

## Antiepileptic drugs: generic versus branded treatments

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Antiepileptic drugs (AEDs) are relatively cheap but high volumes of prescriptions mean that substantial drug-budget savings may be possible by switching from innovator brands to cheaper generic drugs. Such savings have been achieved in many other treatment areas. However, more caution may be needed in the case of epilepsy because of the narrow therapeutic range of most AEDs; clinical principles of prescribing, which include making only cautious and gradual changes to dosing; the health and socioeconomic impact of breakthrough seizures or toxicity; and the need for long-term consistency of supply. Many physicians and patient groups are insufficiently reassured by current definitions of similarity between generics and innovator brands. Switching to the cheapest generic AED may offer drug-budget savings that outweigh any risk to patient safety. But to date, this cost-benefit analysis has not been done. We propose that all changes to established principles of treating epilepsy are evidence based and that the risks of switching are clearly defined.

### Introduction

Epilepsy is a common and chronic disorder with a prevalence of between 0.5% and 1% in most countries.<sup>1</sup> Antiepileptic drugs (AEDs) are not generally considered to be expensive, but the large volume of prescriptions dispensed makes overall spending on these drugs high—and like all medical treatments, there is increasing interest in measures that might contain costs.

For many people with epilepsy, the disorder is characterised by its uncertainty and unpredictability. Seizures can occur without warning and result in inconvenience, embarrassment, injury, and occasionally, death.<sup>2,3</sup> The psychological and social consequences of seizures can be substantial—for example, the loss of a driving licence may have a disastrous effect on employment and independence.<sup>4</sup>

By taking AEDs, most people with epilepsy can have good control of seizures and this can enable them to lead a normal life.<sup>5</sup> Up to 70% of people with the disorder can be completely seizure-free on an appropriate drug and dose for their epileptic syndrome. This usually requires careful and rigid adherence to drug regimens, which involve taking tablets regularly, two or three times each day for many years, sometimes for a lifetime. Unfortunately, physicians who monitor patients with epilepsy have no validated laboratory measures to judge efficacy of treatment. For example, there are wide variations in each person's response to treatment, and with the exception of phenytoin and possibly phenobarbital, the concentration of AEDs in the serum provides little information about a person's likelihood of suffering seizures or side-effects.<sup>6</sup> Outside the acute setting, physicians generally recommend that changes or substitutions to these regimens are made over many weeks or months. The possibility of breakthrough seizures, side-effects, and toxicity as a result of some drugs shows that there should be caution and consistency when prescribing.

There are advantages to generic prescribing. For example, the names of generic drugs conform to what is taught in medical and pharmacy courses. But the main attraction of generic prescribing is that it is usually cheap. Dispensing generic drugs can rapidly cut pharmaceutical

budgets, and policies of prescribing the cheapest possible generic drug have played a major part in containing drug expenditure. For example, in the UK in 2002 unbranded drugs accounted for 53% of all prescriptions dispensed but only 20% of total drug costs.<sup>7</sup> 4 years after the patent expiry of a branded product, generic drugs will account for about half of the drug's market (UK average) and the average price difference between branded and generic versions of the same drug is about 80%.<sup>8</sup> This means that in the developing world, where branded AEDs may be unaffordable, cheaper generic equivalents widen access to newer, possibly better tolerated, drugs.

Many organisations and governmental bodies who purchase or set tariffs for treatments want to increase the proportion of generic drugs dispensed. Throughout Europe and North America, there are firm guidelines, financial incentives, or even legislation to ensure that the cheapest possible generic substitution is considered from every point from the prescription pad to the dispensing pharmacist.<sup>9</sup>

Currently, several commonly prescribed AEDs can be prescribed generically (table). But do policies of generic AED prescribing guarantee the long-term consistency that is needed when treating patients with epilepsy? Do they reduce costs? And, if they do, are these costs worth any additional risk to patient safety? Here, we present our personal view on this controversial subject.

### Generic treatments

When a drug company produces a successful new drug, patents protect it legally and commercially from other

	Innovator brand (company)	Expected expiry of patent in European Union
Lamotrigine	Lamictal (GSK)	Expired
Gabapentin	Neurontin (Pfizer)	Expired
Topiramate	Topamax (Janssen-Cilag)	2009
Levetiracetam	Keppra (UCB)	2010
Progabalin	Lyrica (Pfizer)	2015
Zonisamide	Zarontin (Eisai)	2015

Table: New antiepileptic drug patent expiry (European Union)

