ORIGINAL ARTICLE

Generic Substitution for Brand Name Antiepileptic Drugs: A Survey

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ABSTRACT: ***Background/Objective:*** There are presently 26 different generic preparations for five brand name antiepileptic drugs (AEDs) on the Canadian market with others likely to be released in the near future. The purpose of this review is to examine the basis for the controversy surrounding generic substitution for brand name antiepileptic drugs, to present the results of a survey of neurologists' and patients' attitudes toward generic substitution and to increase neurologists'awareness of the issues. ***Methods:*** The current federal and provincial regulations pertaining to generic drug approval and substitution are reviewed. Published anecdotal and survey reports of the effectiveness and tolerability of generic substitution for AEDs are reviewed. A pilot questionnaire survey of 83 patients from four adult epilepsy clinics and 46 neurologists from across Canada was undertaken to determine attitudes toward generic substitution. ***Results and Conclusions:*** Several authors have suggested that some AEDs, particularly those with a narrow therapeutic index, may pose problems with generic substitution. Although generic AEDs are lower in price, possible increased side effects and morbidity and the need for closer monitoring could partially offset the cost savings. The results of our survey highlight significant unawareness of the process of generic substitution among both patients and neurologists and reveal a general level of discomfort among neurologists to prescribe generic AEDs. Further data should be obtained about the potential consequences of generic substitution in epilepsy patients.

RÉSUMÉ: Substitution de médicaments génériques à des anticonvulsivants de marques déposées: résultats d'une enquête. ***Introduction/Objectif:*** Il existe présentement 26 préparations génériques différentes de cinq médicaments anticonvulsivants de marques déposées (MAC) sur le marché Canadien et d'autres sont sans doute sur le point d'être introduits sous peu. Le but de cette revue est d'examiner les fondements de la controverse entourant la substitution de préparations génériques à des médicaments de marques déposées dans le traitement de l'épilepsie, de présenter les résultats d'une enquête sur l'attitude des neurologues et des patients concernant la substitution d'une préparation générique et de susciter une prise de conscience chez les neurologues à ce sujet. ***Méthodes:*** Les règlements fédéraux et provinciaux actuels concernant l'approbation des préparations génériques et la substitution sont revus. Des rapports anecdotiques et des rapports d'enquêtes publiés sur l'efficacité et la tolérabilité de préparations génériques de MACs sont revus. Une enquête pilote effectuée par questionnaire chez 83 patients de 4 cliniques d'épilepsie pour adultes et chez 46 neurologues à travers le Canada a été effectuée afin de déterminer les attitudes envers la substitution de préparations génériques. Résultats et ***Conclusions:*** Plusieurs auteurs ont suggéré que la substitution d'une préparation générique de certains MACs, particulièrement ceux qui ont un index thérapeutique étroit, peut poser des problèmes. Bien que les MACs génériques soient moins coûteux, une augmentation possible des effets secondaires et de la morbidité ainsi que la nécessité d'une surveillance plus étroite pourraient réduire partiellement l'épargne au niveau du coût des médicaments. Les résultats de notre enquête soulignent la méconnaissance significative chez les patients et chez les neurologues du processus de substitution d'une préparation générique et révèle un niveau général d'inconfort chez les neurologues dans la prescription de MACs génériques. D'autres données devraient être obtenues sur les conséquences potentielles de la substitution de préparations génériques chez les patients épileptiques.

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A generic drug contains identical amounts of the same medicinal ingredient(s) as the original brand name drug, in a comparable dosage form, but does not necessarily contain the same non-medicinal ingredients. Generic drugs must meet federal manufacturing standards for identity, strength, quality, purity and potency and provincial standards for clinical equivalence.[1,2] However, differences in non-medicinal ingredients and manufacturing process may result in variations between generic and brand name products in such factors as taste, shelf life, dissolution rate and extent, *in vivo* pharmacokinetics and appearance.[3]

Generic drugs can be marketed after 20 years from the time the patent is first applied for in Canada, which may precede the actual release of the drug to market by several years. The original manufacturer may apply for many patents: for the chemical,

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different dosage forms or strengths and even the manufacturing process, and each generic manufacturer must determine if enough of the important patents have expired to make it worthwhile to market a particular drug.[4]

Generic drugs offer the promise of considerable cost savings which may be partially offset, however, if their use results in increased health care costs due to increased blood level or patient monitoring, reduced efficacy or an increase in side effects.

