

Generic substitution of anti-epileptic drugs.

A needed battle?

Raidah S. Al-Baradie, MD, ABMS.

ABSTRACT

إن العواقب السريرية والاقتصادية لاستبدال أدوية الصرع التجارية لم تدرس بعد. في بعض الأحيان، استبدال أدوية الصرع التجارية قد تزيد من فائدة الصيدلية ولكنها ليست دائما توفر كلفة الرعاية الصحية لأدوية الصرع. تعتبر أدوية الصرع رخيصة نسبيا، ولكن وصفها بكميات كبيرة يعني أن توفر ميزانية الدواء ضخم، وهذا التوفير قد يحصل عندما تستبدل أدوية الصرع الأصلية المبتكرة بالأدوية التجارية الرخيصة. هذا التوفير يتحقق في مجالات أخرى للعلاج، ومع ذلك فإننا بحاجة لأخذ الاحتياطات اللازمة لأن بعض أدوية الصرع لها علامة علاجية ضيقة ولا تذوب بسرعة، كما إن لها حرائك دوائية غير خطية. وهذا يعني أن مدى التساوي الحيوي لأدوية الصرع التجارية المرخصة لا تعطي نفس النتائج سواء من ناحية فعاليتها أو كونها آمنة وذلك بالمقارنة مع النتائج التي يمكن الحصول عليها من أدوية الصرع الأصلية المبتكرة. ولذلك يجب أن لا نضحى بإمكانية التحكم بالتشنجات لمجرد قلة التكلفة، حيث أن الهدف الأساسي من إعطاء الأدوية لمرضى الصرع هو التحكم بالتشنجات بدون تأثيرات جانبية. إن استخدام الأدوية الرخيصة قد يساعد في توفير الميزانية مقابل قلة أمانها للمريض. للأسف حتى يومنا هذا لم يتم إجراء أي دراسة تغطي هذه الأدوية من ناحية تكلفتها وفوائدها على حدا سواء. وعليه نقترح أن كل تغييرات لتحقيق علاج الصرع الرئيسي، يجب أن تكون مدروسة بشكل مكثف لمعرفة وتحديد مدى فعاليتها أو مضرتها على المريض بوضوح.

The clinical and economic consequences of generic antiepileptic drug (AED) substitution are not yet fully understood. Generic substitution may increase pharmacy utilization, but it may not always save health care costs for AEDs. The 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 for epilepsy because of the narrow therapeutic index, low solubility, and non-linear pharmacokinetics of some AEDs. This means that the ranges of bioequivalence that are authorized for generic formulations do not

offer the same results regarding effectiveness and safety as those obtained by brand name drugs. This is why seizure control should not be sacrificed on the basis of cost alone, as the major endpoint in treating epilepsy with AEDs is seizure control without adverse effects. 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 carried out. We propose that all changes to established principles of treating epilepsy are evidence based and that the risks of switching are clearly defined.

Neurosciences 2008; Vol. 13 (3): 211-216

From the Department of Pediatrics King Faisal University, King Fahd Hospital Of The University, Al-Khobar, Kingdom of Saudi Arabia.

Address correspondence and reprint request to: Dr. Raidah S. Al-Baradie, King Faisal University, King Fahd Hospital Of The University, Al-Khobar, Kingdom of Saudi Arabia. Tel. +966 (3) 8966666 Ext. 3174. Fax. +966 (3) 8966709. E-mail: raidah_albaradie@hotmail.com

Epilepsy is the most common serious neurological disorder and is one of the world's most prevalent non-communicable diseases. It is estimated that the condition affects approximately 50 million people, around 40 million of them living in developing countries.¹ The incidence of epilepsy in low-income countries may be as high as 190 per 100,000 people.² Consequently, in the context of the large and rapidly increasing populations in these countries, epilepsy is a significant health and socioeconomic burden requiring urgent attention.³ In this connection it is worth noting the World Health Organization's (WHO) aim of easing the burden of mental and neurological illnesses that affect 400 million people.⁴ This burden has been quantified by various means throughout the world. Recently, there has been so much attention regarding the use of generic AEDs. The implications of generic drug failure could be related to seizure control, personal injury, or injury to others. In addition, 66% of sudden unexpected

death in epilepsy (SUDEP) cases have sub-therapeutic AED serum concentrations, and approximately 75% of SUDEP cases have frequent drug or dose changes.^{5,6} There are advantages to generic prescribing. For example, the names of generic drugs conform to what is taught in medical and pharmacy courses. However, 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.⁷ Four years after the patent expiry of a branded product, generic drugs will account for approximately half of the drug's market (UK average) and the average price difference between branded and generic versions of the same drug is approximately 80%.⁸ This means that in the developing world, where branded AEDs may be unaffordable, cheaper generic equivalents widen access to newer, possibly better tolerated, drugs.

