Alleviating concerns around generic antiepileptic medications

Epilepsy features the unpredictable onset of seizures that can be devastating to a patient's quality of life. Fortunately there are medications available to control the onset of seizures. But because these have to be taken over the long term, healthcare providers need to consider whether to take advantage of cheap generic alternatives to brand-name antiepileptic drugs (AEDs).

Generic AEDs have been the subject of controversy since anecdotal reports and observational studies indicated adverse consequences in some patients who switched from branded to generic AEDs. The UK medical journal *The Lancet*, for example, warned, 'Until firm evidence supporting the safety of generics switching becomes available, we should err on the side of caution and ensure that AEDs are excluded from any sweeping policies that promote automatic generics substitution' [1].

Several recent publications have tried to disentangle the factors involved, to see whether such doubts are valid, or whether generic AEDs have been misrepresented through the use of too much anecdote and not enough scientifically rigorous investigation.

A commentary in the journal *Clinical Pharmacology & Therapeutics* examines reasons why generic AEDs are cause for concern [2], and provides potentially reassuring explanations for recent observations regarding their use. First, Professor Moore and co-authors consider general issues around the use of generic drugs, such as the plasma concentration of the drug's active substance which, in order to meet the US FDA approval, must be within 80 to 125 per cent of that obtained with the originator product—a range known as the equivalence boundary. While this range may be acceptable for the treatment of some conditions, such as cardiovascular disease, when it comes to AEDs, such a difference in plasma concentration could, in theory, cause over- or under-dosing resulting in toxicity or treatment failure. As Professor Moore and co-authors point out, however, even individual tablets of the same medication can produce as much as a 40 per cent difference in the amount of active ingredient absorbed by the patient. If a seizure occurs following fluctuations between tablets of the same drug, rather than following a switch between brands, such incidents may go under-reported compared to when it occurs after generics substitution.

Other potential differences between branded products and generics include the presence of different ratios of isomers in a racemic mixture, which may show the same pharmacokinetic profile but may have a different activity profile, as well as the possible confusion or mistrust for patients from different appearance, colour, and so on, which again could lead to non-compliance and treatment failure or toxicity. In the meantime, both branded and generic products can vary in quality, depending on where they were manufactured, and so switching between even branded medications can also potentially have adverse consequences for patients.

Regarding clinical effects, as Professor Moore and co-authors outline, there are few formal, scientifically sound studies on the consequences of switching from brand-name to generic drugs and back. In favour of generics, they point to a meta-analysis by Kesselheim et al. comparing brand-name AEDs to generics, and found no clinical difference in randomised clinical trials. They also highlight an observational study by Gagne et al. revealing that prescription refilling itself is associated with an increased risk of seizure, with no statistically significant difference between seizures after refill with branded products compared to a switch to generic drug alternatives, or from generics back to brand-name originator. It appears, therefore, that the event of prescription refilling can itself create circumstances leading to seizures, possibly through causing confusion or upset to a patient's routine, delaying the timing of medication, and transiently reducing the level of systemically active drug. The problem, therefore, is not necessarily anything to do with generics. [3, 4].

A more recent study in 2011 supports the use of generic AEDs by looking at bioequivalence, or availability of active ingredient in the blood circulation—assessed as total drug exposure and peak concentration during fasting and fed bioequivalence studies. Kraus et al. obtained data on Abbreviated New Drug Application through a freedom of information request, and found that the total drug exposure was similar between generic AEDs and reference products. Peak plasma concentrations varied more.

Curiously, the study found that switches between generic products cause greater variation in plasma concentration than generics substitutions of reference products, indicating that generics substitution may not be such a problem after all [5].

In 2012, a systematic review of clinical studies of innovator versus generic AEDs adds to the debate. Talati et al. found that while there appears to be a similar efficacy, tolerability and safety after initiating treatment with either innovator or generic AEDs, a switch from one form to the other may result in more hospitalisations and longer hospital stays. The study was underpowered, however, limited by trial size and the range and quality of drugs considered [6].

As Professor Moore and co-authors suggest, more adequately controlled and powered clinical trials and meta-analyses are required to enable scientifically sound decisions to be made over the safety of generics substitution for the treatment of epilepsy.

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