

With increasing numbers of people living with epilepsy reporting adverse outcomes from generic substitution, *The Epilepsy Report* asked internationally respected neuropharmacologist Professor Frank Vajda to explain why this is occurring.

Generic substitution in epilepsy: a controversial issue



Professor FJE Vajda

A decision to dispense the cheaper generic drugs is one that pharmacists confront every day. The price to the patient and profitability must be balanced. There are government pressures to contain expenditure. The main consideration must be the patients' health and welfare, although pharmacists make a larger profit on the generics, and patients save marginally.

With different classes of drugs, such as painkillers substitution may be appropriate. In areas such as antiepileptics, switching can present problems. The proof for drugs to be accepted as generically equivalent is not comparable to the proof of safety and efficacy required to have a drug initially registered.

It may be appropriate to substitute the cheaper drugs where the consequences are minimal but more hazardous to make a substitution which was not intended by the doctor. Changing brands may lead to potential destabilisation of seizure control. Adverse effects may arise following a substitution.

A controversy about generic substitution of drugs with a so-called narrow therapeutic index²⁻⁵ has been discussed at Government, doctor and specialist level for decades. Providing information to patients and to those dispensing the prescriptions may help in arriving at a rational decision in deciding when to offer and accept substitution.

What is generic substitution?

Generic drug substitution is based on the principle that all drugs with the same basic components have identical effects. The original drug, so-called designer drug, takes a decade to develop. It is rigorously tested, and costs a lot of money to manufacture. The copy drug is less stringently evaluated, hence it is cheaper. Although claimed to be the same, this depends on the definition of 'the same drug'.⁵

In the 1960s Australia experienced an outbreak of antiepileptic drug poisoning (intoxication) involving phenytoin (Dilantin)⁶ amongst patients who were taking the same brand of the drug, but which had been replaced by a new formulation several months earlier. No change was made to the anticonvulsant component but there was a change in the material used as a filler (excipient) in the new formula. Tests showed a marked variation between products with elevations in the blood levels of the new drug, causing undesirable symptoms. Since then, experts have been rightly concerned about generic substitutions, which are rapidly increasing. Concerns have emerged that some unexpected treatment failures and adverse events in previously stable patients may have been due to drug substitution.^{4,7-10}

Epilepsy is a difficult condition to

treat. Standard bioequivalence testing – designed to see if two drugs are the same – may not necessarily assure safety and efficacy of generic substitutes, particularly for drugs with a narrow therapeutic index, meaning those drugs whose concentrations must be maintained within narrow limits as their effective dose is not markedly different from the dose which may cause either side – effects or loss of seizure control.

The need for improved standardisation

The lack of quality control for the introduction of generics is startling. In the USA and Australia bioequivalence between a generic and proprietary drug is established by measuring blood concentrations in cross-over studies in small numbers of healthy subjects. These studies are inappropriately simplistic, usually disregarding the effects of multiple drug dosing or loading practices, meals, drug-drug interactions and the effects of concurrent diseases and other treatments.

Requirements for a new drug to be considered therapeutically equivalent are that if values for blood concentrations are not more than 20% below or 25% above those for the reference drug¹¹, they are considered equivalent. These limits are wide. There is no scientific evidence that such variability can be tolerated safely by patients with epilepsy.

Current bioavailability studies are only

an indirect measure of activity. Variations in enzyme activity of the gut wall or liver, stomach acidity or intestinal motility will affect the ability of a drug to enter the blood stream and hence reach the brain. We cannot strictly speak of the bioavailability of a particular preparation, but only of that preparation in a given individual.¹² Many sites of action within the body such as the brain and the heart are not readily accessible. Measurements of plasma levels are not regarded as an infallible guide to dose adjustment, but only as a supportive guide.¹³ For a patient who is stabilised on one drug, the range of differences between preparations may result in loss of control.

Potential implications of substitution

The financial benefit of generic prescribing can be enjoyed by patients. Healthcare systems and pharmacists must make their businesses profitable. A balance must be struck between savings by patients, profit by the pharmacist, savings by government and patient welfare. The effects of potential therapeutic non-equivalence in products with a narrow therapeutic index outweigh the economic advantages of generic substitution.

Breakthrough seizures, seizures while driving, loss of licence, toxicity, increased doctor visits, increased ordering of plasma levels and loss of work time, are all potential implications. Generic substitution of anticonvulsants may cause confusion and anxiety.⁷ These hidden costs represent a serious flaw in the economic calculation for generic substitution, as initiated by the chemist.

Many generic names look and sound similar, others quite different. Generic substitutes are of a different colour or shape to the original. The patients may become confused and alarmed getting tablets that look odd. Patients may take more than one preparation of the same drug, not understanding that they are variations on a common active substance.

The real question is switchability for patients who are stabilised on drugs with a narrow therapeutic index, not prescribability at initiation of therapy. It may be correct to prescribe or dispense a generic equivalent, but once a patient is stabilised on that brand, it should not be switched. Providers of medicines

should be wary of generic substitution as a routine. Any substitution without prior consideration of potential consequences and without adequately informing the patient, should be resisted.

Experience with antiepileptic medications

There are numerous published reports of clinical non-equivalence resulting in breakthrough of seizures upon generic substitution.^{4,8-10,14-16} An observational report describes nearly 3,000 patients from 48 general practices in Yorkshire, treated with a different supply of the same antiepileptic medication over two years.¹⁵ Patients were asked to report their

experiences, and over half responded. Almost 20% reported a change in supply of medicines and of these, 29.5% perceived

problems. Of these, 36% had their problems validated by their local doctor. The medications included three major antiepileptic drugs: phenytoin, sodium valproate and carbamazepine. All types of switches, from branded medications to generic or the reverse, were involved.

