EPILEPSY CURRENTS

Current Literature
In Clinical Science

Brand Spanking? The Presumptive Risks of Generic Antiepileptic Drugs

Generic Antiepileptic Drugs and Associated Medical Resource Utilization in the United States

Labiner DM, Paradis PE, Manjunath R, Duh MS, Lafeuille M-H, Latrémouille-Viau D, Lefebvre P, Helmers SL. *Neurology* 2010;74:1566–1574.

OBJECTIVE: To evaluate whether generic substitution was associated with any difference in medical resource utilization for 5 widely used antiepileptic drugs (AEDs) in the United States. METHODS: Health insurance claims from PharMetrics Database, representing over 90 health plans between January 2000 and October 2007, were analyzed. Adult patients with epilepsy, continuously treated with carbamazepine, gabapentin, phenytoin, primidone, or zonisamide, were selected. An open-cohort design was used to classify patients into mutually exclusive periods of brand vs generic use of AEDs. Pharmacy and medical utilization were compared between the 2 periods with multivariate regression analyses. Results were stratified into epilepsy-related medical services, and stable (≤2 outpatient visits per year and no emergency room visit) vs unstable epilepsy. Time-to-event analyses were also performed for all services and epilepsy-related endpoints. RESULTS: A total of 18,125 patients were observed in the stable group and 15,500 patients in the unstable group. After adjustment of covariates, periods of generic AED treatment were associated with increased use of all prescription drugs (incidence rate ratio [IRR] [95% confidence interval (CI)] = 1.13 [1.13–1.14]) and higher epilepsy-related medical utilization rates (hospitalizations: IRR [95% CI] = 1.24 [1.19–1.30]; outpatient visits: IRR [95% CI] = 1.14 [1.13–1.16]; lengths of hospital stays: IRR [95% CI] = 1.29 [1.27–1.32]). Generic-use periods were associated with increased utilization rates in stable and unstable patients and with 20% increased risk of injury, compared to periods with brand use of AEDs. CONCLUSIONS: Generic antiepileptic drug use was associated with significantly greater medical utilization and risk of epilepsy-related medical events, compared to brand use. This relationship was observed even in patients characterized as stable.

Commentary

In a room full of epilepsy physicians—or their patients—the one topic most likely to cause the proverbial excrement to strike the rotating blades is that of generic antiepileptic drugs (AEDs). Passions run high, with those at one end of the worry spectrum convinced that the widespread use of generics poses a primordial threat to the well-being of patients with seizures, while those at the other end seem equally convinced that the former group, as one clinical pharmacologist said to me not long ago, "must believe in some vital force outside of pharmacokinetics."

The first group probably outnumbers the second by at least 2:1. Yet a very important stakeholder remaining firmly in the latter camp is the U.S. Food and Drug Administration (FDA), which has insisted, despite all protestations, that there is no convincing evidence that generic AEDs pose any danger, and thus no reason to consider altering the FDA's typical standards for generic preparations for this category. Those standards are often misunderstood, in that physicians hear something about "80%" and "125%" and think that patients may have their levels go up and down by a quarter; in reality those numbers refer to 90% confidence intervals, and the most a given generic preparation could vary from the brand, while still remaining within those limits, is about 5 to 8% (1).

This has been inadequate to assuage the fears of many physicians, who aver that their practices are full of previously well epilepsy patients who "fell off the seizure-free wagon" (or the side-effect wagon) with no identifiable cause except that recent switch at the pharmacy. The only evidentiary basis to support these concerns has been a couple of studies showing increased healthcare utilization among users of generic lamotrigine and topiramate relative to the branded preparations (2, 3).

Labiner and colleagues have now entered this fray with a study that is similar in concept to the aforementioned, but considerably larger and involving five different AEDs instead of just one. The drugs chosen—phenytoin (PHT), carbamazepine, primidone, gabapentin, and zonisamide—were those for which over 100 users of brand and generic preparations for

Epilepsy Currents, Vol. 11, No. 2 (March/April) 2011 pp. 54–55

epilepsy could be identified in a huge managed-care database over a period of nearly seven years. Costs analyzed included outpatient and ER visits, outpatient pharmacy, and inpatient costs, with a number of covariates accounted for in the analyses. Healthcare costs were considered epilepsy-related if a seizure or epilepsy diagnosis was coded. Patients were subclassified into stable (≤2 outpatient visits for epilepsy in the previous year), and unstable.