The substitution of generics for brand name drugs with a narrow therapeutic index (NTI) poses potential problems.[3,5-7] An argument can also be made that the increased use of generics is a negative incentive for the major pharmaceutical companies to develop certain drugs or invest in new applications for indications which may emerge once they are marketed. The original producers of the drug bear the research and development costs while the companies producing generics also benefit despite the fact that they did not contribute to the development of that drug and in general, do little to promote new drug development.

In Canada, there are presently 10 generic brands of valproic acid, 7 of carbamazepine, 4 of carbamazepine controlled release formulation, 3 of primidone and 2 of clobazam (Drug Product Database, Health Canada). We will review the theoretical basis for the controversy concerning generic substitution in epilepsy, the scant published data on the use of generics in epilepsy and the results of a survey of Canadian neurologists and epilepsy patients on their attitudes toward generic substitution of AEDs.

Are generic and brand name AEDs equivalent?

While the federal government's Health Protection Branch (HPB) establishes the standard for product *bioequivalence*, determination of product *interchangeability* is a provincial domain. The provinces consider not only bioequivalence but also include comparative clinical studies, manufacturing documentation, laboratory analysis, and cost in determining interchangeability.[2]

For second entry new drugs (i.e. generic drugs), pharmaceutical manufacturers are permitted to file an Abbreviated New Drugs Submission (ANDS) to the HPB which demonstrates that, in comparison with the Canadian reference product, the new drug: (a) is pharmaceutically equivalent, (b) is bioequivalent, (c) has the same route of administration and (d) has the the same conditions of use .[8]

The bioavailability of a generic drug is compared with that of the brand name drug by administering each as single doses to the same volunteers at different times. Approximately 12 to 18 serum samples are collected per subject per dose and a plot is made of serum concentration versus time. From this plot, a number of important pharmacokinetic parameters are calculated which measure the rate and extent of drug absorption and predict the mean steady-state serum concentration during chronic administration.[3]

If the generic and brand name products have the same form and contain the same dose of the same active ingredient(s), and have similar pharmacokinetic profiles, they are said to be *bio - equivalent.* For drugs with uncomplicated characteristics, the following pharmacokinetic properties determine bioequivalence:[9]

a) The 90% confidence interval of the mean area under the time-absorption curve (AUC) of the test product should be within 80 percent to 125 percent of the reference product. This indicates that the *amount* of drug absorbed is the same.
b) The relative mean measured maximum concentration (C_{max}) of the test to reference product should be between 80 percent and 125 percent. This indicates that the *rate* of absorption is the same.

Bioequivalence implies (but does not guarantee) that a drug will have the same therapeutic and adverse effects as the reference drug. It should be noted that these studies are almost always carried out in fasting, young, healthy, male adults, close to their ideal body weight, using single doses of the drug rather than in actual patients with epilepsy taking multiple doses and often multiple medications that may interact. The pharmacokinetics of generic drugs may differ in special populations such as the elderly, pregnant women, children and the neurologically handicapped compared to the test population. There are also recommendations by some authors that slow-release preparations should have additional pharmacokinetic parameters related to the rate of absorption determined in order to gauge bioequivalence.[5]

Interchangeability has not been rigorously studied with narrow-therapeutic index agents in patient populations under conditions of typical clinical use. Furthermore, it must be recognized that there are two different aspects to the question: (1) initiation of therapy with a generic drug and (2) substitution of generics in patients who have been stabilized on brand name drugs with a narrow therapeutic index. It is the latter situation, because of the possibility of escape from control or dose-related toxicity, which is of most concern to clinicians.

