**Risk management in epilepsy: generic substitution and continuity of supply**

Morgan Feely, FRCP; Pam Crawford, FRCP; Günter Krämer, MD; Alan Guberman, FRCP(C)

**ABSTRACT**

The use of generic medicines is widely advocated as a means of reducing healthcare costs. Generic drugs need to meet bioequivalence specifications but, with epilepsy, there is concern that permitted differences in bioavailability may be sufficient to allow loss of seizure control or toxicity in susceptible patients. Where generics are dispensed, whether in response to a generic prescription or generic substitution, difficulties with continuity of supply can lead to frequent “switches” between formulations. As newer antiepileptic drugs lose patent protection, further research is needed to assess the potential risk of switches and subsequent potential additional costs associated with adverse consequences.

**KEY WORDS**

Epilepsy, antiepileptic drugs, generic substitution, bioequivalence, pharmacokinetics

**INTRODUCTION**

Generic prescribing has become widely established as a cost containment measure for health service budgets within both the primary and secondary healthcare sectors. In the developed world, physicians are routinely encouraged by healthcare management to prescribe products generically, with computer prescribing systems often automatically converting brand names to generic prescriptions. As a consequence, the proportion of prescriptions written and/or dispensed generically has increased markedly over recent years [1]. In many markets, if a prescription is written for a brand name product, generic substitution by the pharmacist is encouraged. Lack of continuity in supply is the main problem associated with generics reported by pharmacists [2]. When a number of manufacturers produce a specific generic medicine, pharmacists may wish (or need) to change their supplier, according to availability and/or price. Continuity of supply is further compromised if a patient visits different pharmacies with their prescription.

A detailed discussion of the process for licensing generic medicines is outside the scope of this article, but in the majority of therapeutic areas, the cost savings associated with generic medicines outweigh any potential disadvantages [3,4]. However, concerns have been raised over the potential risks for patient care with generic substitution for critical dose drugs employed in conditions where there are highly individualised dosing requirements [5]. Foremost amongst such agents are the antiepileptic drugs (AEDs), and a number of experts and professional bodies recommend caution with generic substitution and urge attention to continuity of supply [6-11]. This review summarises some of the issues (Table 1) and evidence [12] on this topic, which may

### Table 1: Key issues for consideration by pharmacists (and physicians) concerning generic substitution of AEDs [11]

<table>
<thead>
<tr>
<th>Issue</th>
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<tbody>
<tr>
<td>Characteristics of epilepsy – serious consequences of loss of seizure control</td>
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<tr>
<td>Characteristics of AEDs – potential for adverse events, narrow therapeutic index, individual variation in response</td>
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<td>Complexity of management regimen – need for slow titration, risk of drug interactions</td>
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<td>Bioequivalence vs. therapeutic equivalence – permitted range of bioavailability, evaluation of bioequivalence, individual variation</td>
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<td>Continuity of supply – initial switch to a generic, changes in suppliers over time</td>
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<td>Economic impact – potential savings versus potential costs</td>
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<td>Legal situation and informed consent – implications if generic substitution results in seizure/adverse events</td>
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<td>Compliance/adherence – impact of patient anxiety following a change to medication</td>
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prompt more thorough risk assessments for generic substitution of AEDs and continuity of supply issues in epilepsy. Pharmacists working in the areas of formulary and/or prescribing policy development, in particular, may need to ensure appropriate attention is given to these issues.

Antiepileptic drugs
In patients with epilepsy establishing seizure control, without producing unacceptable adverse events, can be difficult. A stepwise approach needs to be taken and often various doses and/or a number of AEDs may have to be tried in order to identify a regimen which is both effective and well tolerated by an individual patient. If slow titration of a single agent to the maximum tolerated dose fails to provide seizure control, the dose should be tapered to allow the gradual substitution of an alternative agent. In some patients, additional AEDs may be required as adjunctive therapy, again with titration of each agent according to the therapeutic response. Many AEDs induce (or inhibit) hepatic microsomal enzymes, increasing (or reducing) the rate of metabolism of concomitant drugs. This further complicates the AED regimen in patients receiving polypharmacy, adding to concerns about the potential for adverse consequences if any aspect of this finally balanced therapy is inadvertently disturbed. As a result, many patients with epilepsy are on a regimen that has been carefully individualised to obtain the optimal response.