Generic treatments. A generic is a pharmaceutical product which is marketed under the International Non-proprietary Name (INN) and meets internationally standardized requirements for "essential similarity" to the originator's product (henceforth called "brand" or "proprietary" product): same qualitative and quantitative composition in terms of active substances, same pharmaceutical form, same strength, same route of administration, and equivalent bioavailability (bioequivalence). Two products are considered to be bioequivalent "if their bioavailability after administration in the same molecular dose are similar to such a degree that their effect, with respect to both efficacy and safety, will be essentially the same (Committee, 2001)."⁹ In many countries there is a mandatory requirement or at least an encouragement for "automatic" substitution of brand products with cheaper generic products. For example, in Germany an ad hoc commission of the German Chapter of the International League Against Epilepsy (ILAE) advised against including carbamazepine (CBZ) and valproic acid (VPA) in the "automatic" generic substitution that would have resulted in mandatory prescribing of generic AEDs.¹⁰ One of the aspects emphasized was that physicians should generally refrain from switching seizure-free patients.¹¹ The Pharmaceutical Society, too, expressly pointed out that antiepileptics are among the preparations or formulations, where substitution may be critical. The Society generally recommended to refrain from substitution in cases where these "might raise the concern in the patient (antiepileptics) that he or she might experience a deterioration of his or her clinical picture as a result of preparations being

switched," adding that it is irrelevant "if the concerns are rationally founded or not."¹² It is important to mention that substitution of generic AEDs refers not just to from the brand to generic AED, but also to the switch from a generic to the brand formulation as well as between generic products. Bioequivalence does not necessarily equal therapeutic equivalence for certain seizure medications.¹³

What is therapeutic equivalence? The official Federal Drug Association (FDA) definition of bioavailability is "the rate and extent to which the active ingredient of active moiety is absorbed from a drug product and becomes available at the site of action." For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action. The key measures of bioavailability include the time to maximum concentration, maximum concentration, and area under the curve (AUC_{0-t} and $AUC_{0-\infty}$). Therapeutically equivalent products must meet the following general criteria: 1) they are approved as safe and effective; 2) they are pharmaceutical equivalents in that they (a) contain identical amounts of the same active drug ingredient in the same dosage form and route of administration, and (b) meet compendial or other applicable standards of strength, quality, purity, and identity; 3) they are bioequivalent in that (a) they do not present a known or acceptable in vitro standard, or (b) if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard; 4) they are adequately labeled; 5) they are manufactured in compliance with current good manufacturing practice regulations.¹⁴ The official FDA definition of bioequivalence is "the rate and extent of absorption do not show a significant difference from the rate and extent of absorption of the reference drug when administered at the same molar dose of the therapeutic ingredient under similar experimental condition in either a single dose or multiple doses; or the extent of absorption of the test drug does not show a significant difference from the extent of absorption of the reference drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses and the difference from the reference drug in the rate of absorption of the drug is intentional, is reflected in its proposed labeling, is not essential to attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug." Thus, the FDA's position is that there is no evidence that a bioequivalent generic product manufactured to meet its specifications could not be used interchangeably with the corresponding brand-