Process of generic substitution

For patients who are eligible for provincial drug assistance, provincial drug programs reimburse the pharmacist for the lowest priced interchangeable drug product. Many private drug plans have a similar policy called LCA or "lowest cost alternative". For this reason, pharmacists usually dispense the lowest priced interchangeable drug product available when filling prescriptions for patients eligible for provincial assistance. This occurs regardless of whether the physician writes a prescription for the generic or brand name medication. However, if the physician writes "no substitution" on a prescription stating the brand name of the medication, then the patient must pay the difference in price between the generic and brand name medication, unless the physician also submits documentation showing that the patient has experienced a significant adverse drug effect due to the generic medication. If a physician writes a prescription stating the generic name of the medication, then the patient may still request the brand name at the pharmacy, but the patient will have to pay the difference.[2]

If the patient is a cash paying customer, then the pharmacist will usually dispense the generic medication unless the patient requests the brand name or the physician writes "no substitution" on a prescription stating the brand name of the medication. If the patient then receives the brand name medication, he/she will pay the higher price. Private insurers usually have regulations mandating reimbursement only for the price of a generic, if available, or for that price plus part of the price difference

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between generic and brand-name drug (Ontario College of Pharmacists, personal communication).[2]

Unfortunately, this process of generic substitution often occurs without the notification or consent of either the patient or the physician. Moreover, this process leaves open the possibility of the patient being switched repeatedly from one generic formulation to another since pharmacies may receive supplies from different manufacturers over time. Adding to the confusion is the fact that different pharmacies stock different generics, and if the patient is admitted to hospital, yet another generic product may be used. For these reasons it must be recognized that starting a patient on a generic for initiation of therapy is very likely to lead to substitution of one or more generics from different manufacturers at some point in the future.

Use of generics in epileptic patients

Widespread recognition exists that certain medications are not interchangeable. This mandate has been applied to some commonly used drugs including digoxin and warfarin.

The following risk factors for problems with generic substitution apply to certain antiepileptic drugs: low water solubility (PHT & CBZ); non-linear pharmacokinetics (PHTand valproate [VPA]); and narrow therapeutic range (PHT, CBZ & VPA). Antiepileptic drugs, such as phenytoin (PHT) and carbamazepine (CBZ), have long been recognized as drugs which should not be substituted because of their narrow therapeutic index and pharmacologic properties.[3,5] Carbamazepine, phenytoin and valproate are listed as narrow therapeutic index drugs by the FDA and there are seven states which restrict the substitution of one or more of these drugs.[5]

Apart from pharmacokinetic considerations, antiepileptic drugs are generally used to treat a potentially serious condition. Unexpected breakthrough seizures in a controlled patient could lead to adverse psychosocial consequences such as loss of job or driver's licence, physical injury or, rarely, death. In a controlled epileptic patient who is driving, an unexpected seizure could also endanger pedestrians or other motorists. Physicians or pharmacists could potentially be held legally liable for serious consequences arising from either a loss of seizure control or increased side effects attributable to generic substitution about which the patient was not informed.

The 80 to 125% range in bioavailability that the HPB currently allows appears to be too wide for AEDs with a narrow therapeutic index. In such cases, substitution with a generic drug having a bioavailability at the high end of the range could result in a rise in plasma concentration with risk of drug intoxication. Substitution with a generic drug having a bioavailability at the low end of the range could result in a fall in plasma concentration with risk of breakthrough seizures. Theoretically, if patients are switched from one formulation to another, they could experience swings in plasma concentration of almost 50% (given the allowable range of 80 to 125%).[3] Swings of this magnitude, however, would be extremely unlikely given the fact that the 90% confidence interval for bioavailability must fall entirely within the designated 80-125% range compared to the brand name product. Anecdotal experience in the US nevertheless suggests that neurologists would be more comfortable if generics were required to have an AUC which was ± 10% of the AUC of the brand name drug.