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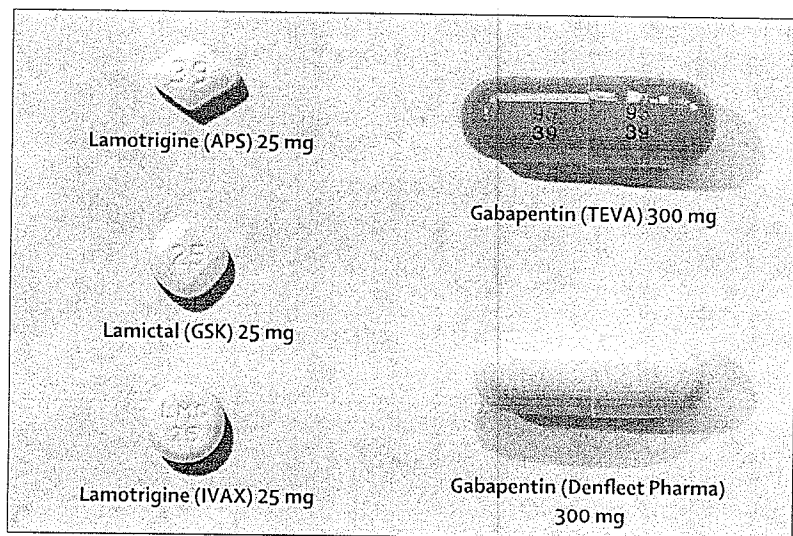


Figure: Lamotrigine and gabapentin: example of tablet appearance from different manufacturers

companies. In the European Union, the patenting process, usually complete by the phase II trial stage, can give a 10 year period of exclusive production and marketing rights to the manufacturer of the “innovator” product. Pricing during this period usually ensures continued research and development and also a profit, which is partly reinvested in developing new drugs.

When this time period is over, other manufacturers may seek licences to market forms of the innovator product. If it can be shown that a formulation is “essentially similar” in its qualitative and quantitative composition—in terms of its active substances having the same pharmaceutical form and bioequivalence—then additional clinical trials are not needed. The formulation can be marketed as “generic” without the need for expensive regulatory clinical trials.<sup>9</sup>

#### Clinical issues: what is the evidence for therapeutic equivalence?

Most of the commonly prescribed AEDs are either off-patent or will be soon. The proportion of generic dispensing is high despite long-standing concerns that epilepsy might be different from other disorders<sup>10</sup> and the lack of clear prescribing guidance from governmental bodies such as the UK National Institute for Health and Clinical Excellence (NICE).<sup>6</sup> For example, the patent for lamotrigine expired in 2004, and within 1 year 50% of prescriptions were being dispensed generically, with an estimated overall drug-budget saving of 35%. Why do some groups, including patient associations,<sup>11</sup> have reservations?

First, the drugs look different (figure). Most neurologists can give anecdotal accounts of patients who are confused by the different appearances of drugs and who subsequently reach a toxic state after combining generic and branded forms. Prospective incident reporting of

this type of mistake is notoriously poor, but there is evidence to suggest that problems occur.<sup>11</sup> Even where tablets are made to look similar, supplies that are imported from abroad via wholesalers (parallel imports) may be packaged and labelled differently, leading to further confusion.

Second, there is a concern that the standard definition of “essential similarity” between generics and innovator brands is insufficiently strict for drugs used to treat epilepsy. Most physicians regard AEDs as having a narrow therapeutic index and therefore may make dose changes in the order of only 5–10% in response to clinical events (such as poor seizure control or symptoms of toxicity). But from the perspective of drug manufacture, “similarity” is typically defined in terms of bioavailability—with no requirement to prove therapeutic equivalence. The European Agency for the Evaluation of Medicinal Products recommends that bioequivalence between generic treatments and innovator brands is achieved when 90% confidence intervals lie between 80% and 125% of the innovator brand for key parameters such as area under single dose-time curve at time  $t$  (AUC), and maximum concentration reached ( $C_{max}$ ).<sup>10</sup> This rule implies that there could be as much as a 56% increase or a 36% decrease in bioavailability when switching between different generic formulations. By contrast, within-brand variability will probably be very small. For example, the UK Medicines and Healthcare Products Regulatory Agency licence for the original branded formulation of lamotrigine requires that during its manufacture, the amounts of excipient and active ingredients are controlled to the nearest 1 mg (0.5% of average daily dose).

Third, there is further concern about industry tests of bioequivalence only being on small numbers of healthy volunteers (about 20–30) rather than on large numbers of the patients that will ultimately be treated, and whose concurrent illnesses or other treatments may affect drug pharmacology.<sup>10</sup> Together, these concerns suggest that switching between branded and generic formulations introduces additional uncertainty.

Most of these potential problems apply to generic drugs used in treatment areas other than epilepsy. Are the risks less acceptable for people with epilepsy? The clinical, and corresponding social consequences of seizures and side-effects can be serious, and current evidence has not quantified this risk. There have been a few clinical trials that consider therapeutic equivalence but with mixed results.<sup>13</sup> Generally, these trials suggest no evidence of therapeutic inequivalence, but are insufficiently powered to provide the more important proof of therapeutic non-inferiority in a clinically relevant group.

