FROM CLINICAL TRIALS TO CLINICAL PRACTICE:
TRANSLATING EPILEPSY RESEARCH INTO PATIENT CARE

Interview with Jacqueline A. French, MD

Dr Jacqueline A. French is a Professor in the Department of Neurology at the University of Pennsylvania. She is the co-director of the Penn Epilepsy Center and director of clinical drug trials. Dr French trained in neurology at Mount Sinai Hospital in New York, and did her fellowship training in EEG and epilepsy at Mount Sinai Hospital and Yale University.

Dr French has focused her research efforts on new antiepileptic drug development. She has written many articles, editorials, and chapters and has edited 2 books on this subject, and is the co-director of a biannual symposium on trial design and its implications. She has been active in creating practice parameters, serving on committees of the American Academy of Neurology and the American Epilepsy Society, and chairing several practice parameter task forces. She chairs 2 American Epilepsy Society task forces on antiepileptic drugs, one on creation of guidelines, and the other on implementation of multicenter trials. She has served as an ad hoc reviewer for many journals, is an editor for Epileptic Disorders, and is the Epilepsy Section Editor of Clinical Neuropharmacology. She currently serves on the board of the American Society of Experimental Therapeutics, and is chair of its web committee.

A senior clinical editor for Advanced Studies in Medicine (ASiM) interviewed Dr French to discuss how trial results can be applied to the daily management of patients with new-onset epilepsy and the considerations when starting a patient on antiepileptic drugs.

ASiM: When you examine a clinical trial in new-onset epilepsy, how relevant are the results to your daily clinical practice?

Dr French: I think that trials of this nature are very important and relevant in telling us how new antiepileptic drugs (AEDs) are going to behave in individuals with newly diagnosed epilepsy. A lot of the clinical trials that are performed when a drug is in development are performed in patients with refractory partial epilepsy. These patients usually have an average of 10 seizures a month, which is not typical for patients that are seen in most physicians' offices. Having some information regarding how the drug behaves in patients who are somewhat less ill is therefore very important and relevant. At the same time, however, it is equally important to look at the details of any specific trial and see how relevant that particular trial is to the individual patient a physician is treating.

ASiM: When you are treating a patient with new-onset epilepsy, do you use clinical trial data to guide treatment decisions?

Dr French: Absolutely. I look at trial results when I am thinking about a given patient, not only to determine whether the drug is effective in this specific population but also whether to expect side effects and in considering the average dose used in individuals in those trials.

In the trial by Dr Privitera, patients were randomized to 2 specific doses, thus physicians could not tell from that trial what the more useful dose would be. It seems that 100 mg of topiramate and 200 mg of topiramate are relatively equivalent in efficacy when compared with 600 mg of carbamazepine; however, I do not know that it was the most useful or the best tolerated dose.
AS/M: In your opinion, are clinical trials, such as the trial conducted by Dr Privitera, necessary to carry out before we can start using a new AED?

Dr French: That is a difficult, and somewhat of a 2-sided question. I think that if a physician has some clinical experience with a drug and if there are reasons to think that the drug will be useful, it is reasonable to try it in specific populations. Let me give you an example in which a physician may use a medication before he/she has absolutely definitive evidence that the drug will be effective. There is a great deal of evidence that lamotrigine is a very safe drug in pregnancy and that lamotrigine does not appear to increase the amount of teratogenicity or the amount of birth defects compared with the population not taking AEDs. Therefore, it is certainly reasonable to use lamotrigine early in patients with newly diagnosed epilepsy if a physician is aware that they are planning a pregnancy.

In this case we do have good data from randomized trials for the use of lamotrigine in newly diagnosed patients, but its safety in pregnancy may have led to earlier adoption of the drug, even in the absence of this strong trial data.

