Dr William R. Garnett is Professor of Pharmacy and Neurology at the Virginia Commonwealth University/Medical College of Virginia in Richmond. He has more than 25 years of experience in epilepsy research including the evaluation of new antiepileptic drugs (AEDs), new formulations of AEDs, drug-drug interactions and side effects with AEDs, the pharmacoeconomics of epilepsy care, and quality of life in patients with epilepsy.

A senior clinical editor for Advanced Studies in Pharmacy (ASiP) interviewed Dr Garnett about the challenges faced by practicing pharmacists in treating patients with epilepsy and the dilemma of whether or when to switch to generic formulations of AEDs.

ASiP: What do you think would help community pharmacists feel more comfortable with patients with epilepsy?

Dr Garnett: The community pharmacy setting is certainly a big opportunity for interacting with patients, and there are community pharmacists who have gotten involved with patient counseling and monitoring. Epilepsy, quite frankly, has not been a disorder that has been as “popular” with pharmacists. They are more likely to monitor cholesterol or blood sugar in patients with diabetes, or work with asthma patients, in their pharmacies.

I think there is a misunderstanding of epilepsy that permeates healthcare providers, and that includes physicians, nurses, and pharmacists. I think people are afraid of it, to some extent. When somebody has a seizure it is pretty dramatic. And, while epilepsy does not indicate that someone is mentally retarded, there is a significantly higher instance of epilepsy in the mentally retarded population. So, perhaps some of these patients just may not be as attractive as a person with diabetes.

A pharmacist in a community-based practice, in my opinion, clearly has an opportunity to educate patients/parents. Because a community pharmacy is a less stressful environment than a clinic or the hospital, the patient can ask his/her questions and have them answered. We have considered the idea of having a certified advanced training program for epilepsy, as there is for diabetes educators. Epilepsy is such a multifaceted disorder; it is not just one disease. Pharmacists are answering patients’ questions, but with preparation and training, there is more they can do. It is important for community pharmacists to realize their potential role and then provide them with the background and the tools to consult with patients.

ASiP: From a pharmacist’s perspective, what are the main issues for an individual with epilepsy? What do you consider when you see certain groups of patients with epilepsy, such as women, children, the elderly, or people with comorbid disorders?

Dr Garnett: There are some issues that extend to all of the special populations. First, is the patient seizure-free, not just “well controlled”? I will see patients who say they are “well controlled”—they tell me they are only having 1 seizure a month. That is not well controlled. They still cannot drive, and they are still, perhaps, underemployed or unemployed because of [the seizures]. They often need a caregiver. And the longer the patient has epilepsy and the more seizures he/she has, the harder it is to control. There are some patients with, perhaps, multiple brain insults, who may never be completely seizure-free, and there may be a population that is genetical-
ly refractory to the current medications, but the goal should be for the patient to be completely seizure-free.

The second question should be, are they tolerating the current dose of their medication? There are people who may be seizure-free, but they cannot wake up in the morning. Perhaps they are overly sedated on a medication or they have gained a significant amount of weight and are no longer healthy or feeling good about themselves. A patient can be seizure-free but have intolerable side effects. So, there is a balance between the benefit (being seizure-free) and the risk (the side effects).

Next, I think about compliance. In general, drugs that can be taken once and twice daily lead to better compliance, which, due to fewer missed doses, leads to better seizure control. The data are pretty clear that once- and twice-daily dosing is pretty comparable. With dosing 3 or 4 times a day, compliance (or adherence) drops off. Joyce Cramer found that for once-or twice-daily dosing, compliance was 87% and 81%, respectively. For 3 times a day it was roughly 75%, and for 4 times a day it was about 40%. The missed doses cause fluctuation in serum drug concentrations, which leads to fluctuation in response. So for any patient, I am thinking about seizure frequency, seizure control, adverse events, and compliance. I also think about drug interactions, and the potential for an interaction.