Many traditional AEDs (phenytoin, carbamazepine, sodium valproate) are considered to have a narrow therapeutic index (i.e. only a small relative difference in dose between therapeutic and toxic effects), so slight variations in drug absorption could result in significant negative health outcomes [13]. The FDA considers a drug to have a narrow therapeutic index if:
• there is less than a two-fold difference between the minimum toxic concentration and the minimum effective concentration; and
• safe and effective use requires careful titration and patient monitoring [10,14].

Whilst some people may argue that carbamazepine and, in particular, valproate only just meet the first part of the definition for a narrow therapeutic index, it is the way these AEDs are used in practice, requiring careful titration to balance efficacy and toxicity, that makes them narrow therapeutic drugs for many patients with epilepsy.

Case study: A male patient (age 50 years) had his phenytoin dose increased from 300 mg/day to 400 mg/day and developed clinical intoxication prior to being transferred to the clinic of MF. He subsequently had poor seizure control on 350 mg/day, with two plasma level evaluations of 9.0 and 9.5 mg/l (36 and 38 µmol/l). A dose increase from 350 to 375 mg (7%) then produced an increase in plasma level to 15 mg/l (60 µmol/l) (> 50% increase) and seizure control without adverse events, whilst previously a further 25 mg/day (6.5%) caused intoxication. This case illustrates how, in a susceptible patient, a small increase in phenytoin dose (~5%) can create a large (~50%) change in plasma concentration, making optimisation of therapy very difficult (even with a consistent formulation).

Most AEDs have characteristics that increase the risk of problems with generic substitution (Table 2). Agents with limited water solubility are more sensitive to differences in formulation affecting drug dissolution and absorption [15]. Non-linear pharmacokinetics (as illustrated in case above) and pharmacokinetic interactions with other AEDs, or other concomitant medication, (of which the clinical effects may be unpredictable) are also key considerations. Once a patient with epilepsy has been successfully stabilised, a change in formulation (bioavailability) could compromise their care.

<table>
<thead>
<tr>
<th>AED</th>
<th>Low water solubility</th>
<th>Narrow therapeutic index</th>
<th>Non-linear pharmacokinetics</th>
<th>Drug interactions with AEDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Yes</td>
<td>Yes*</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>No</td>
<td>No</td>
<td>N o (linear up to 600 mg)</td>
<td>N o</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Yes</td>
<td>No</td>
<td>N o (linear up to 450 mg)</td>
<td>Yes</td>
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<tr>
<td>Phenytoin</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Topiramate</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Valproate</td>
<td>No</td>
<td>Yes*</td>
<td>Yes</td>
<td>Yes</td>
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</table>

* Meet definitions for narrow therapeutic index, but have wider therapeutic index than phenytoin

A single breakthrough seizure can have major implications for the patient, at the social level (e.g. employment problems; loss of driving licence) and at the personal level (e.g. loss of confidence, risk of injury or even death). Treatment failure (breakthrough seizures or toxicity) may result in injury and/or hospitalisation, and is likely to have clinical implications, due to the potential difficulty and time required, to re-establish seizure control for the patient [11,12,16]. Thus, paradoxically, if treatment failure results from generic substitution, rather than achieving a cost saving, expensive subsequent medical costs may be incurred.

Bioequivalence standards
Generic substitution is not normally regarded as a change in treatment. Generic products must have the same dose and form as the innovator brand and have demonstrated “equivalent” bioavailability (similar blood concentration profile over time) to the brand in order to obtain a product licence. However, this is generally based on small single dose, cross-over studies in just 12-36 healthy volunteers [12]. Formulations are generally consi-
dered to be ‘bioequivalent’ if the mean area under the curve (AUC), peak concentration (Cmax) and time of peak concentration (Tmax) for the generic product is within 80-125% (90% confidence interval) of the mean for the originator brand [3,4,17,18]. By definition, there is a 10% chance that a tested presentation would have a mean response outside the specified limits [5].