Another example may be topiramate. The trial by Dr Privitera included patients that had partial or generalized tonic-clonic convulsions. It was the physician’s choice whether the patient should be randomized to topiramate versus carbamazepine if the physician thought the patient had partial epilepsy, or topiramate versus valproate if the physician thought the patient had idiopathic generalized epilepsy. As a result, there are some data on idiopathic generalized epilepsy included in this trial. However, it is probably not sufficient to tell us with absolute certainty that topiramate is an effective drug for primary generalized epilepsy. This makes topiramate no different from all of the other newer AEDs because there really are no good data for any of the new drugs in primary generalized epilepsy compared to partial epilepsy. Because the choices are very narrow among the older drugs that are effective in this condition and because there are no good data for any of the drugs, I would tend to say that it is very reasonable to use the newer AEDs in primary generalized epilepsy. Although we do not have as much data, we can base our treatment decisions on the experience that we have had with these drugs and on the fact that many of the older drugs are not effective, thus the choices for this syndrome are quite limited.

AS/M: When you are selecting therapy for a patient with new-onset epilepsy, to what extent do you rely on clinical trial data as opposed to your own clinical experience and that of your colleagues?

Dr French: As I mentioned, most of the trial data during drug development come from patients with refractory epilepsy. The concern here is that refractory patients may respond preferentially to drugs that may not be as effective in patients with newly diagnosed epilepsy who may have a different underlying pathophysiology. Therefore, it certainly seems reasonable to conduct separate AED trials in patients with newly diagnosed epilepsy, and it seems reasonable to continually add to our knowledge base. However, physicians cannot go from there to saying that under no circumstances would they use a drug in newly diagnosed patients before there was trial evidence for its use in this population. I do think that we can feel a greater comfort level when that trial has been done, and has shown that the drug is equal in effectiveness to the standards.

AS/M: When you examine the results of a clinical trial in newly diagnosed epilepsy, what aspects of trial design and what outcomes measures are most important to you?

Dr French: For newly diagnosed patients, the best type of data that can be obtained in a randomized trial would probably be when a drug is compared with placebo, because physicians can clearly see a definitive effect that is over and above a placebo effect. However, I think everybody can recognize that conducting placebo-controlled trials in patients with active epilepsy is not appropriate in most circumstances, thus physicians have to look at other types of trials. One type of trial that has been performed is called an active control equivalence trial, during which a drug is compared with the drug that the individual may have gotten if the new drugs did not exist (for the most part, this would be carbamazepine). For example, an investigator may compare topiramate versus carbamazepine or lamotrigine versus carbamazepine. Based on these trials, the newer drug can be shown to be as effective as the drug the physician would have chosen if the new drug had not existed. However, there is always the small possibility that the study population does not respond to either drug. If this were to be the case, the active control equivalence trial would show no difference between the 2 treatments, just as if both treatments worked.
However, we all tend to think that the drugs that were used in these trials (ie, carbamazepine and, in the case of topiramate, valproate) are effective drugs in newly diagnosed populations, and certainly there are a lot of data to support this. Therefore, the absence of a difference between these 2 agents is reasonably good proof of efficacy, as long as the study has enough patients in it to demonstrate a difference, if a difference did exist. Obviously, if you enrolled 10 patients in a study and showed no difference between groups, that could occur just by statistical chance. Most of the clinical trials in newly diagnosed epilepsy are powered with a large enough number of patients that a physician has a certain comfort level with the results.

The second question is: What should the outcome measure be? One important outcome measure is to look at how many patients remain seizure-free and over what period of time. However, there may be some difficulties in directly comparing 2 drugs that are used differently. For example, carbamazepine can be titrated relatively rapidly compared with some of the newer agents. As a result, it would not be surprising to think that more seizure breakthroughs may occur with the comparator agent during the early phases of the study when the patients are still being titrated. This could happen with topiramate, lamotrigine, or any slowly titrated medication. Therefore, it seems reasonable to wait until patients are on an established therapeutic dose of medication before starting a comparison.

Another outcomes measure is the number of patients who discontinued drug therapy because of intolerable side effects or idiosyncratic reactions, such as rash. In this case, rather than looking at efficacy (which is just a pure “seizures or no seizures” type of outcome), these studies examine therapeutic effectiveness in terms of how many patients were able to remain on the drug and remain seizure-free on the drug. It is reasonable to think that if a drug is not tolerated, there is no way that it can render somebody seizure-free.

