DOES USE OF GENERIC MEDICATIONS POSE RISK WITH REGARD TO SEIZURE CONTROL? YES

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There is a growing perception by public health authorities in many countries of the need to control escalating health care costs by encouragement of prescription of generic drugs; is widely considered a simple and effective way of restricting expenditure on medication (3, 4).

Currently all the traditional and most of the new antiepileptic drugs (AEDs) are available as generic products (1, 12, 13, 20). Reduced cost is the driving force in the widespread use of generics as substitutions for branded products (18). However, in the prescribing of AEDs, this economic driving force has raised the question of whether patients with epilepsy should be switched to generic AEDs only on the basis of cost without considering the uniqueness of epilepsy as a disease

Substitution of a cheaper generic alternative can result in great substantial savings. However, there is a concern that substitution of an original brand by a generic alternative **is associated with real or potential costs**, such as the need for monitoring plasma levels and the cost of managing loss of seizure control (2,3)

Generic substitution does raise **a number of medical issues**, particularly for drugs with a narrow therapeutic window and for conditions where loss of optimal disease control may have serious consequences. Antiepileptic drugs represent a class of drugs for which these medical issues are potentially important. Some of the traditional AEDs have complicated pharmacokinetics and important dose-related side effects, resulting in narrow therapeutic windows and the need for careful dose titration in individual patients. **Any loss of seizure control may carry a risk of injury and of social consequences.**

A growing number of neurologists, professional societies and patients consider that substitution had resulted in **either breakthrough seizures or new adverse effects** (10, 11, 15, 17). For instance, compared to matched controls, the risk for loss of seizure control after switch to generic formulation of lamotrigine was significantly elevated by a factor of 17; adverse events were three times more frequent (6). Consecutive determinations of serum levels suggest that these problems were related to changes in the pharmacokinetics of different formulations. In another recent study, multiple-generic substitution of topiramate was significantly associated with negative outcomes, such as hospitalizations and injuries, and increased health care costs (8).

Consequently, guidelines have been published by professional bodies in several countries to provide a safe and satisfactory framework for generic substitution of AEDs (7, 15, 19). In certain countries, health authorities have set out exclusion lists for drugs for which generic substitution is associated with an identified risk, including, in some cases, AEDs.

However, the risk for the loss of seizure control should be further evaluated (3, 4, 9, 12). The observational studies, not the RCT, identified trends in drug or health services utilization that the authors attributed to changes in seizure control (14). In the absence of better data, physicians may want to consider more intensive monitoring of high-risk patients taking AEDs when any switch occurs, that also increase costs.

Optimization of AED pharmacotherapy requires individualization, perhaps even small deviations in bioavailability have the potential to result in loss of seizure control in some patients. Generic drugs are expected to be essentially similar to their corresponding brand-name drugs. However, the generic drug may differ in the manufacturing process used, in the excipients with which the active principle is associated in the final drug product, and in the appearance of the drug product (shape, color, or both). These differences may influence dissolution rates in the gastrointestinal tract and, thus, absorption of the drug substance and overall pharmacokinetics. Moreover, the shelf life of the generic may not be identical to that of the original brand.

Bioequivalence studies are performed only in healthy volunteers and not in patients and it are assumed that data obtained in the former group can be transposed simply to the latter. However, these two groups may differ in a number of ways. For example, many patients with epilepsy take multiple medications that may affect drug metabolism and disposition. There is generally no information on bioequivalence in patients with co-morbidities and co-medications, children and the elderly. Also, single-dose bioequivalence studies are not necessarily relevant to the chronic use of AEDs.

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