name drug.¹⁵ The bioequivalence of a generic versus the brand product is demonstrated by comparing critical pharmacokinetic parameters after single and/or repeated administration of both products in an adequate number of healthy volunteers and/or patients with disorder of interest. In order to receive marketing authorization, the 90% confidence interval for the ratios between the pharmacokinetic parameters of the generic and those of the brand product must fall within the 80-125% range.⁹ Although this may be interpreted as implying that plasma drug levels after administration of a particular generic can be reduced by as much as 45% compared with those observed with another generic, in practice such a difference does not occur because the need to maintain the 90% confidence intervals within the acceptable range implies that, typically, mean plasma concentrations after administration of the generic do not differ by more than 5-6% from those observed after administration of the brand product. This variability is relatively modest when compared not only with interindividual difference in pharmacokinetics, but also with differences in plasma drug levels observed over time even within subjects under the influence of physiological, pathological, and environmental factors, in addition to variation in compliance.^{16,17} It should also be noted that not even the brand product is exempt from variability over time. In the European Union, for example, differences in content of active principle between lots of the same product can fall within 95-105% of the normal value. In addition, at times the manufacturer of the brand product may modify the production/formulation characteristics to an extent that requires conduction of bioequivalence studies to exclude important pharmacokinetic differences. The acceptability limits for these tests are identical to those applied for approval of a generic.¹⁸

Bioequivalence studies. Some anticonvulsants are marketed as twice-daily (bid) preparations despite relatively short half-lives. Although "efficacy" with bid dosing might have been demonstrated for FDA approval and labeling guidelines, clinical experience suggests that some of these drugs are more effective and better tolerated when given more frequently than recommended by the label. Similarly, if the time to peak level varies widely among patients taking a drug, that drug might have to be taken 2, 3, or 4 times a day, depending on the patient. This is a problem that might be addressed by an extended release preparation. There are circumstances in which such preparations are different, but not necessarily better.¹⁹ However, extended-release formulations often make drugs easier to take, make patients' lives easier, at least for epilepsy, and thus can improve treatment outcomes. Conversely, for some drugs, pharmacodynamic effects may last much longer than predicted by half-lives alone. Such drugs

could be taken less often, at least by some, regardless of their half-lives. Do generics differ meaningfully from brand-name anticonvulsants? Often, the answer is no,²⁰ but not always. There should be more formal comparative studies of different formulations of the same drug in clinical populations. In the mean time, however, absence of proof is not proof of absence. The FDA may need to add more rigors to the process for developing and approving truly equivalent generics. The final goals should be a reliable consumer experience and better medical care. The average bioequivalence analysis compares the population means and total variances (sum of within- and between- subject variances) between the generic (test) and the reference product that is usually the brand drug (AED). The distribution of the area under the drug concentration-time curve (AUC) or plasma exposure and C_{max} (peak plasma concentration) of interest assessed in bioequivalence are not taken into account. The average bioequivalence approach does not address whether the individual mean ratios (of AUC and/or C_{max}) differ from individual to individual. If they do differ, that is, if individuals vary in their ratios of average responses (for example, AUC, C_{max}) to 2 formulations, a subject-by-formulation interaction is present.²¹ In addition, in a common 2-way crossover bioequivalence study the within-subject variability or intra subject variance and the subject-by-formulation interaction of the formulations under study are not taken into account.²² Thus, ordinary average bioequivalence address the question of "prescribability" of a generic product, but does not ensure the "switchability" between "prescribable" formulations. The necessity of assuring switchability of 2 formulations, namely that a patient on one formulation can be switched to another and retain essentially the same efficacy and safety, can be addressed by individual bioequivalence. The problems with bioequivalence studies are that it is not a multiple dose study, not in individuals with the disease or in individuals taking other common drugs. It does not measure the efficacy for the generic product, and it is usually not published in peer-reviewed literature. It has variability of the brand name product not usually known. The Abbreviated New Drug Application (ANDA) must be the same active gradient, with the same dosage form as innovator product, and it must demonstrate bioequivalence with the innovator product. Examples of FDA categories of multi-source drugs are category A: drug products that FDA considers to be therapeutically equivalent to other pharmaceutically equivalent products, and category B: drug products that FDA at this time, considers not to be therapeutically equivalent to other pharmaceutically equivalent products. Category A subsets are designated AA, AN, AO, AP, or AT, depending on the dosage form and there are no known or suspected bioequivalence