However, physicians do have to be somewhat careful looking at outcomes, such as effectiveness. If large numbers of patients drop out early in the trial, it may be difficult to ensure that the drug that is well tolerated is equally as effective as the drug that is poorly tolerated, once there are unequal dropout numbers. Therefore, I like to look at both of those outcomes. I like to look at pure efficacy in terms of how many patients will remain seizure-free and effectiveness, which is a combination of seizure freedom and tolerability.

**AS/M:** If you were to design a clinical trial that would provide you with the most relevant and the most useful clinical information, how would this differ from the trial designs that have been mandated by the US Food and Drug Administration (FDA)?

**Dr French:** The trials that we have been discussing, which are active control equivalence trials, are not acceptable to the US regulatory authorities as proof of usefulness of AEDs in the newly diagnosed population. The FDA has required that the drugs demonstrate a difference between themselves and whatever their comparator may be. For example, if you conducted a placebo-controlled trial, there would be a difference between the new drug and the placebo comparator. When you do an equivalence trial, all you can say is that there is no difference in the outcome between the 2 drugs. We accept this result as showing that the new drug was equally as effective as the standard. But there is a small concern (which is apparently a big concern to the FDA) that this result may mean that neither drug was effective.

This concern has led to a small number of drugs gaining approval based on short placebo-controlled trials in which patients were randomized to the active new drug versus placebo. Obviously, there are ethical considerations with keeping people with active epilepsy in a placebo-controlled situation for long time periods. As a result, these are very short trials. Once the patient has a predetermined number of seizures they are considered a failure and exit the trial. For example, one of these studies was performed over 10 days.

I have several concerns regarding these trials. Ten days may be too short a time period to examine newly diagnosed epilepsy, especially when individuals usually remain on therapy for years. Ten days may be too short to demonstrate the effectiveness of a drug. The only information a physician can learn from this type of trial is that the new drug is better than nothing. From a clinical perspective, knowing that a drug is better than nothing is not enough. At the very least, if investigators do a placebo-controlled trial, they need another arm, which would be an arm of the standard effective therapy. This would show whether the drug is not only better than nothing but as good as the other drugs that you could be providing. Otherwise, I think we only have half of the answer.

I do hope that eventually the US regulatory authorities will regard active control equivalence trials as a high
standard of evidence, as long as these are adequately powered and performed in a proper manner. Interestingly, the European regulatory authorities not only accept information from active control equivalence trials, but actually require this information for a drug to gain approval in the newly diagnosed population. They think that it is important to show that the study drug provides the same amount of usefulness and efficacy as the other drugs that have already been approved for use.

ASiM: If you were to design the ideal clinical trial in newly diagnosed patients, how would you go about doing this?

Dr French: As I mentioned earlier in this interview, the ideal trial in newly diagnosed patients should be adequately powered to be able to show a difference between treatment arms if a difference exists. As compared with active control equivalence trials, trials of this nature are called noninferiority trials because they are powered to show that new drugs are not inferior to the standard drug by any more than a predetermined margin. I much prefer trials in which physicians in both arms are allowed, in a blinded fashion, to titrate patients’ medication to the dose that is appropriate for them and does not produce toxicity. I think that this allows the physician to really see the usefulness of a drug under conditions similar to clinical practice. Investigators also have to be very careful regarding the titration schedules to make sure that patients are not titrating too quickly in one arm compared with another arm (eg, investigators should look at a number of outcome variables).

In the future, one method that I think would be very useful is to not only look at the seizure outcomes but to look at the overall long-term health of the individual. We know that some of the older drugs (eg, carbamazepine) have effects on homeostasis in the body that go beyond the standard side effects that we usually think about, such as ataxia and fatigue. As a hepatic enzyme inducer, carbamazepine may alter the metabolism of intrinsic compounds in the body, leading to changes in hormone, cholesterol and vitamin levels, thyroid function, and bone metabolism. The trials conducted in newly diagnosed epilepsy are some of our longer trials and can often follow patients for 1 year or more. It would be useful to know over the course of the year how these other measures are changing, and what the tradeoffs are of using one medication versus another.

