Antiepileptic drugs: the drawbacks of generic substitution

The need to curb the rising costs of health care has led policy-makers in many countries to consider widespread generic substitution of brand-name drugs as an effective means to cut costs. For example, on January 5, 2010, the NHS in England began a 3-month consultation to seek views on plans to automatically substitute branded drugs with generic versions in primary care. However, doctors, patients, and advocacy groups—in England and elsewhere—are concerned that generic antiepileptic drugs (AEDs) might not be therapeutically equivalent to branded drugs, which could put patients at risk of breakthrough seizures or other adverse events. Thus, any proposal to implement widespread generic substitution needs careful consideration.

Anecdotal evidence, case reports, and database reviews have suggested an association between generic switching and poor outcomes. According to a retrospective review of medical and pharmacy claims in Canada, the rates of switchback (switching back to a branded drug after generic substitution) were greater for AEDs than for non-AEDs, and health-care costs were greater in patients who received generic topiramate compared with the branded version. Furthermore, the risk of head injury or fracture was almost three times greater in patients who switched from one generic version of topiramate to another, compared with patients who continued on the branded version. However, good-quality prospective data on outcomes after switching are lacking, and the view of the US Food and Drug Administration (FDA) is that approved branded and generic drugs can be used interchangeably.

The FDA and the European Medicines Agency have strict standards for approval of generic drugs: a generic drug is deemed to be equivalent to a branded drug if the 90% confidence intervals for the mean of several key pharmacokinetic parameters for a generic drug are within 80–125% of those of the brand-name drug. However, such bioequivalence studies are done in small numbers of healthy volunteers and may not be generalisable to patients with epilepsy. Furthermore, the narrow therapeutic range of AEDs means that drug concentrations must be maintained within a narrow window to be effective. Variations from this therapeutic range, even by a small margin, can increase the risk of detrimental outcomes. Switching between different generic versions is particularly problematic: two different generic drugs could, in theory, have bioequivalence values at the two extremes of the 80–125% range, causing large fluctuations in serum concentrations if patients switch from one generic version to another.

Although generic switching is unlikely to be problematic for many patients, experts believe that there may be a subset of patients who might be more susceptible to variations in AED concentrations. The NIH is currently reviewing the protocol of a study that aims to shed light on this issue by investigating bio-inequivalence in an “enriched” population of patients—that is, patients with epilepsy who experienced problems after a previous switch to a generic AED.

Generic substitution of branded drugs is already common in many countries. In many US states, for example, physicians must stipulate whether prescription of a particular brand of AED is necessary. However, in practice, a patient’s ability to obtain a branded drug is determined by their insurance company: some insurers will accept a physician’s order that a branded drug is medically necessary; some may accept the order but charge hefty co-payments, which essentially means that branded drugs are not affordable for many patients; and some simply do not cover branded drugs. And in Australia, clinicians may forbid generic substitution on the prescription, but this order is often ignored by pharmacists, who receive financial incentives from the government to dispense generic drugs.

The generic substitution of AEDs is a complex and controversial area, with little hard evidence to inform clinical practice. Seizures are unpredictable and can occur at random, and it is difficult to establish a cause-and-effect relation between switching drugs and breakthrough seizures. The consequences of a change in treatment can be devastating for patients: breakthrough seizures may result in the loss of a driving licence or employment, or even risk of physical injury. Prescription of generic drugs per se is not unacceptable—indeed, many patients are treated successfully with generic drugs; however, maintaining consistency of formulation is crucial. Until firm evidence supporting the safety of generic switching becomes available, we should err on the side of caution and ensure that AEDs are excluded from any sweeping policies that promote automatic generic substitution. —The Lancet Neurology