Under generic prescribing/substitution, if there are multiple generic manufacturers for an agent, it is possible for patients to receive a different generic preparation each time they present a prescription. When patients are switched between different generic formulations, there is potential for greater variation in drug pharmacokinetics than from brand-to-generic or generic-to-brand substitution (Figure 1) [15]. It is theoretically possible for the “average” patient to experience an almost 50% increase in serum concentration if switched from a low bioavailability generic formulation (e.g. 80% of brand) to a high bioavailability (e.g. 120% of brand) generic formulation. Conversely, the average patient could have an almost 33% decrease in serum concentration if switched from a high to a low bioavailability generic formulation [15].

Another concern is that bioavailability may vary more widely in patients with epilepsy, who unlike the young healthy volunteers used in bioequivalence studies, cover a wide age range, may have other concurrent diseases and are often receiving potentially interacting medications. The ratio of generic to branded bioavailability in individual patients with epilepsy reported to the FDA varied from 74-142% [15].

**Documented problems**

Recent reviews have examined the potential impact of generic substitution with AEDs, with particular regard to agents with a narrow therapeutic index (phenytoin, carbamazepine and valproate) [4,12,17]. With these agents, it is widely recognised that even slight variations in drug bioavailability can result in reduced efficacy or increased toxicity [19-23]. A UK survey among patients with epilepsy found that 30% of 1333 respondents had perceived problems after a switch in source of AED; problems were medically validated in around a third of these patients and included increased seizure frequency and increased adverse events [24]. In another retrospective survey of 81 Canadian patients, 14% reported problems when switching from a brand AED to a generic product [25].

A recent report on the findings from a survey of US neurologists indicated that 196 neurologists (68% of responders) had observed breakthrough seizures after a switch from brand to generic AED, whilst 56% reported observing increased adverse events [26]. Problems were also reported with switching between different generic preparations of the same AED(s) (33% reported breakthrough seizures in at least one patient and 27% reported tolerability problems). Furthermore, 231 (82%) considered that the Food and Drug Administration (FDA) standards for AED bioequivalence were not sufficiently narrow [26].

Many crossover-designed pharmacokinetics studies in healthy volunteers and patients have been conducted to compare Cmax, AUC and other parameters following brand and generic AED administration, with many identifying wide variations in the pharmacokinetic profiles of some generic formulations [12]. Importantly, some studies have identified generic formulations of carbamazepine [27-29] and phenytoin [30] that fail to meet bioequivalence standards. Case reports and case series have reported increased seizures in patients associated with switches to generic AEDs, in association with phenytoin [19], carbamazepine [20-22,31], valproate [23] and primidone [32,33]. In an open crossover study in which 14 patients stabilised on a branded carbamazepine for at least 35 days were switched to a generic formulation, seven patients reported severe adverse events (e.g. dizziness, double vision) one day after the switch. The generic formulation had a higher bioavailability but met the rules for bioequivalence [31].

In the most recent report, eight patients were identified whose seizures increased following a switch to a generic phenytoin preparation. Mean phenytoin serum concentrations were almost...
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30% lower with the generic preparation, but returned to normal on switch back to the brand [19]. Possible explanations included the observation of bioequivalence for the generic to the brand under fasted, but not fed, conditions and that the most dramatic differences were seen in patients with higher plasma levels where non-linear pharmacokinetics may become apparent.

If there is sudden (unexpected) loss of seizure control or the development of drug toxicity, the pharmacist (and physician) will generally consider a number of causes:
- Poor patient compliance or inappropriate dose modification
- Drug interactions with a new medication (prescribed or over-the-counter)
- Effect of concomitant illness on drug absorption or metabolism, or on the condition itself.