Although newer antiepileptic drugs such as lamotrigine, vigabatrin, gabapentin and topiramate are not considered to have a narrow therapeutic range, the relationship of plasma concentration to their clinical effects has not yet been fully established.[10] Certainly, despite the lack of a clear-cut therapeutic range in populations of epileptic patients, in any individual patient plasma concentration must bear some relationship to both clinical response and acute toxicity.

Lamotrigine illustrates how serum levels may bear a relationship to a potentially serious side effect. The initial titration rate of lamotrigine has been shown to be related to the incidence of serious rash.[11] Specific dosage guidelines have been established for initiation of therapy with lamotrigine depending on the age of the patient and whether the patient is taking valproate concurrently. A generic preparation with increased bioavailability could theoretically lead to an increased incidence of serious rash.

Several reports from various countries have been published showing clinical nonequivalence with breakthrough seizures or increased seizure frequency following generic substitution with phenytoin, carbamazepine, valproic acid, and primidone.[7,12-23] In certain instances problems may have been related to a specific country's drug regulations or non-adherence to those regulations. Some of these instances of clinical non-equivalence were based on variations in shelf-life compared to the brand name drug which led to decreased dissolution and bioavailability. Many neurologists have also reported anecdotal evidence that suggests that changes in drug blood levels may occur if a patient is switched from one company's preparation to another.

Implicit in the HPB guidelines for bioequivalence is the assumption that a variation between 80 to 125% in mean steady-state serum concentration of antiepileptic drugs can be tolerated safely. However, there is no scientific evidence to support the assertion that current HPB standards (or any other range of variability) can be tolerated safely by patients with epilepsy.[3] FDA (in the US) and HPB standards allow a variation between 80 to 125%, yet approval has been granted to some generics despite bioavailability ratios measured in individual subjects that have varied from 74-142%.[3,6]

Several published reports have noted an increase in toxicity upon switching to a different formulation of an AED.[16-18,24] A British Epilepsy Association survey found that 46.5% of people perceived a deterioration in their condition after being switched to a different supply of the same AED.[7,25]

A study conducted by Crawford et al[7] found a somewhat lower incidence of problems. A questionnaire was sent to 2,285 patients (58% response rate) being treated for epilepsy in 40 UK general practices. The mean duration of epilepsy was 14 years; mean seizure frequency was 7.3/mo; 45.3% were seizure-free with no side effects, 12.7% seizure-free with side effects, 26.4% were well-controlled and 15.8% poorly-controlled. Current AEDs were carbamazepine in 37.8%, valproate in 39.2% and phenytoin in 32.6%. Monotherapy was being used in 73.9%. Three quarters of the patients "took a close interest in their medication". Two hundred and fifty-one patients (18.7%) recalled a "switch"; 74 (29.5%) reported perceived problems after a switch; 27 (10.8%) reported problems which were attributed to the switch by the patient's general practitioner

Table 1: Patient Demographic Data (N=83)

Gender	**N**
Male	38
Female	42
Unavailable	3
Age (yr)	
20-29	22
30-39	20
40-49	22
50-59	12
60+	7

Table 2: Patient Epilepsy Profiles

How long have you had epilepsy?	**N**
<10 yr	15
10-14 yr	15
15-19 yr	6
20-24 yr	10
25-29 yr	8
30+ yr	21
Unavailable	8
How many seizures have you had in the past year?	
0-10	36
11-20	11
21-30	5
30-50	3
>50	15
Unavailable	13
Has your epilepsy been difficult to control?	
No	24
Somewhat	24
Yes	30
Unavailable	5

Table 3: Patient Sources of Prescription Drug Funding

Do you have insurance coverage for your antiepileptic drugs?	**Percentage (N=80)**
None	16%
Private insurance	48%
Public (provincial) insurance	25%
Both	11%
Does your insurance plan pay for brand name antiepileptic drugs?	**(N=78)**
Yes	45%
No	10%
Not sure	17%
Yes, but I have to pay a little bit extra	28%