Then, after all of those questions are answered, I start to individualize treatment to special groups. We are concerned about the effect of AEDs on women who would like to have a family, and any time a woman is taking a medication, there is certainly the potential for teratogenic effects. Probably 95% of women who use AEDs can deliver a normal, healthy baby. We are hearing a lot more about the teratogenicity of AEDs, but there are a lot of unknowns with teratogenic reporting because it occurs in very few people. Phenytoin has an incidence of major congenital malformations around 4%. Valproate and carbamazepine are both associated with spina bifida at rates of about 1%. However, the 1% incidence was reported before the recommendations to give pregnant women on AEDs large doses of folic acid. The assumption has been that folic acid is required as the neural tube develops, and that a folic acid deficiency leads to spina bifida and other neurological complications of AEDs. The problem is I do not know if folic acid is truly preventative. It is recommended that a pregnant female [with epilepsy] take, not just 1 mg that you would give to an otherwise healthy female, but 5 mg, which was not tested clinically; it was determined by consensus. There are no prospective data to show that 5 mg actually reduces the rate [of teratogenic effects].

All of the second-generation drugs, starting with felbamate (at least in animal models) seem to have less of a teratogenic potential. They have a different US Food and Drug Administration [FDA] pregnancy rating than the first-generation drugs, but we also have very limited patient exposure. To put that in perspective, it was 25 years before the reported incidence of spina bifida with valproate was realized. It was not a situation in which the drug went on the market and people knew immediately that there was a 1% incidence of spina bifida with it. Major congenital malformations occur in 1 out of 1000, or 1 out of 10 000 births, so you have got to give the drug to a lot of people before you actually see a trend. Even normal women will occasionally have a baby with major congenital malformations, so you have to measure the teratogenicity rates against the rate in the general population. Women with epilepsy have a higher rate [of major malformations] anyway, and if the patient has seizures during the pregnancy, that can lead to teratogenic effects as well. The valproate story is still emerging, and it shows that a drug needs to be on the market for a while before we can get a feel for its teratogenic potential. The pregnancy registry in the United States has been collecting data on AED use and teratogenic effects. Patients can enroll by calling 1-888-233-2334 or online at http://www.aedpregnancyregistry.org/.

The best thing you can do for a woman who has epilepsy is to make her seizure-free. If she has been seizure-free for an appropriate amount of time—and this would be on an individual case basis—and wishes to become pregnant, possibly take her off the drug, or give AEDs in the lowest dose possible, and most likely increased doses in the third trimester because the kinetics change.

There are some AEDs that induce the metabolism and clearance of birth control pills making the birth control pills less effective, and therefore, creating the potential for breakthrough pregnancies. So women need to be cautioned about that. Drugs like carbamazepine, oxcarbazepine, topiramate, phenytoin, and phenobarbital do that. On the other hand, there may also be a problem with decreased fertility. Some AEDs are associated with a decreased incidence of fertility and libido.
There is concern about whether enzyme-inducing drugs lower vitamin D. That has been a greater problem with phenytoin. Carbamazepine and phenobarbital are also enzyme inducers, but there is not quite as much data showing osteoporosis. Women taking AEDs ought to have calcium supplementation. The amount of calcium is probably not different from that recommended for otherwise healthy women, and bone density indices should also be done on women taking AEDs.

There are some specific issues with the elderly. They have altered pharmacokinetics, in general. They tend to eliminate drugs more slowly than younger patients, because either their kidneys or liver do not work as well. It also appears that the elderly may respond to lower levels of drug or there may be differences in the receptor sites, implying a pharmacodynamic change that is hard to quantify. The elderly also often take multiple medications, making drug interactions more likely.

Very importantly, epilepsy is misdiagnosed and underdiagnosed in the elderly. The elderly, as a group, are probably more sensitive to the label of epilepsy and may be more likely to harbor some of the myths and misconceptions about epilepsy. There are some who associate epilepsy with demonic possession. Also, their response to seizures may be different. They may have a longer postictal state and the clinical presentation may be different. They also have the problems of falls associated either with drug side effects or the seizures.

Pediatric populations, like the elderly, have different pharmacokinetic profiles from adults. Also, the formulation becomes as important as the particular drug. AEDs come in different formulations: liquid, suspension, sprinkles, dispersible tablets (ie, chewable), and extended-release. Both children and the elderly may require a particular formulation for optimal compliance. Children are also sometimes not able to report their own seizures.