Two other series in Britain, confirm problems with antiepileptic drug substitution.^{4,14} A survey of almost 1,500 people with epilepsy whose records were obtained from general practitioners, indicated that 10% reported problems thought to be related to substitution.¹⁴ A further 18.7% described problems unable to be directly related to switching because of lack of carefully documented data.

A questionnaire of 2,285 people across 556 general practices yielded 155 patient replies concerned with generic substitution of antiepileptic drugs⁴, an incidence rate of approximately 7%. Assuming this voluntary reporting system underestimates the true incidence, this incidence is cause for concern. The small amount of money saved by generic prescribing was outweighed by the negative effects for the person with epilepsy.

A specific area of antiepileptic drug

substitution is discussed by Chapell¹⁶ referring to an interview of 800 patients, 470 of whom responded. One hundred and twenty nine (27%) said that they had experienced switching and 16% claimed a breakthrough seizure. Twenty-five percent claimed to have had more frequent seizures and 36% felt worse. Having a seizure after several seizure-free years can be devastating.

Anecdotal cases of diminished epileptic control in individuals, affected by substitution have also been documented.¹⁴ These reports are less valuable than controlled or open clinical trials, but they highlight concern by individual doctors and patients about possible adverse effects related to

substitution.

There is a need for more formal comparative studies of different formulations of the same drug.

“There is no scientific evidence that such variability can be tolerated safely by patients with epilepsy”

Considerations for pharmacists

Consequences of generic substitution are often lost in commercial and political discussion about limiting manufacturers' profits.¹⁷ This should not distract from the clinical consequences.

The pharmacy also has every right to optimise profits and patients should not be disadvantaged in relation to price. However, the overriding concern must be the patients' interest and welfare.

Ideally, every pharmacy should have a written protocol for dispensing generic and branded products. Many pharmacies have a policy of asking all patients if they would like the cheaper alternative. *It should be appreciated by pharmacists and their staff that substitution should only be offered under certain circumstances.* Pharmacy staff should consider the questions outlined above prior to any substitution. Advice and information offered to patients should remain consistent across all pharmacy staff.¹

With regard to automatic generic substitution, pharmacy assistants should always refer a patient to the pharmacist for information about the substituted

product. If there is a question of the appropriateness of such an action, as with antiepileptics, the pharmacist ought to contact the doctor before changing medication. The patient must be an integral part of every decision made about their care. *They should be informed about the possibility of adverse effects before switching.* This simply does not happen frequently. For many antiepileptic drugs there is little cost incentive to switch to generics when patients' welfare may be put at risk and there is no significant saving with many older drugs.

It is not only differences in bioavailability that may cause problems to a patient after switching. Confusion experienced as a result of different brands and differently appearing medications may cause compliance problems related to feelings of uncertainty.

Considerations for regulatory bodies

The impact of this debate has prompted numerous associations to issue statements on antiepileptic drug substitution. The American Academy of Neurology discourages the use of generic drugs based on anecdotal evidence.¹⁸ The Epilepsy Society of Australia is in favour of patients being *maintained* on drugs, on which treatment was initiated. If epilepsy is well controlled, it is thought inadvisable to substitute another brand. This applies not only to designer drugs, but also confirms that if the initial treatment is with a *particular generic*, then that particular brand should be continued.

Four suggestions have been offered to the scientific and regulatory authorities to assist in the assurance of generic equivalence:³

Manufacturers of generic drugs should be required to:

- Indicate the variability for each marketed dosage form, on the package insert.
- Volunteers involved in bioequivalence studies should receive each dosage form at least twice.
- Calculations of bioavailability should be improved.
- It is suggested that 16 persons with two repetitions per subject of two dosage forms requiring no more than

64 drug administrations, should satisfy these ends.

The Government's minimum pricing policy has the potential to place pharmacists in an difficult position. When a more expensive brand is prescribed and patients are to pay a premium, they will often demand a less expensive brand. Pharmacists are tempted to make substitutions without reference to the prescriber. In some states there is nothing specific in government legislation requiring pharmacists to obtain doctor's consent for such substitutions and no barrier to pharmacists' selection. An update of legislation on this issue is warranted.

Conclusion

Antiepileptic medications comprise a special category of narrow therapeutic index drugs. As a number of generic preparations are available, it is likely that each patient will end up with a series of different substitutions – this is undesirable. Bioequivalence studies for generic preparations are carried out in small populations, as a single dose administration, often in low dose. These studies do not parallel the clinical situation of patients often on multiple medications, sometimes elderly, occasionally fasting, pregnant women, children and handicapped patients. Switching may be confusing and should be avoided. Current guidelines represent approximate criteria for genuine equivalence. Switching between preparations is not recommended, whether switching from designer drug to generics or vice-versa.

The benefits of substitution are purely economic, outweighed by potentially serious consequences such as seizures, injuries, visits to the doctor, more laboratory tests, loss of work or drivers' licence.

A balance should be struck between the economic interests of the pharmacist and the cost to the patient. Patient welfare and seizure control should not be jeopardised.

Regulatory authorities, prescribers, pharmacists and specialists should all be aware of the potential risks of substitution in the case of epilepsy – a life threatening disorder. ■

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