Table 4. Patient Attitudes Toward Generic Drugs

Question	**Percentage (N=83)**
Are you currently taking any generic antiepileptic drugs?	
Yes	20%
No	58%
Not sure	22%

Likert scale questions	**Scale**	**Median**	**N**
Generic antiepileptic drugs are exactly the same (except in appearance and price) as the brand name drug.	1= Yes, agree 7= No, disagree	2	79
Generic antiepileptic drugs work just as well.	1= Yes, agree 7= No, disagree	2	76
Generic antiepileptic drugs are just as safe.	1= Yes, agree 7= No, disagree	2	76
Would you prefer to take brand name or generic antiepileptic drugs?	1= Must be generic 7= Must be brand name	4	82

Table 5: Process of Generic Substitution

Question	**Percentage (N=81)**
Are you aware that when you get a generic medication refilled, you may not always get the same manufacturer's generic?	
Yes	14%
No	86%

Likert scale questions	**Scale**	**Median**	**N**
When you go to pick up your prescription at the pharmacy, does your pharmacist ask you if you want the generic or brand name drug?	1= Always asks 7= Never asks	7	80
When you go to pick up your prescription at the pharmacy, does your pharmacist tell you if you are getting the generic or the brand name drug?	1= Always asks 7= Never asks	7	80
If the pharmacist were to tell you that he/she is giving you the same anti-epileptic drug, but it has a different color and/or shape than the one that you are currently taking, how would this make you feel?	1= Wouldn't bother me 7= Would bother me a lot	1	62

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Table 6: Switching Between Brand and Generic AEDs

Question	Percentage (N=81)		
Have you ever switched from a brand name antiepileptic drug to a generic brand?			
Yes	17%		
No	61%		
Not sure	22%		
Have you ever experienced any problems after switching from a brand name to a generic antiepileptic drug?			
Yes	14%		
No	86%		
Likert scale questions	**Scale**	**Median**	**N**
Do you feel that switching from a brand name drug to a generic antiepileptic drug may cause problems (less control of my epilepsy or side effects)?	1= No, not at all 7= Yes, definitely	4	78

("validated"). Possible sources of bias are related to the fact that the ones who experienced problems were more likely to recall or be aware of the switch to generics and patients who were aware of the switch may have been more likely to attribute possible side effects or seizures to the switch.

All three of the most-commonly prescribed AEDs were associated with "validated" problems resulting from switching to a different formulation: 13 on valproic acid (1 breakthrough seizure, 3 increased seizure frequency); 10 on carbamazepine (5 increased seizure frequency); 4 on phenytoin (all related to side effects). This study raises concerns about the safety of switching patients with epilepsy to generic AEDs but the methodology can be criticized since data were collected retrospectively and there was lack of a control group.

While generic medications offer the potential for cost reduction, consideration must be given to any resulting increases in health care costs which could potentially offset all or part of these savings.[3] The American Academy of Neurology (AAN) Statement on Generic Substitution of Antiepileptic Medications recommends that physicians "should monitor blood levels closely at the time of any known or suspected switch." The need for extra blood level monitoring applies to the traditional AEDs but not to the newer agents and presumes either the development of dose-related toxicity or increased seizures. There are also certain fully-controlled patients in whom the occurrence of a seizure would be particularly harmful, either socially or psychologically. Blood level monitoring with any switch in formulation would be advisable in this group. Breakthrough seizures or toxicity could also lead to increases in physician visits and loss of work hours.[6]

Accurate cost estimates for these potential increases in physician visits and monitoring are difficult to measure, but Jumao-as et al found the additional costs in the USA averaged $140 US per patient, per annum (in 1989).[19]