problems. When the actual or potential bioequivalence problems have been resolved with adequate in vivo and/or in vitro evidence supporting bioequivalence, these are designated AB.²³ Drug products may be classified into the following 4 categories: (a) narrow therapeutic window and low intra subject variability; (b) narrow therapeutic window and high intra subject variability; (c) wide therapeutic window and low-to-medium intra subject variability; and (d) wide therapeutic window and high intra subject variability. The AEDs, like most drugs, fall into category “c” whereas phenytoin (PHT) (in certain patients) may fall into category “b”. This leads to the question of whether this inference holds for all patients or if there is a segment or a subset of epileptic patients who have a narrow therapeutic window and/or higher intra subject variability to certain AEDs than others.²⁴ The rational and principles of individual bioequivalence address the switchability issues better than those of average bioequivalence. However, the models for individual bioequivalence are more complicated than the traditional average bioequivalence models. This may raise the following important questions:

a) Have there been rigorous studies documenting that average bioequivalence failed in assessing bioequivalence of generic AEDs?

b) Is there evidence that subject-by-formulation interactions are important in bioequivalence analysis of AEDs?

c) What populations are appropriate for individual bioequivalence analysis—healthy subjects or patients?

d) Is the intra subject variability of an individual patient to a switch from a brand to a generic greater than to switch from one batch to another of the same formulation of either the brand or the generic product?²⁵

Is there a problem with generic substitution of AEDs? The answer to this important question is based on some case reports, retrospective, and prospective studies. Case reports were primarily with phenytoin and carbamazepine, and they typically reported problem patients, which cover a range from breakthrough seizures to serious toxicity. There were no data on total number who successfully had generic substitution.²⁶ Phenytoin retrospective:²⁷ a retrospective chart review of 8 institutionalized developmentally delayed patients. It mandated switch from Dilantin (phenytoin extended) to generic phenytoin extended. All doses remained the same. There was no change in drugs that could interact. This demonstrated increased switching problems and lower phenytoin level. Also, phenytoin serum concentrations were found to be 21-30% lower on generics.^{27,28} However, in a phenytoin prospective study of 10 children using brand name or generic phenytoin preparation for 3 months and then crossover, the mean trough phenytoin concentrations

for brand was 11.9 +/- 4.9 mcg/ml, and for generic 14.2 +/- 8.2 mcg/ml.²⁹ Wilder,²⁴ studied the effect of a high fat meal on absorption and bioavailability of Dilantin brand to Mylan generic and concluded that there was a significant difference in bioavailability between products when given with food. He predicted to produce a 37% decrease in phenytoin concentrations when Mylan product was substituted, and to produce a 102% increase in phenytoin concentrations when Dilantin was substituted for generic product. Carbamazepine prospective studies,^{30,31} which were carried out as a double-blind crossover comparison of a single generic carbamazepine product (Epitol) and 3 generic products to brand name carbamazepine found no statistically significant difference between these products. Meyer³² concluded from his prospective study that the generic products were all more rapidly absorbed than the innovator, but simulations of steady-state concentrations indicated that it would be unlikely that these differences would have any significant clinical effect. An excellent association was seen between the C_{max}, and the percent of drug dissolved in vitro. Although the FDA approved some generic AEDs, for example, Phenobarbital, Dilantin suspension (AB), Dilantin kapseals (AB), Depakene (AB for capsule; AA for syrup), Tegretol (AB), Zarontin (AB for capsule; AA for syrup), Neurontin (AB), Lamictal 25 mg chewable (AB), Lamictal other strengths (AB), Topamax (AB), Zonegran (AB), and Trileptal (AB), there are many difficulties with FDA standards because these are single dose studies with normal volunteers with no efficacy data for generic product, broad range for establishing bioequivalence, problems with consistency across generic products, no accounting for consequences of generic substitution, and no accounting for drugs with narrow therapeutic window. An electronic survey of members of the German, Austrian, and Swiss Branches of the ILAE was conducted with the primary objective of collecting experiences of physicians with generics in epilepsy patients in Germany, Austria, and Switzerland. A total of 2,800 e-mails were sent out. The response rate was 21.6% (606 responders). Of the 480 physicians who had used generic AEDs, approximately half of the physicians (49.2%) reported problems when switching from a branded preparation to a generic AED. There were comparatively few reports of problems when switching from one generic to another (31.3%) or from generic to brand preparation (16.3%). Some of the problems observed with generic AEDs include additional telephone contacts (39%), additional visits to the practice (30.8%), hospitalization (21.7%), visits to the emergency physician/room (15.4%), problems in the physician-patient relation (15%), sick notes (10.8%), injuries to the patient (3.8%), and others (5.2%) such as loss of driver's license