One of the emerging trends right now is looking at comorbid disorders, such as migraine or bipolar disorder. Is it possible to treat those conditions with one drug? People with epilepsy have comorbid disorders. They tend to have anxiety, depression, and like everybody else, they will have other diseases. When there are other disorders, there are most likely other medications, which set up the potential for drug-drug interactions, either through synergistic activity or through enzyme induction and enzyme inhibition. Epilepsy is complex, requiring multilayered considerations. It is not like treating hypertension.

**AS/P: Why is phenytoin still being used?**

*Dr Garnett:* Phenytoin is the number one prescribed AED in this country, not necessarily because anybody thinks it is the best drug, other than for status epilepticus. When a patient goes to the emergency room for a seizure, they are often started on a hydantoin (phenytoin/fosphenytoin) and continued on phenytoin after discharge. Or, they see their primary care physician [PCP] with a history of tonic-clonic seizures and the PCP starts them on phenytoin. Epileptologists probably do not favor long-term phenytoin, but they are not always the ones to initiate therapy for new-onset seizures.

As we move up in degree of specialization, the physician may be more inclined to switch the patient to a different drug. For example, a general neurologist may see a patient 3 or 4 days after he/she has been in the emergency room. Now the patient is on a maintenance dose of phenytoin; to add another drug, and to taper one up and taper phenytoin down is a risk. Some physicians will do it and some will not. An epileptologist, who sees only epilepsy patients, is probably going to be more likely to switch AEDs. But, if a patient is on phenytoin and doing well, there is the old adage, “If it ain’t broke, you don’t fix it.”

**AS/P: If a patient has found a drug that makes him/her seizure-free, but he/she is having some of the adverse effects with AEDs (eg, somnolence, significant weight gain), how does the pharmacist counsel or work with the patient to deal with those effects?**

*Dr Garnett:* The first question I ask is whether it is an idiopathic reaction or if it is a concentration-dependent effect. If someone is taking immediate-release carbamazepine but complains of sleepiness in the morning, maybe it is because he/she is having high peaks [elevated blood concentration], and if you convert him/her over to a sustained-release formulation.
that delivers lower peaks and higher troughs, that may maintain seizure control and reduce the side effects. There is a trend in all branches of medicine to develop extended-release formulations of drugs because once- or twice-daily dosing improves compliance and extended-release formulations give lower peaks and higher troughs. There is less fluctuation, less chance of toxicity, less chance of breakthrough seizures.

Unfortunately, a patient may say “I can’t tolerate this medicine because I’m sleepy” and the general practitioner may choose to switch drugs. Sometimes physicians are too quick to stop the drug, or look for something else, when a dosing adjustment might be the answer.

The healthcare provider also has to determine if the side effects are concentration-dependent. If the provider knows that the patient is going to have breakthrough seizures if their dose is reduced, the provider may have to reduce the dose and add a second drug to avoid the seizure while addressing side effects. Central nervous system effects (drowsiness, vertigo, sedation) tend to be concentration-dependent; rashes tend to be idiopathic. If somebody develops a rash on carbamazepine or lamotrigine, the provider is not going to lower the dose and see if their Stevens-Johnson reaction gets better.

**ASiP:** What are the current issues with generic forms of drugs and how do pharmacists feel about these formulations?

*Dr Garnett:* I think the bigger question is how do the HMOs [health maintenance organizations] and third-party payers feel about them. Clearly, third-party payers, including the federal government, are pushing for generic drugs. Mark McClelland [Press Secretary for the President of the United States] has said that changing to generic drugs is part of the Medicaid Medication Management Program. Personally, I think that patients taking drugs with very narrow therapeutic indices should be on one brand and stay with it. If a patient is started on a particular brand of generic drug, he/she can be titrated to the desired response and can stay on that generic drug. The problem is that there is no guarantee that a patient can stay on one generic because of large-group purchasing. The purchaser may be buying different brands of generic drugs each month. If I could guarantee that someone could start on generic phenytoin, as an example, and I knew that they could stay on that one brand of generic, I have no problem recommending that.