CANADIAN PATIENT AND NEUROLOGIST SURVEYS

Patient survey

Methods

University-based adult epilepsy clinics in four provinces, were randomly chosen for the survey: Vancouver (Dr. Michael Jones), Calgary (Dr. Marianne Lee), Ottawa (Dr. Alan Guberman) and Halifax (Dr. Mark Sadler). Up to 25 patients were randomly chosen from each clinic to respond to a written 20-item questionnaire entitled: "Antiepileptic Drugs Survey". At the top of the questionnaire appeared the statement: "The following questions are intended to obtain your opinions on the use of brand name and generic antiepileptic drugs … Please note that your answers will be kept strictly confidential, and that no name is required." The first eight questions were related to demographic information and the severity of the patient's seizures. The last 12 questions dealt with understanding of and attitudes toward generic AEDs.

Results

Results from the 83 responders to the patient survey are shown in Tables 1 to 6.

Neurologist survey

Methods

A questionnaire on attitudes toward and understanding of generic AEDs was mailed to 110 randomly selected adult neurologists from across Canada. It was stated that replies would

Table 7: Process of Generic Substitution

Question*	Percentage of Neurologists choosing response (N=46)		
When you write a prescription for an AED using the brand name, your understanding is that:			
• The pharmacist always dispenses the brand name.	22%		
• The pharmacist always dispenses an interchangeable generic if available.	61%		
• If you write "no substitutions" or the patient specifically requests the brand name, the brand name is dispensed.	57%		
• If the patient is on a provincial assistance plan, the patient must pay the difference in cost between the generic and the brand name even if you write "no substitutions".	63%		
Likert scale questions	**Scale**	**Median**	**N**
Do you feel that the differences in color and/or shape between generic and brand name drugs may be confusing to patients?	1= Not confusing 7= Very confusing	5	46

* Note: Neurologists could circle more than one choice for this question. The 46 neurologists who responded to this question circled a total of 93 choices.

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Table 8: Switching Between Brand and Generic AEDs

Question*	**Percentage of Neurologists choosing response (N=46)**
Which (if any) of the following drugs do you feel could be safely switched to a generic if the patient is currently on the brand name?	
Clobazam	54%
Phenytoin	57%
Primidone	67%
Lamotrigine	30%
Valproic acid	50%
Carbamazepine	43%

Likert scale questions	**Scale**	**Median**	**N**
Have any of your patients experienced problems after switching from a brand name antiepileptic drug to a generic?	1= Never 7= Frequently	2	46
Do you feel that a significant number of your patients would be anxious about a switch from a brand name newer generation AED to the generic?	1= Not at all anxious 7= Very anxious	4.5	46

* Note: Neurologists could circle more than one choice for this question. The 46 neurologists who responded to this question circled a total of 139 choices.

Table 9: Neurologist Attitudes Toward Starting Patients on Generic AEDs

If you were to start a patient on a specific newergeneration AED, would you prescribe the generic?*	**Percentage of Neurologists choosing response (N=46)**
• No, because I always prescribe the brand name and write "no substitutions".	7%
• No, unless the patient had no insurance coverage (public or private) and could not afford the brand name drug.	48%
• Yes, because I am concerned about cost saving and do not anticipate any additional problems with the generic.	30%
• Yes, unless the patient specifically requested the brand name medication.	22%
• Other	17%

*Note: Neurologists could circle more than one choice for this question. The 46 neurologists who responded to this question circled a total of 57 choices.

be kept anonymous. Forty-six replies were received. There were 6 responders from BC, 8 from AB, 2 from MB, 9 from ON, 4 from NB, and 17 did not specify a province. Eleven of the 46 had expertise in epilepsy.

Results

Results from the responders to the neurologist survey are shown in Tables 7 to 9.

Discussion of Survey Results

This survey is a pilot study and results must be interpreted cautiously due to the small samples, the fact that the patients were drawn from an epilepsy clinic population and the large proportion of non-responders in the neurologist survey.

