IDENTIFYING TREATMENT CHANGES ASSOCIATED WITH REMISSION IN REFRACTORY EPILEPSY

Based on a poster presented by French JA,* Anand K,† Hauser WA,‡ Callaghan BC§

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This study was designed to assess remission rates in a cohort of refractory adult epilepsy patients. The cohort was identified from a retrospective review of 3224 charts at the University of Pennsylvania Epilepsy Center. During the evaluation period (2000–2003), 246 patients were identified as drug refractory (ie, were having at least 1 seizure per month and had failed at least 2 antiepileptic drugs [AEDs] at the index date [first visit in 2000]). The remission rate in this cohort was 15.5% over 3 years [or 5% per year] and all of these patients remained seizure free at the end of the observation period. Remission was defined as being seizure free for at least the last 6 months of observation.

Chart review also provided an opportunity to look for predictors of remission. Regarding types of epilepsy syndromes in this cohort, 80.5% were localization-related seizures, 11% symptomatic generalized, 6.9% idiopathic generalized, and 1.6% other syndromes. Remission rates based on these classifications were 16.7% localization-related, 0% symptomatic generalized, and 29.4% idiopathic generalized. Negative predictors of remission included a history of status epilepticus, mental retardation, and Lennox-Gastaut syndrome. Factors unrelated to remission rate were duration of epilepsy, age of onset, and number of AEDs failed. There was a nonsignificant trend toward idiopathic generalized seizures as a positive predictor of remission.

In fact, another aspect of the study [designed to show whether any medication [additions or changes] may be associated with remission] showed that, on average, 1.3 AEDs were tried per person and 1.1 AEDs were stopped during observation. Overall, 11% became seizure free with a change in AED therapy, 0.4% with no change in therapy, and 4.5% with surgery. Therefore, seizure freedom is not always directly attributable to recent interventions. In fact, surgery was the most effective intervention: over 50% of the patients that underwent surgery became seizure free.1

These results are consistent with remission rates found in children and suggest that larger, prospective studies would provide insight into predictors of remission.

REFERENCE


IDENTIFYING BARRIERS TO PREVENTION AND DIAGNOSIS OF BONE LOSS IN EPILEPSY

Based on a poster presented by Elliott JO,* Darby JM,† Jacobson MP*†

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Many neurologists are unaware of the increased risk of osteoporosis with antiepileptic drug (AED) use
and, if they are aware, are not sure how to treat it. Therefore, prevention of osteoporosis is practiced even less frequently.

This study was a retrospective chart review of 101 consecutive adult patients seen at an inner-city neurology clinic in Philadelphia, Pennsylvania, during the first 4 months of 2004. Patients' charts were reviewed to determine the barriers to the clinic's strategies for prevention and diagnosis of bone loss.

The most common barriers to prevention of osteoporosis were compliance, cost, and forgetfulness (in descending order). For example, of 87 patients prescribed supplements, 47 took a multivitamin and 34 took calcium supplements when both supplements were prescribed. Cost was a barrier because the cost of over-the-counter medications and supplements can be prohibitive for patients with low incomes. Some patients also had difficulty remembering to take the supplements. Other minor barriers to preventive measures included discontinuation of the prescribed supplements by the primary care physician (PCP), trouble with swallowing pills, refusal to take supplements, and a belief that taking a multivitamin increases appetite.

Dual x-ray absorptiometry (DXA) scans are recommended by this clinic based on the number of years of AED exposure. For this cohort, the average length of AED exposure was 21 years. DXA scan was recommended for 47 of 101 subjects. Of these 47 patients, only 28 (60%) actually obtained the DXA scan (17 females, 11 males). Of these 28 patients, 72% (n = 20) had abnormal results. Some of the reasons for failure to have the DXA scan included neurological/cognitive impairment including mental retardation (ie, the patients were unable to understand how to obtain or the importance of having the DXA scan); physical impairment that prevented travel to the scanning facility or having the scan performed, including cerebral palsy, spasticity, and obesity; and pregnancy. Even if the DXA is performed, there are barriers to diagnosis, such as the PCP's failure to follow up with the neurologist, results not being sent by the PCP, and loss to follow-up at the clinic. The greatest challenge to screening was clearly related to managed care; 75% of subjects belonged to HMOs requiring referrals for DXA scans. This process is time consuming and may act as a significant disincentive to effective screening. For example, patients with private insurance are able to have a DXA scan as a "walk-in" at the clinic.