ASiM: Therefore, if you could design your perfect trial, it would last a couple of years?

Dr French: Yes; the longer the better.

ASiM: Moving away from trials and into the clinic, when you are selecting an AED for a patient who is newly diagnosed with epilepsy, what factors are most important to consider?

Dr French: Recent studies, such as the study by Kwan and Brodie, demonstrate that patients with newly diagnosed epilepsy are extremely sensitive to drug effect. Most patients (approximately 60%) will not only respond to the first drug that they are placed on, but will also respond to reasonably low doses of that drug. For these patients, it does not really matter which AED is selected because they will respond to any medication. This is obviously very good, but it also means that the burden is on the physician to choose a medication that is going to be very safe and well tolerated. Knowing that most newly diagnosed patients who I see will respond to medication, I want to choose a drug that will give them an optimal quality of life. This is particularly important when you consider that it is likely that they will stay on the first drug they are placed on for many years.

ASiM: What are some of the most formidable challenges that you as a clinician face when caring for a patient with new-onset epilepsy?

Dr French: Patients who have just been diagnosed with epilepsy are often in a state of shock, and their whole world has been turned upside down. Often, they were previously healthy, and suddenly they have become a patient or a person with a chronic illness, which takes a lot of counseling and discussion.

When selecting therapy for that person, the physician has to be thinking not only about what is going to happen in the next 6 months or 1 year but what is going to happen to that person over the next several years of his/her life. The physician has to consider how the therapy that he/she chooses is going to impact those next several years. An example of this would be the woman who has just gotten engaged. The physician needs to think ahead and realize that over the next several years she may be contemplating having a child. The selection of AED right now has to be made with the understanding that she may go through a pregnancy on that medication.
Similarly, if the physician is caring for an elderly individual with epilepsy, even someone who is otherwise very healthy, the physician needs to plan into the future when selecting an AED. Over the course of the next several years, the patient may develop high blood pressure, high cholesterol, or other medical problems that will require treatment. Choosing an AED now that is not going to interfere with these other therapies will greatly simplify the patient’s care in the future.

When selecting an AED, we need to think about the long-term implications of that choice. Although many patients with newly diagnosed epilepsy will only be on the drug for 1 or 2 years and may be able to discontinue the medication altogether, many people elect to remain on AED treatment indefinitely. The impact of the seizures that they experienced before they were placed on medication is profound and, even when patients remain seizure-free for a number of years, we cannot guarantee that they will not have a recurrent seizure once the medication is withdrawn.

AS/M: With the introduction of so many new AEDs over the past 10 years, what has the impact been on the treatment of patients with new-onset epilepsy?

Dr French: Well, that is a multipart question. I would say that the choices that were available 15 years ago, before the newer drugs were introduced, were definitely inadequate. This is especially true for certain patient groups, such as women of childbearing age, the elderly, people with concurrent medical conditions, and patients with idiopathic generalized epilepsy. The availability of a larger choice of medications, in addition to drugs that do not alter liver metabolism and that tend to be well tolerated, has been a great boon for individuals with newly diagnosed epilepsy. Unfortunately, however, we are not necessarily taking advantage of these new choices as well as we should. The older drugs are still more commonly prescribed for patients who are diagnosed with epilepsy, and there has been a very slow uptake of the newer drugs in general use. Certainly, in epilepsy centers and in many physicians’ practices, the newer drugs have been accepted more readily, but there are large pockets where the older AEDs, phenytoin in particular, are still the drugs of choice. I think that we have to get the word out that the newer medications can have a very profound impact. They need to be included among the armamentarium that physicians consider as they select therapy for newly diagnosed patients.

AS/M: In your opinion, why have physicians been reluctant to use the newer AEDs?

Dr French: One of the main reasons is that only one of the newer drugs to date has been specifically approved for use in the newly diagnosed population. Many physicians are not comfortable prescribing a drug that has not been FDA approved for an indication.