and/or employment, and prolonged hospitalization. More than half of the physicians using generic AEDs (51.3%) reported having changed their prescribing behavior in most cases (23.8%) by excluding the “aut idem” option or by other notes on the prescription. Sixteen percent advised their patients to insist on the prescribed drug in the pharmacy, and 15.8% performed increased serum level follow-ups. Other changes (5.2%) included actively informing on the risks of unauthorized switches even if performed by general physicians, the use of preparations that are identical to the branded preparations or also returning to branded preparations.¹⁰ Numerous publications on generic AEDs are available from the past few years.³³ However, there is practically no evidence-based data on the effects of the use of generics except from a small, randomized, double-blind, cross-over study from the early 1990s, comparing the pharmacokinetic and therapeutic bioequivalence of branded and a generic carbamazepine preparation.³⁰ More recently, there have been reports of increased switching problems with phenytoin from the United States,²⁷ and also for Phenobarbital from Africa.³⁴ In a US Survey, the percentages for the reported problems were significantly higher.³⁵ When switching from a branded preparation to a generic, the rate of seizure recurrences observed was 68%, and 56% for increased side effect. In contrast, a disturbed physician-patient relation was reported by only 9.5% in the US survey, but for 15% in the German, Austrian, and Swiss group. Insurance formulary decisions and pharmacy benefit managers tend to make general or global policy decisions without regard to specific disease or drug and usually consider publication in the FDA Orange Book sufficient evidence for bioequivalence. It is primarily driven by financial concerns and purchase agreements, and it may provide for appeals and alternatives.

What are the recommendations based on the opinion of experts? There is considerable heterogeneity in several scientific organizations published recommendations, based on the opinion of experts.

A. The American Academy of Neurology (AAN) recently issued a position statement on coverage of AEDs for the treatment of epilepsy with the following principles: 1) The AAN opposes generic substitution of AEDs without the attending physician’s approval. 2) The AAN supports the use of new-generation AEDs. 3) The AAN opposes prior requirements by public and private formularies.^{2,36} Berg suggested to physicians, who care for patients having breakthrough seizures or side effects related to generic substitutions to obtain AED blood levels, a similar AED blood level at the same time of day once the patient is again stable on the brand (or initial generic) AED, and compliance history,

and if the patient is willing to consider the possibility of using generic AED at a future time. Berg suggested that the generated data should be reported to FDA using MedWatch.^{37,38}

B. The German Section of the International League against Epilepsy requested that AEDs be excluded from regulations allowing “automatic” substitution of brand products with generics. More specifically, the document recommends not substituting products in seizure-free patients. While generic substitution in patients with persistent seizures may be acceptable provided that plasma drug levels are monitored during the switch.¹⁰

C. The committee responsible for the guidelines published by the UK National Institute for Clinical Excellence “did not consider that it had adequate evidence to make recommendations on the use of generic products in the treatment of epilepsy.”³⁹

D. The guidelines of the Scottish Intercollegiate Guidelines Network (SIGN) for the treatment of epilepsies in adults’ states that formulations of AEDs are not interchangeable and generic substitution should not be employed.⁴⁰

What do we do? We need to determine patient’s need for generic substitution and to consider the consequences of possible problems, financial considerations, and insurance requirements. If generic substitution is a problem, we should determine the best way to work around the issue. There should be an increase in the interactions between the pharmacy benefit managers and boards making formulary decisions and to balance the education of patients and caregivers. Also cooperation between medicine, pharmacy, and nursing is highly indicated.

What about future needs? The issue of generic drug substitution is complex. Although the FDA requires that 2 drugs are similar as demonstrated by bioequivalence data, therapeutic equivalence and bioequivalence are not necessarily the same. For AEDs, the therapeutic range over which they are effective may be narrow and, it may represent suboptimal care for epileptic patients. Therefore, we need a tighter definition of bioequivalence. Also, we need to improve study methods that address things like brand products variability, multiple doses, and clinical consequences of failures. This can be achieved by preparing a prospective randomized trial of generic substitution with AEDs. A role for consistent dispensing of the same generic product must be organized.

