A high-stakes decision: Generic substitution of antiepileptic drugs

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ABSTRACT

In recent years, generic versions of several antiepileptic drugs have been approved and released to the US market. This article reviews some of the concerns associated with generic substitution of antiepileptic drugs.

KEYWORDS

antiepileptic, generic medications, seizure

For pharmacists practicing in mental health and neurology who are concerned with drug budgets and cost-effective drug therapy, the last several years have brought good fortune as several cost-saving generic drugs have been brought to the market. Generically available second-generation antipsychotics, newer antidepressants, and mood stabilizers have brought down the costs associated with the treatment of psychiatric disorders. Generic antiepileptic drugs (AEDs) have similarly made the treatment of seizure disorders less costly, but not without significant controversy.

Since 2005, generic versions of Neurontin® (gabapentin, released in 2005), Zonegran® (zonisamide, 2005), Lamictal® (lamotrigine, 2006), Trileptal® (oxcarbazepine, 2007), Depakote® (divalproex delayed-release, 2008), Topamax® (topiramate, 2009), Keppra® (levetiracetam, 2009), and Gabitril (tiagabine, 2011) have all been approved and released to the U.S. market.[1] Extended-release formulations for lamotrigine, divalproex, and levetiracetam have also recently become generically available. Many of these drugs are widely used for epilepsy, a condition characterized by recurrent unprovoked seizures that can put the patient as risk for injuries, morbidity, and mortality.

The pharmaceutical industry's potential loss of revenue from generic availability of these drugs has served as a call to action for drug manufacturers. The industry has been proactive in supporting state-level legislation to amend pharmacy practice laws to exempt AEDs from automatic generic substitution laws. A recent review cited a National Conference of State Legislatures survey that indicated 24 states had bills introduced that would restrict generic substitution of AEDs by pharmacists.[2] Epilepsy-specific drug substitution legislation has passed in Connecticut, Hawaii, Illinois, Tennessee, and Utah. Drug companies have also funded research studies that suggest switching to generic AEDs is associated with an increased risk of breakthrough seizures and increased medical costs.[2]

On the other side, pharmacy benefit managers (PBMs) and professional societies representing retail pharmacies have expressed opposition to generic substitution legislation. PBMs have sponsored research studies that have produced favorable findings for generic AED switching.[3]

Upon expiration of a branded drug's patent and marketing exclusivity period, generic manufacturers are permitted to develop their own versions of the branded drug product. The generic manufacturer establishes their drug's equivalence to the reference drug on the basis of bioequivalence studies carried out in twelve or more healthy adults. The Food and Drug Administration (FDA) requires that pharmacokinetic parameters, such as area under the curve (AUC) and peak concentration (Cmax), for the comparator product should fall within 80-125% of the values for the reference product,[4] although differences may exist in product appearance and excipients used. The FDA deems that approved generics are therapeutically equivalent to their corresponding branded drug products.

In the case of AEDs, the episodic, unpredictable, and potentially life-threatening nature of seizures makes the practice of substitution of drugs a very controversial one. A single breakthrough seizure in a previously seizure-free individual may lead to severe limitations on activity, such as loss of driving privileges and curtailed employment.

The case supporting the practice of AED substitution is predicated on the bioequivalence standards established by the FDA. Since pharmacokinetic parameters of generic products have been demonstrated to be nearly identical to the branded agents, generics are expected to be therapeutically equivalent. The cost savings associated with the use of generics benefit the patient and the health care system, especially if they result in improved access and adherence to treatment.

Older AEDs, including phenytoin, carbamazepine, and valproate, that had a narrow therapeutic index (NTI)

and/or nonlinear pharmacokinetics presented unique problems. In these cases smaller variations between branded and generic drugs have a greater potential to lead to poor seizure control or increased toxicity. However, most of the newer AEDs have more favorable dissolution characteristics and pharmacokinetic profiles which make these issues less significant.

Arguably, the most significant concern with the use of generic AEDs is potential variations ***between*** different generic products. Price competition between numerous generic manufacturers can lead to the availability of several generics of the same drug. While each generic product must produce mean AUCs and Cmax within a range of variability of the innovator product, there is the potential of up to a 40% difference between two approved generics. When combined with the frequent switches of generics supplied by wholesalers and pharmacies, the patient may be put at significant risk. There are a few studies that suggest that generic-generic differences may lead to clinically significant problems.[5] One must also consider the potential variations between manufacturer lots and potential physiologic changes with aging and drug accumulation that may also affect drug kinetics and clinical response.

The pharmacist is left with the responsibility of ensuring that selection of AED products for patients is done with patient safety as a primary concern. Whenever possible, drug from the same manufacturer should be supplied to patients with seizure disorders to minimize factors that may contribute to changes in clinical response. Monitoring of adverse effect reports, seizure frequency, and AED blood levels is critical to assess and potentially predict problems with drug therapy. It is also important to educate prescribers, consumers, and family members regarding the benefits and potential risks of generic AED use so that all involved individuals can make informed decisions about their therapy.

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