHD [8, 9]. A relatively recent study suggested that there was a higher rate of sudden unexplained death in children taking this medication. The argument was relatively simple one. If stimulant medication taken for ADHD is not associated with an increased rate of sudden unexplained death then the percentage of children taking methylphenidate who have a sudden unexplained death should be the same as the percentage of children taking methylphenidate who died as passengers in car accidents. However, if more children who died of sudden unexplained death were taking methylphenidate than those who died in car accidents then it would appear that there is an association between the drug and sudden unexplained death. Gould *et al.* [10], having addressed a large number of possible confounding factors, still found a higher rate of children taking methylphenidate in those who died of a sudden unexplained death than in those who died as passengers in motor vehicle accidents. However, as already stated, an association does not prove causality. Stimulant medication has been is prescribed for several decades without any clear association with sudden unexplained death having been shown. The general consensus is that no clear conclusion could be drawn about any association between taking stimulant medication and sudden unexplained death; however, it is clear that sudden unexplained death is very rare phenomenon in children and that stimulant medication can be of great benefit in treating children with ADHD. At this stage, it is important to state that sudden unexplained death is "an adverse event" that has been reported in children taking stimulant medication but that it cannot justifiably be described as "an adverse effect" on the basis of the evidence available so far.

Because it is so important to undertake a very careful assessment of causality before deciding whether an association is an adverse effect rather than an adverse event, it might be reasonable to expect that the majority of reports in the literature would be on adverse events which, by definition, must be much more common than adverse effects. Furthermore, because scientific precision is important, one might expect that there would be far fewer publications on "side effects", since this term is usually unacceptably vague, than there would be on either "adverse events" or "adverse effects". A Medline search (18 December 2010) revealed exactly the opposite to what might have been expected. The imprecise term "side effects" returned 126,942 references, the broad term adverse events returned 43,170 references and the more specific term "adverse effects" returned 60,741 references. This simple search of one of the most respectable medical databases might suggest that authors are not using these terms in the most appropriate way.

The editors of this journal recommend strongly that all those who submit papers to medical or scientific journals should think carefully about the precision of the terminology they are use when writing about "adverse effects", "adverse events" and "side-effects".

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