References

1. World Health Organization. The Global Campaign Against Epilepsy. Information Pack for the launch of the Global Campaign’s Second Phase, 12–13 February 2001). Geneva: World Health Organization; 2000.

2. Placencia M, Sander JW, Roman M, Madera A, Crespo F, Cascante S, et al. The characteristics of epilepsy in a largely untreated population in rural Ecuador. *J Neurol Neurosurg Psychiatry* 1994; 57: 320-325.
3. World Health Organization. The global burden of mental and neurological problems. WHO Fact Sheet No. 217). Geneva: World Health Organization; 1999.
4. World Health Organization. Raising awareness, fighting stigma, improving care. WHO Press Release WHO/67. Geneva: World Health Organization; 1999.
5. Nashef L, Hindocha N, Makoff A. Risk factors in sudden death in epilepsy (SUDEP): the quest for mechanisms. *Epilepsia* 2007; 48: 859-871.
6. Nilsson L, Bergman U, Diwan V, Farahmand BY, Persson PG, Tomson T. Antiepileptic drug therapy and its management in sudden unexpected death in epilepsy: case-control study. *Epilepsia* 2001; 42: 667-673.
7. House of Commons Health Committee. The Influence of the Pharmaceutical Industry: fourth report. 2005 Mar 22. Report No: HC 42-I, II. London: Stationery Office Ltd; 2005.
8. IMS Health. Generics: moving up the value chain to higher priced products. IMS Health 2004 May 18; [accessed 2007 March 13]. Available from: http://open.imshealth.com/webshop2/IMSinclude/i_article_20040518b.asp
9. Committee for Proprietary Medicine Product (CPMP) of European Agency for Evaluation of Medicinal Product (EMA). [Cited 2006 January 2] Note for guidance for the investigational of bioavailability and bioequivalence, 26 July 2001, EMA, London. Available from: <http://www.eudra.org.emea.html>
10. Krämer G, Steinhoff BJ, Feucht M, Pfäfflin M, May TW. Experience with generic drugs in epilepsy patients: an electronic survey of members of German, Austrian and Swiss Branches of the ILAE. *Epilepsia* 2007; 48: 609-611.
11. Kramer G, Schneble H, Wolf P (ad-hoc-Kommission der Deutschen Sektion der Internationalen Liga gegen Epilepsie). Risiken der neuen aut-idem-regelung für die Behandlung mit Antiepileptika. *Akt Neurol* 2002; 29: 115-122.
12. Blume H, Bauer KG, Dingermann T, Mutschler E, Zundorf I. Gute Substitutionspraxis-GSP. *Deutsche Apotheker-Zeitung* 2002; 142: 1205-1214.
13. Schachter SC. Testimony before the Advisory Committee for Pharmaceutical Science, Food and Drug Administration. 1999 Sept 23; Rockville (MD). [Cited 2008 June 4] Available from: <http://www.fda.gov/ohrms/DOCKETS/DOCKETS/06p0405/06p-0405-cp00001-toc.htm>
14. Lesser RP, Krauss G. Buy some today: can generic be safely substituted for brand-name drug? *Neurology* 2001; 57: 571-573.
15. Nightingale SL. Therapeutic equivalence of generic drug: letter to health practitioners; 2001 [Accessed 2008 June 4]. Available at: <http://www.fda.gov/cder/news/nightentlett.htm>.
16. Graves NM, Holmes GB, Leppik IE. Compliant populations: variability in serum concentrations. *Epilepsy Res Suppl* 1988; 1: 91-99.
17. Gatti G, Furlanut M, Perucca E. Interindividual variability in the metabolism of antiepileptic drugs and its clinical implications. In: Pacific GM, Pelkonen O, editors. Interindividual Variability in Human Drug Metabolism. London (UK): Taylor and Francis Ltd; 2001. p. 157-180.
18. Perucca E, Albani F. Recommendations of the Italian League against Epilepsy working group on generic products of antiepileptic drugs. *Epilepsia* 2006; 47 Suppl 5: 16-20.