#### The economic debate: by how much do generics reduce cost?

Prescribing generic drugs undoubtedly reduces drug expenditure, but the balance between overall long-term

savings and ongoing innovation may be more difficult to achieve. The pharmaceutical industry is highly regulated and does not necessarily behave in a way that will guarantee low costs and consistency of drug supply.

Many costs that are associated with the use of generics are not accounted for when considering drug budgets. Extra clinic appointments and time spent educating people about formulation changes are expensive. Infrequent but serious adverse events may result in hospital admissions and will be very costly. The medicolegal issues surrounding liability after such events are also not clear. Several economic models and threshold-sensitivity analyses have highlighted that drug-budget savings may be eroded by additional costs borne elsewhere.<sup>14,15</sup> Surprisingly, given the willingness to accept policies of generic prescribing on the basis of cost, there are no data to quantify the overall economic benefits of switching to the cheapest available brands.

Some organisations, such as the European Commission, are concerned that the structure and behaviour of the market for drugs may not result in ongoing drug innovation or effective supply of generic drugs.<sup>16</sup> There have been examples of generic drug price volatility: for example, in 1999 the overall level of prices paid by the UK National Health Service increased by around 45% during the course of the year.<sup>17</sup> There were persistent problems with supply across various generic preparations even after the shortfall in production had been made up.

Many explanations for this unpredictability are offered by business and governmental analysts. First, the market for individual generics is not always overwhelmed by suppliers. In 1999, the UK Department of Health estimated that 40 of the top 200 generic drugs had three or fewer licence holders.<sup>17</sup> Manufacturers are usually international, and recently companies that have traditionally concentrated on innovator products either produce generics directly or have wholly owned subsidiaries involved in generic manufacture. For example, Novartis, the world's sixth largest producer of branded drugs, is now one of the world's largest manufacturers of generics.<sup>7</sup> These examples suggest that the competition between producers of generic and branded drugs may not be as fierce as might be hoped.

Patients taking AEDs require consistency, and the small number of licence holders for each AED who rely on the profitability of individual drugs may not be able to guarantee consistent long-term supply of the drug. Individual manufacturers are under no obligation to continue producing treatments if their profit margins are too low. Therefore, over several years, a patient who is prescribed the cheapest possible generic drug may face many switches between innovator brand and different generic forms of their AED, as different companies enter and withdraw from the market. Furthermore, when companies withdraw from the market, overall supply is not guaranteed. Most

neurologists will be aware of the recent difficulties with worldwide supply of paraldehyde, primidone, and ethosuximide, where manufacturers considered stopping production of these AEDs altogether. Decisions like this can cause further stress to patients, who then face the uncertainty of switchover regimens that may not be clinically needed.

### Conclusions

People with epilepsy and the neurologists who treat them have historically been cautious when it comes to generic prescribing. Switching between formulations introduces additional risk for people who are generally averse to change and undermines the message of consistency, which is important when treating epilepsy. The definition of "essential similarity" between generic drugs and innovator brands is determined by small bioequivalence studies in healthy volunteers, and the reliance on the "80–125% rule" seems inappropriate in epilepsy. Generic prescribing can undoubtedly reduce drug budgets in many treatment areas and make drugs affordable to a wider range of patients, particularly in the developing world. But data about long-term cost and the clinical effectiveness of policies such as dispensing of the cheapest possible generic in epilepsy are lacking. There is widespread concern that prescribing the cheapest possible generic does not guarantee the consistency that is a core principle when treating people with epilepsy. By contrast with many other disorders, the clinical and social consequences of even transient treatment failure can be very severe.

We argue for an evidence-based approach. Before radical changes in the treatment of epilepsy are made, the unique features of this disorder should be acknowledged, and dispensing the cheapest possible generic should be shown to be safe in adequately powered, clinically relevant, randomised controlled trials. It should also be shown that observed risks can be justified by significant and sustained cost savings. These studies could be funded by those who seek to gain financially from the use of generics, including the generic manufacturers themselves.

In the meantime, when patients are maintained on the lowest dose of AED treatment that controls their seizures, we would recommend that: people do not switch between brands or non-branded generics; if there is a switch both patient and prescriber are made aware of this; and if a person has breakthrough seizures, their physician asks whether there have been any changes to the form of their treatment. Life with epilepsy is uncertain enough: it is important to provide patients who rely on AEDs with evidence that generic substitution is safe before imposing additional uncertainty on them.

### Contributors

Both authors were involved in the research, drafting, and submission of the article.

**Conflicts of interest**

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