However, the possible impact of a change in drug formulation, such as that occurring with a switch in drug supply from originator brand to generic supplier or between different generic manufacturers, should not be forgotten.

Differing rules on generic substitution
In Europe, a number of the countries that allow generic substitution have formal or informal exemptions for some or all AEDs (Table 3). Concerns about the uncontrolled substitution of AEDs have been raised, e.g. by the German Section of the International League Against Epilepsy [8,9]. As a consequence, in Germany, AEDs are excluded from lists for mandatory use of generics; the prescriber can rule out substitution at the pharmacy by crossing out the “aut idem” field on the prescription. In the UK, general practitioners are recommended to prescribe all anticonvulsants by brand name, so that patients are not transferred from one preparation or formulation to another without full clinical assessment and re-titration [34]; however, this advice is not always followed in clinical practice. If a prescription is written as the generic (approved) name, a generic preparation will be dispensed.

The US FDA has listed carbamazepine, phenytoin and valproate as products with a narrow therapeutic index and there is an ongoing debate on whether more stringent bioequivalence standards are needed [10,26]. As a consequence, a number of states have issued restrictions on their generic substitution [10]; these include methods for the prescriber to indicate an unwillingness for substitution, e.g. a DAW (dispense as written) or DNS (do not substitute) notation on the prescription. Concern has been expressed at the need to ‘first fail’ on a generic drug before a brand-name drug can be prescribed under the requirements of some US states/medical systems [6].

In Canada, mandatory generic substitution is required by a number of drug benefit programmes, unless for instance the patient has had an adverse event with a generic product requiring the specified use of the brand.

Continuity of supply
Recently issued guidance from the UK National Institute for Clinical Excellence [7] states that “changing the formulation or brand of AED (antiepileptic drug) is not recommended because different preparations may vary in bioavailability or have different pharmacokinetic profiles and, thus, increased potential for reduced effect or excessive side effects”. Once an effective AED treatment regimen is identified for a patient, continuity of treatment is important to maintain seizure control [7,11]. Thus, stabilised patients with epilepsy should remain on the same source of medication and same formulation/presentation wherever possible.

Some authors express concern about the medico-legal situation, if adverse consequences arise from generic substitution [10,11,15,25,26]. This issue is also complicated by the concept of informed consent. The question arises of legal responsibility if a breakthrough seizure occurs when the formulation a patient has previously received is changed for another, considered by the regulatory authorities to be equivalent, without the informed consent of the patient (or the physician). These concerns are further compounded by difficulties with continuity of supply for generic medications.

Conclusions
The issue of generic prescribing and dispensing of AEDs is thus not just a matter of generic versus brand-name product supply, but also uncontrolled switching between generic formulations. The potential clinical impact of multiple generic switching on patients with epilepsy is not known. It is difficult to predict which patients with epilepsy may have problems associated with a

<table>
<thead>
<tr>
<th>Table 3: Status of generic substitution in different European countries</th>
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<tr>
<td>Pharmacy substitution not allowed</td>
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<tr>
<td>Austria</td>
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<td>Belgium</td>
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<tr>
<td>Czech Republic (unless brand is out of stock)</td>
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<tr>
<td>Greece</td>
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<tr>
<td>Ireland (may change in 2005)</td>
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<tr>
<td>UK</td>
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switch in formulation. As already covered, loss of seizure control can have a big impact on the patient's quality of life, as well as clinical and financial implications to the primary and/or secondary health care system.

While newer AEDs (e.g. gabapentin, lamotrigine, topiramate) may appear to have a wider therapeutic index, titration in very small increments is often employed, so switching between the originator brand and a generic, or between generics from different manufacturers, may still expose patients to sudden changes in pharmacokinetic profile that could have clinical implications. Some countries extend concerns over generic supply in epilepsy to all AEDs (old and new); certainly the consequences of loss of seizure control are the same regardless of the therapy that has failed. Caution is therefore advised before generic substitution of newly off-patent AEDs, especially in high risk patients with a history of poorly-controlled epilepsy.

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