In addition, with this very large increase in the number of available AEDs over a very short period of time, physicians may not be as familiar with the newer drugs, and they may have some questions and concerns about how to use them. Also, because these AEDs do not have an FDA indication for new-onset epilepsy, the Physicians’ Desk Reference (and other references) may only list the new AEDs as add-on treatment options in refractory epilepsy.

AS/M: With so many AEDs now available, how do you help your patients make an informed decision when selecting a medication that is best for them?

Dr French: When a patient comes in with newly diagnosed epilepsy, we usually have a reasonably long discussion and I get to know who the patient is and what he/she is anticipating his/her life to be over the next several years. And often, knowing the specific epilepsy type, the patient’s circumstances, and past medical history, the AED selection will come down to maybe 2 or 3 optimal choices. Among those choices, I discuss the pros and cons and the potential side effects of the different drugs with the patient, and we will decide together what the most optimal treatment may be as the initial choice. I tell the patient that if there are problems with this initial medication, we have other options and we can always switch to another drug.

AS/M: Given the paucity of available data, how can practitioners make informed treatment decisions to optimize patient outcome?

Dr French: The American Academy of Neurology and the American Epilepsy Society recently published a report on the efficacy and tolerability of newer AEDs. I think that these guidelines are somewhat helpful in terms of letting physicians know the data. The guidelines specifically identify 4 drugs for which there is good evidence from active control equivalence trials to support their use in newly diagnosed epilepsy. These 4 medications are gabapentin, lamotrigine, topiramate, and oxcarbazepine (only oxcarbazepine is FDA approved for use as monotherapy in newly diag-
nosed epilepsy). Physicians should avail themselves of the guidelines, in addition to several other review materials that have addressed this issue.

**ASiM:** In your opinion, are the potential benefits of newer AEDs worth the increased cost? Are they worth the risk we take as a result of the fact that these drugs have not been around for as long as the older medications?

**Dr French:** I would say that the older drugs are certainly still appropriate for a large number of individuals, but there are many individuals where the cost-benefit analysis may be more complex than just the price of one drug versus the price of another drug. For example, almost all of the older AEDs are hepatic enzyme inducers, which means that the metabolism of many commonly prescribed medications is substantially increased, sometimes doubled, by the presence of carbamazepine, phenytoin, or phenobarbital. If a patient is taking a lipid-lowering agent that is metabolized by these hepatic enzymes, the dose of the lipid-lowering medication may have to be doubled to compensate for this rapid metabolism. However, these lipid-lowering medications tend to be more expensive than the newer AEDs, particularly in the low AED doses that are typically required for newly diagnosed patients. Therefore, you may actually be more than doubling the cost of healthcare for an individual by selecting the cheaper carbamazepine or phenytoin compared with one of the newer agents, such as topiramate, gabapentin, lamotrigine, or levetiracetam, which do not induce hepatic metabolism.

You also have to think about the cost of serum drug levels and other routine monitoring tests. For example, carbamazepine reduces the white blood cell count—not to a dangerous level, but most patients on the medication do require routine blood counts and liver function tests. I mentioned earlier in this interview that carbamazepine may affect the results of thyroid function tests. Although carbamazepine likely does not actually alter thyroid function, physicians may erroneously look at these thyroid function tests, become concerned, and order more tests. Thus, there are other costs associated with the older AEDs, in addition to just the cost of the pill. I am not saying, by any means, that all patients should be started on newer drugs, but physicians have to look at the long-term impact of one drug versus another drug—economically and in terms of quality of life.

The long-term impact of AEDs is somewhat of a philosophical discussion of the devil that you know versus the devil that you do not know. It is very difficult to say that the newer drugs cannot possibly have long-term consequences of which we are not yet aware. At the same time, certainly with the drugs that were introduced in the early ’90s, we do have a large amount of experience with more than 100 000 patients treated—in some cases, more than 1 000 000 patients treated. We are getting to a certain comfort level that these drugs are not going to produce unexpected adverse events.

**REFERENCES**