The bottom line—use of a generic AED was associated with a significant increase in healthcare costs, both for drugs and for total utilization. This was true for both stable and unstable patients, and for both epilepsy-related and all-cause healthcare use. The incidence of injuries (e.g., fracture, head injury), both total and epilepsy-related, was higher during periods of generic use. Furthermore, time-to-event analyses revealed that the fraction of patients requiring healthcare was consistently and significantly greater with generic use than with brand formulations.

These results are quite convincing, as far as they go. The problem is that pharmacoepidemiology—the population study of drug effects—is made exceptionally complicated by the fact that prescriptions are not chance events: they are conscious decisions made with the input of both physicians and patients. Thus, the limitations of study design and large-scale analysis that apply to all epidemiologic investigation are compounded by the need to analyze deliberate choices, which introduces additional potential biases.

The authors themselves posit two explanations for their findings. The first is that dose fluctuations as a result of generic AEDs cause patients to have instability in health states, since AEDs are a low-therapeutic-index drug class. With respect to this explanation—since it was clearly the primary hypothesis—the choice to study phenytoin was a curious one, since this is a drug of such pharmacokinetic oddity that not even the stoutest defender of generics would deny the need for a consistent formulation. In fact, since it is well known that changes of even 5 to 7% in phenytoin bioavailability can cause large changes in drug level, one would expect that any problems pertaining to the use of generic AEDs would be greatly exacerbated among PHT users. It is not clear that this was the case here; the authors mention in a single sentence that their results were similar when phenytoin was excluded (despite the fact that this comprises fully half their data) but do not present the numbers.

The second proposed explanation is a "nocebo" effect; that is, that patients, knowingly exposed to a preparation with an inferior reputation, might be more inclined to seek additional healthcare. This is certainly a real possibility, to which I might add a third: the potential for confounding, with an additional variable being responsible for both the increased use of generics and the additional use of healthcare resources. Perhaps those of lower socioeconomic status, or less stability in employment, or worse overall health, are more likely to need more drugs (and need them to be cheaper), have more discontinuity in their care (with more switching), take worse care of their health, or have less insurance coverage for branded preparations. The fact that the data may have been similar with or without PHT actually adds to the suspicion that there could be some systematic confound, for the reasons mentioned above.

Fundamentally, then, these data are indirect, and as such must be contraposed with other indirect evidence suggesting that generics are unlikely to be problematic. One such piece of data is Kwan and Brodie's finding that the vast majority of patients who become seizure-free do so at very low AED doses (4), implying that the perception of epilepsy treatment as a tricky "knife's edge" balancing act may be wholly overblown, and that small changes in drug dose are very unlikely to make a real difference. Another important piece of data with a very similar implication is the finding of Pennell et al. that pregnant women on lamotrigine were unlikely to have a seizure recurrence unless the level dropped by more than 35% (5).

In the final assessment, the findings of this large study are consistent with those of other studies using a similar design. So, we should now instead employ different study designs to corroborate—or refute—these findings. Until that time we should all be mindful of the socioeconomic implications of badmouthing generic drugs: in our current system, they are effectively the only price check we have on the cost of medications, and as a consequence, they are also the only impetus we have to impel pharmaceutical companies to engage in continued innovation in this space.

by Scott Mintzer, MD

References

1. Bialer M, Midha KK. Generic products of antiepileptic drugs: A perspective on bioequivalence and interchangeability. *Epilepsia* 2010;51:941–950.
2. Duh MS, Andermann F, Paradis PE, Weiner J, Manjunath R, Crémieux PY. The economic consequences of generic substitution for antiepileptic drugs in a public payer setting: The case of lamotrigine. *Dis Manag* 2007;10:216–225.
3. Duh MS, Paradis PE, Latremouille-Viau D, Greenberg PE, Lee SP, Durkin MB, Wan GJ, Rupnow MFT, LeLorier J. The risks and costs of multiple-generic substitution of topiramate. *Neurology* 2009;72:2122–2129.
4. Kwan P, Brodie MJ. Effectiveness of first antiepileptic drug. *Epilepsia*. 2001;42:1255–1260.
5. Pennell PB, Peng L, Newport DJ, Ritchie JC, Koganti A, Holley DK, Newman M, Stowe ZN. Lamotrigine in pregnancy: Clearance, therapeutic drug monitoring, and seizure frequency. *Neurology* 2008;70:2130–2136.