There are many reasons why patients may not take the initiative necessary to maintain their own good health, and many theories have been put forth to explain this lack of initiative. Patients may have logistical issues (eg, low income or limited transportation) or psychological issues, such as underappreciating the severity of the disorder, their susceptibility to the disorder (especially because osteoporosis is an invisible disease), or not being ready to adopt a lifestyle change. Therefore, successful programs of prevention and detection require an understanding by the physician of the patient's health behavior and motives. The clinician knows best each patient's profile and can adapt message delivery accordingly. More concretely, regarding bone loss with AED use, patients can be educated about the price difference between supplements from health food stores and large discount retail stores, the different formulations of supplements (eg, liquid or chewable), and nutritional value and sources of calcium with dietary handouts. For some patients, obtaining the necessary nutritional components through diet may offer the highest chances of success, as this reduces the "medicalization" of osteoporosis prevention. Sadly, optimal nutrition is not always achieved in this fast-food world.

REFERENCE


A SURVEY OF THERAPEUTIC EQUIVALENCE OF GENERIC ANTIEPILEPTIC DRUGS

Based on a poster presented by Wilner AN
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As cost considerations play an increasingly larger role in medical practice, the push toward using generic drugs is growing stronger. Recent reports in the literature suggest that the therapeutic equivalence of generic antiepileptic drugs (AEDs) may not be suf-
Sufficient to use them in every case. Yet, surveys are showing that many physicians in the United States and Canada are unaware of the frequency with which their prescriptions are switched for the generic counterparts. The US Food and Drug Administration (FDA) defines bioequivalence as 80% or greater and 125% or less average maximum plasma concentrations of the branded drug.

This survey was designed to assess the effects of generic substitution of AEDs on patients with epilepsy. The questionnaire was mailed to 6420 American neurologists in July 2003. The response rate was approximately 5% (n = 301). The 13-question survey covered several areas of generic versus brand drug use during the past year, such as frequency of breakthrough seizures and increased side effects, and increases in resource utilization as a result of switching to generic drugs, in addition to attitudes regarding pharmacy authority to switch to generic drugs and FDA definitions of bioequivalence for AEDs. Demographic questions on size of epilepsy practice, type of patient insurance, and area of country were also included.

Regarding a switch from brand name to generic drugs, 68% of respondents reported breakthrough seizures and 56% reported increased side effects in their patients. Regarding a switch between generic AEDs, the figures were 33% and 27%, respectively. Addressing these effects with generic drugs resulted in extra phone consultations (n = 188), office visits (n = 166), emergency room visits (n = 128), reports of missed work by the patient (n = 77), and hospital admissions (n = 46). Importantly, these adverse consequences also led to patient injury (n = 23), and 25 neurologists reported that the physician-patient relationship was undermined.

Physician response to address these consequences included adding “dispense as written” on the script (n = 167), changing the prescription to a formulation that is not easily substituted to generic (n = 88), asking the patient to request the same brand of generic at each refill (n = 60), and monitoring blood levels (n = 17). A total of 21 neurologists indicated that they would institute no change.

Most respondents did not agree with the FDA’s definition of bioequivalence and even more (90%) disapproved of generic substitutions of AEDs by pharmacists.

These results strongly suggest that generic substitution of AEDs leads to suboptimal care with very important consequences for the patient’s life (injury, missed work), use of medical resources, and the physician-patient relationship, in addition to the less quantifiable effects on patient self-esteem, frustration, and fear from poorly controlled epilepsy. Further scientific studies on therapeutic equivalence of generic AEDs are clearly needed. Until these studies are completed, AED therapy should not be determined on the basis of acquisition cost alone because other factors clearly influence cost effectiveness. The primary treatment goal for epilepsy is seizure control, and treatment choice depends on the individual patient’s clinical profile.

REFERENCES

INTERIM RESULTS OF A MULTINATIONAL PREGNANCY REGISTRY OF LAMOTRIGINE USERS
Based on a poster presented by Messenheimer JA,* Tennis P‡ Cunningham MC‡
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As part of the continued international efforts toward comprehensive pregnancy registries of antiepileptic drug (AED) users, this registry, sponsored...
by GlaxoSmithKline, is focused on pregnancies exposed to lamotrigine. It is a worldwide observational study launched in 1992. Pregnancies are defined as prospective if they are registered before any information about the outcome of the pregnancy is known. Information on retrospective cases is also captured but is not used in risk analyses. The definition and classification of major congenital malformations are based on criteria from the US Centers for Disease Control and Prevention. Each reported malformation is reviewed by a pediatrician, and the methods and conclusions are reviewed by an independent scientific committee every 6 months. Recruitment is voluntary and is submitted through healthcare providers (e.g., obstetricians, neurologists, and primary care providers).