Patient survey

The patients surveyed in this study are representative of the type of adult patient followed in epilepsy clinics. The seizures in these patients were largely uncontrolled and longstanding. These patients would perhaps be expected to be better informed about their epilepsy, their medication and more concerned about seizure control and side effects than less severe cases who are followed in the community. The patients generally were ill-informed about whether they were taking generics (almost 25% were unsure whether they were taking a generic) and about the possibility of covert substitution (86% were unaware that they could receive generics from different manufacturers). Patients generally viewed generics as equivalent to brand name drugs in both their toxicity and efficacy but were equally divided on whether problems might occur with a switch from brand name to generic. Only 17% of the patients were aware of having been switched from brand name to generic but an additional 22% were unsure. When asked whether they had ever had problems with a switch, 14% of those who thought they might have been switched had experienced a problem. This figure is not an accurate estimate, however, of the incidence of such problems because it is unclear whether the switches were all genuine, the retrospective design relies on memory, and not all "problems" following a switch can be attributed to the switch. One interesting and not unexpected feature was that pharmacists virtually never inform patients about whether they are receiving a generic. Patients, however, do not seem overly concerned about the issue of generic substitution, perhaps reflecting an unawareness of the issue. Patients appear to rely on their pharmacist and physician to make the decision that a generic drug is safe for them.

Neurologist survey

The neurologists responding were a cross section of Canadian community-based and academic adult neurologists including 11 epileptologists. There was some lack of information concerning the procedures which occur when a prescription is dispensed at the pharmacy (for example, 22% were not aware that a generic could be substituted by the pharmacist despite writing the brand name). A range of 30% to 67% of the responders felt that any individual generic AED could be safely substituted for the brand name drug. There was only a small number of problems attributed to generic substitution in the group's experience. Neurologists were almost evenly divided over the question of whether various brand name AEDs could be safely switched to

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generics and were usually uncomfortable about starting a patient on the generic preparation of one of the newer AEDs. Neurologists generally overestimated the degree of patient anxiety around switching to generics, based on the patient survey results. These results must be interpreted in the light of the small number of responders (N=46) and the design of the questionnaire which did not explore all the various options for certain questions. Nevertheless, it is apparent that neurologists do not have a good grasp of the issues around generics and are substantially divided in their opinions.

Conclusions

Epilepsy is a chronic and often serious condition which requires long-term pharmacotherapy, frequently with several agents. While generic AEDs offer the potential for cost reduction, and may allow some patients to receive relatively expensive AEDs that they would otherwise not be able to afford, these benefits must be viewed in the context of possible deterioration in seizure control and/or increased toxicity in certain individuals. Both of these potential consequences may partially offset the cost savings from generics. Once generics are initiated or substituted it is very probable that repeated substitution of other generic formulations will occur over time, usually without the approval or knowledge of either the physician or the patient. Several antiepileptic drugs are considered narrow range therapeutic agents and have properties predicting an increased likelihood for problems with generic substitution. A case can therefore be made for the use of brand name drugs in epileptic patients, especially in certain brittle cases on AEDs known to have a narrow therapeutic index. More research is needed to assess the impact of generic drugs in patient populations with epilepsy in order to determine the incidence of breakthrough seizures and toxicity attributable to generic substitution. A prospective study could be undertaken to include patients from both university-based epilepsy clinics and offices of community-based neurologists in several provinces. Data should be obtained on how often generic substitution occurs, whether patients and physicians are informed about the substitution and the consequences on serum levels, seizure control and side effects. Pharmacokinetic data should also be included. The study would ideally be a long-term one in order to determine how often repeated substitutions from different generic manufacturers occurred.

In the meantime, it is recommended that an education program on this issue be undertaken for both clinicians, pharmacists and patients. It is also recommended that HPB consider generic substitution for AEDs as a special case which may need tighter standards than for many other drugs. Furthermore provincial Drug Benefit Plans as well as private insurance plans should consider AEDs as narrow therapeutic index drugs for which generic substitution must be approved by the treating physician.

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