When a generic drug is approved, it is compared against the innovator (the brand name). The generic drug does not have to test itself against any other generic drug. If Drug A (generic) is tested against Drug B (innovator) and has 85% bioavailability, it is FDA approved. Drug C (generic) is tested against Drug B and it has 120% bioavailability, so it also is “equal to” Drug B. So A is equal to B, and B is equal to C, but A is not equal to C. And for the most part, nobody knows how bioavailable the generic drugs are. It is not “sexy” to publish a study that shows Generic Drug A is equal to Innovator Drug B. If their bioavailability did not meet FDA standards, the drug will not be on the market. A manufacturer will not want to publish those data showing that the drug is not comparable to innovator. The manufacturer may test several formulations until they find one that meets the FDA criteria (ie, the 80/125 rule). These are the data that will be submitted to the FDA.

If I know it is 87% versus 115% bioavailability [generic versus innovator], I can make dosing adjustments, but we do not have that information. The FDA says that generics are all therapeutically equivalent. We do not know the variability in drug manufacturing. Does that affect bioavailability? There are no lot-to-lot comparisons. So, we do not have the scientific data to say whether there is a problem at all or, if it is a problem, how much? We do not have comparative bioavailability data for the innovator, either.

Carbamazepine immediate-release has the most data. There are cases in the literature in which patients have been switched between generic formulations and had either breakthrough seizures or increased toxicity. The FDA position has always been that it was an outpatient study, so compliance is not known. That is a valid point, but the issue comes down to that formulations on the market met, at least for that one study, the 80/125 rule, but we do not know if it is between 80% and 100% or between 100% and 125% bioavailability.

**ASiP:** What do you do as a pharmacist? Do you recommend generics? Are you forced to recommend generics?

*Dr Garnett:* Our hospital has been somewhat unique in that we still do not use generic AEDs. We do for many other drugs. My opinion is that patients who use drugs with narrow therapeutic indices should not be switching brands. These include warfarin, AEDs, digoxin, and per-
haps some of the antiarrhythmics. With some other drugs, it probably does not matter if you get 20% or 50% more or less bioavailability.

I am not sure if the HMOs factor all of the costs into their decisions. When a patient is being switched to a generic, it requires more monitoring including more frequent blood level testing, which costs money and therefore negates some of the economic benefits of the generic drug. We just completed a study with generic carbamazepine and showed that although the acquisition costs were less with the generic as compared with the brand-name drug, the overall healthcare costs were more. As long as we follow an approach to healthcare delivery where “I don’t care what your budget does as long as I meet the demands on my budget,” this will remain a problem.

My great hope when the managed care focus emerged was that finally somebody would be looking at the total package, and they would be able to see that medications can reduce overall costs. Yes, medications can be expensive, but if a drug keeps a patient out of the emergency room, keeps them productive and employed, it is worth the cost of that drug. But, we are still silo-based. To me, drugs are very cost effective, if they are appropriately used. Inappropriately used, they obviously are not cost effective. That is where the pharmacist has a role to play—to ensure that they are used appropriately.

**AS/P:** Are there any situations where you feel an improvement could be made in the relationship of pharmacists to physicians and patients?

**Dr Garnett:** I think the pharmacist has a lot of information to offer to prescribers and to patients. Sometimes because they are busy, as in community pharmacies, pharmacists perhaps do not have as much time to counsel patients as they should. Part of the new Medicaid Therapeutic Drug Benefit Bill, in addition to funding drug coverage, will be funding for case management, and pharmacists are one of the professions that would be eligible for reimbursement for managing patients’ drugs. That is in the process of being implemented.

I think pharmacists could be better used in all settings because they have information. With each rounding team in hospital, there should be a clinical pharmacist who sees patients as well. The pharmacist is the member of the healthcare team that has the most educational background in pharmacology, pharmacokinetics, and drug interactions.

Pharmacists also are better able to deal with issues regarding patient compliance and adherence. It is changing a bit, but I think there has always been a paternalistic approach by physicians toward patient compliance. Physicians may tend to think that all they have to do is tell patients to do something and they will do it, and that is very clearly not true. Patients need education. I compare patient education with pharmacokinetics. Patients need a loading dose when they are first diagnosed or first taking the drug, and then they need maintenance educational processes, continuously.

**REFERENCES**