As of March 2004, 785 prospectively registered cases were finalized with known outcomes, 53% of whom were exposed to lamotrigine monotherapy in the first trimester of pregnancy. Based on those monotherapy cases (n = 414), the malformation risk was 2.9%, which is similar to the range reported in the general population (2%–3%) and less than the estimated risk in women with epilepsy exposed to AED monotherapy (3.3%–4.5%). These are interim results, thus final conclusions cannot be made; however, they do not signal an elevated frequency of major malformations among women exposed to lamotrigine monotherapy during pregnancy. With 80% power, the current sample size is sufficient to detect a 1.79- to 2.00-fold increase in the overall risk of major malformations, assuming the background risk is 2% to 3%. The malformations observed to date (n = 12) include esophageal malformation repaired by surgery, cleft soft palate, 2 club feet, hydronephrosis with megaureter, anencephalic fetus, congenital atresia of anus with recto-cutaneous fistula, 3 ventricular septal defects (one minor), fetal hydroyphrosis/oligohydramnios/intrauterine growth, and absent right kidney.

Of note, the risk of malformation rose to 12.5% in those patients exposed to lamotrigine plus valproate polytherapy versus 2.7% with polytherapy without valproate. This increased risk may or may not be related to valproate alone. The data on use of lamotrigine in polytherapy are insufficient to assess whether the risk of malformation associated with other agents is affected by concomitant lamotrigine use. The registry is not powered to determine the relative contributions of each drug or to accurately calculate risk of specific malformations or patterns of malformations based on AED.

As with the other registries reported in this monograph, continued inclusion of prospective cases will provide a more accurate analysis of risk with exposure to lamotrigine therapy during pregnancy. Exposed pregnancies can be reported to the registry at 1-800-336-2176.

**REFERENCES**


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**THE RELATIONSHIP BETWEEN ESTRADIOL AND PROGESTERONE SERUM LEVELS AND CATAMENIAL EPILEPSY**

*Based on a poster presented by Klein P Mid-Atlantic Epilepsy and Sleep Center, Bethesda, Maryland*

Catamenial epilepsy (i.e., increased seizure frequency related to the menstrual cycle) can be difficult to diagnose. Three distinct patterns have been described: perimenstrual, periovulatory, and luteal.

Catamenial epilepsy affects approximately 33% of women with epilepsy, and diagnosis can be made through careful assessment of menstrual and seizure diaries (i.e., seizure type and duration). The most obvious possible cause or contributor to catamenial epilepsy would be progesterone and/or estrogens given the changes in serum concentrations throughout the menstrual cycle. In fact, studies have shown that estrogen and progesterone have opposing effects on seizure threshold (i.e., proconvulsant and anticonvulsant, respectively). The changes in hormone serum levels are even more pronounced during pregnancy, increasing 20-fold compared to peak mid-menstrual...
cycle levels and 200-fold compared to follicular-stage levels. Within 24 to 48 hours postpartum, those levels drop 200-fold to early follicular levels.

This study of 6 pregnant women evaluated the change in serum estradiol and progesterone levels and seizure rate during 3 stages: early pregnancy (months 1 and 2), late pregnancy (months 8 and 9), and postpartum (first 2 months after birth). Serum levels were measured at each month of gestation and during the first 2 months postpartum. Seizures were tracked through patient diaries.

The diaries indicated a total of 29 seizures during months 1, 2, 8, and 9 of pregnancy and each postpartum month. Seizure frequency was highest during months 1 and 2 (n = 13) and least frequent during months 8 and 9 (n = 6). Serum estradiol levels were 437 pg/mL, 11 957 pg/mL, and 35 pg/mL and serum progesterone levels were 28 ng/mL, 158 ng/mL, and -1 ng/mL during each stage of the study.

Statistical analyses indicated no correlation between seizure frequency and serum estradiol levels or between the estradiol/progesterone serum level ratios. However, there was a trend toward an inverse association between serum progesterone levels and seizure frequency.

The results are somewhat surprising given that the changing levels of sex hormones are one of the clearest physiologic markers of pregnancy. As with catamenial epilepsy, the relationship between seizure frequency and changes in sex hormones may be complicated, involving many factors beyond those 2 hormones.

REFERENCES