19. Harris G. Pitch to switch. Bristol-Myers fights to lock in patients before generics hit. Users, mainly poor, of drug for diabetes are wooed with similar substitutes. "Just a another marketing tool." *The Wall Street Journal* 2001 May 21; Sect. A1-A12.
20. Anonymous. Generic drugs: the stalling game. *Consumer Reports* 2001; 66: 36-40.
21. Hauck WW, Hyslop T, Chen ML, Williams RL. Subject-by-formulation interaction in bioequivalence: conceptual and statistical issues. FDA Population/Individual Bioequivalence Working Group. Food and Drug Administration. *Pharm Res* 2000; 17: 375-380.
22. Chen ML. Individual bioequivalence--a regulatory update. *J Biopharm Stat* 1997; 7: 5-11.
23. Endrenyi L, Amidon GL, Midha KK, Skelly JP. Individual bioequivalence: attractive in principle, difficult in practice. *Pharm Res* 1998; 15: 1321-1325.
24. Wilder BJ, Leppik I, Hietpas TJ, Cloyd JC, Randinitis EJ, Cook J. Effect of food on absorption of Dilantin Kapseals and Mylan extended phenytoin sodium capsules. *Neurology* 2001; 57: 582-589.
25. Bialer M. Generic products of antiepileptic drug (AEDs): is it an issue? *Epilepsia* 2007; 48: 1825-1832.
26. Heaney DC, Sander JW. Antiepileptic drugs: generic versus branded treatments. *Lancet Neurol* 2007; 6: 465-468.
27. Burkhardt RT, Leppik IE, Blesi K, Scott S, Gapan SR, Cloyd JC. Lower phenytoin serum levels in persons switched from brand to generic phenytoin. *Neurology* 2004; 63: 1494-1496.
28. Rosenbaum DH, Rowan AJ, Tuchman L, French JA. Comparative bioavailability of a generic phenytoin and Dilantin. *Epilepsia* 1994; 35: 656-660.
29. Mikati M, Bassett N, Schacter S. Double-blind randomized study comparing brand-name and generic phenytoin monotherapy. *Epilepsia* 1992; 33: 359-365.
30. Oles KS, Penry JK, Smith LD, Anderson RL, Dean JC, Riela AR. Therapeutic bioequivalency study of brand name versus generic carbamazepine. *Neurology* 1992; 42: 1147-1153.
31. Silpakit O, Amornpichetkoon M, Kaojarern S. Comparative study of bioavailability and clinical efficacy of carbamazepine in epileptic patients. *Ann Pharmacother* 1997; 31: 548-552.
32. Meyer MC, Straughn AB, Mhatre RM, Shah VR, Williams RL, Lesko LJ. The relative bioavailability and in vivo-in vitro correlations for four marketed carbamazepine tablets. *Pharm Res* 1988; 15: 1787-1791.
33. Crawford P, Feely M, Guberman A, Kramer G. Are there potential problems with generic substitution of antiepileptic drugs? A review of issues. *Seizure* 2006; 15: 165-176.
34. Laroche ML, Traore H, Merle L, Gaulier JM, Viana M, Preux PM. Quality of phenobarbital solid-dosage forms in the urban community of Nouakchott (Mauritania). *Epilepsia* 2005; 46: 1293-1296.
35. Wilner AN. Therapeutic equivalency of generic antiepileptic drugs: results of a survey. *Epilepsy Behav* 2004; 5: 995-998.
36. Assessment: generic substitution for antiepileptic medication. Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 1990; 40: 1641-1643
37. Berg MJ. What's the problem with generic antiepileptic drugs?: a call to action. *Neurology* 2007; 68: 1245-1246.
38. Liow K, Barkley GL, Pollard JR, Harden CL, Bazil CW; The American Academy of Neurology. Position statement on coverage on the coverage of anticonvulsant drugs for the treatment of epilepsy. *Neurology* 2007; 68: 1249-1250.
39. National Institute for Clinical Excellence. Newer drugs for epilepsy. Technology Appraisal 79. 2004 April 28 [2006 March 5] London (UK): National Institute for Clinical Excellence. Available from: www.nice.org.uk/TA079guidance
40. Scottish Intercollegiate Guidelines Network. Diagnosis and management of epilepsy in adults. Guideline no. 70. 2003 April [Cited 2006 August 9]. Available from: www.sign.ac.uk/pdf/sign70.pdf