

Of Doctors and Data

In recommending treatments, neurologists must combine the best available evidence with their clinical judgment. What does this mean for you? BY TOM VALEO

Imagine a woman with epilepsy, who has managed to remain seizure free by taking the anti-seizure medication valproate, is thinking about starting a family.

In doing Internet research to prepare for an appointment with her neurologist, the woman has learned that pregnancy could cause the level of valproate to drop. As a result, she would need to take more to maintain the same protection. However, some of the articles she has found online claim valproate can cause birth defects, while others say the danger is overblown.

Should she ask to be switched to another drug or a combination of drugs? Keep taking the same dose of valproate and risk having a seizure? Ask for the valproate to be increased slightly and hope the drug won't cause birth defects?

The woman feels overwhelmed by questions and by the articles she has found online. Even if she could understand them all perfectly, how would she decide which studies provide the strongest evidence, especially since some of them contradict each other?

Neurologists are trained to evaluate evidence. When an individual neurologist applies the best available evidence in mak-

What made evidence-based medicine feasible was the development of **computer search engines**.

ing decisions about treatment, she is practicing what is called “evidence-based medicine.” A neurologist may even consult evidence-based *guidelines*, which are developed by neurologists who immerse themselves in the medical literature and determine what they believe are the best treatment choices based on the best available evidence.

EVALUATING EVIDENCE

The American Academy of Neurology (AAN), like many medical societies, creates committees of experts to comb the medical literature for all relevant studies about a particular type of treatment. Committee members read all the studies, assess the quality of each, and make treatment recommendations supported by the strongest evidence.

Let’s return to the woman with epilepsy who wants to get pregnant. Her neurologist could refer to guidelines recently developed by a committee that recommended not giving valproate and combinations of anti-seizure medication to pregnant women during their first trimester, because such drugs could increase the risk of birth defects.

Some babies born to women who took valproate during pregnancy were found to have up to a 10-point decrease in verbal IQ, according to studies the committee members considered reliable. Valproate has also been linked to an increased risk of spinal bi-

rida, cleft palate, and other disorders.

“Valproate is a great drug that works wonderfully for epilepsy, but it has specific risks for women with childbearing potential,” says Cynthia Harden, M.D., director of the International Comprehensive Epilepsy Center at the University of Miami’s Miller School of Medicine, and a member of the AAN committee that made the recommendations.

“If babies are born with birth defects, it’s devastating, so I hope neurologists will have very careful and thoughtful conversations with their patients about these risks. Sometimes we can’t find a reasonable alternative to valproate—a truly safe dose is not known at this time—but very often we can achieve success by changing to other medications.”

The committee also recommended monitoring the level of anti-seizure medication in a pregnant woman’s bloodstream to keep the dose at a moderate but effective level.

By discussing the woman’s options and weighing the risks and benefits of a course of action—given the available evidence and factors unique to her—the neurologist is practicing evidence-based medicine. (See box, “What to Ask Your Neurologist.”)

THE POWER OF SEARCH

Neurologic treatments constantly evolve as knowledge about the brain increases. The best treatment yesterday may be

What to Ask Your Neurologist

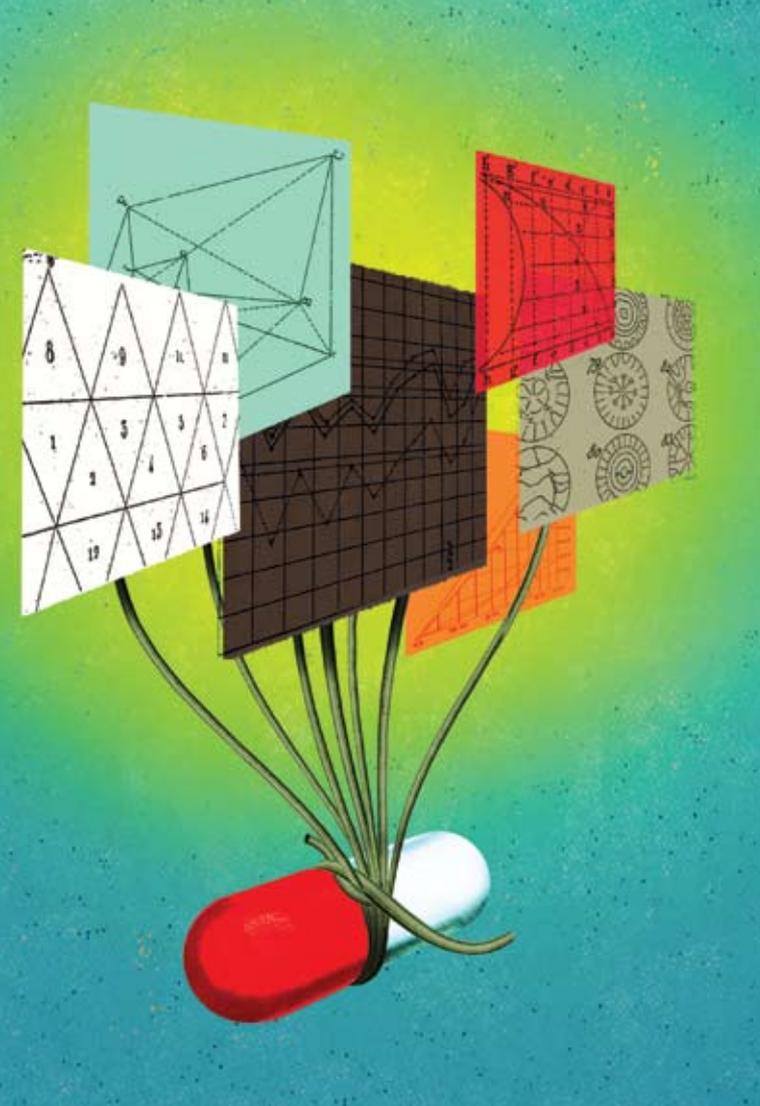
When your neurologist suggests a treatment, you might want to ask a few questions to find out about the evidence that supports it.

- ▶ Why are you recommending this treatment for me?
- ▶ How extensively has this treatment been studied?
- ▶ Has this treatment been studied in people like me (for example, in terms of sex, race, age, and other illnesses)?
- ▶ Is there evidence for this treatment?
- ▶ What is the kind and quality of that evidence?
- ▶ What does the evidence say about the risks and possible side effects?
- ▶ Has the treatment been studied by a physician committee and incorporated into an evidence-based guideline? If so, what does the guideline recommend?

Ideally, the evidence should be based on large studies that include lots of people with the same problem you confront. When appropriate, the studies should be “blinded,” which means neither the researchers nor the participants know who is receiving the actual treatment and who is receiving a placebo—as well as “randomized,” which means that participants are assigned randomly (in a sense, by coin toss) to receive either the treatment or a placebo. The effects of the treatment should be clearly measured and not left to interpretation by the researchers. If more than one study produces similar results, the treatment recommendation are considered even more reliable.

However, the fact that no study exists proving that a particular treatment works is not proof that the treatment is useless, according to Gary Gronseth, M.D., a neurologist at the University of Kansas who wrote a manual on evidence assessment for the AAN. This is one reason why doctors can’t rely on current, external evidence alone.

For more on how to evaluate evidence, including a summary of the different types of clinical trials, read “Proof and Consequences,” March/April 2009, on our Web site at bit.ly/NNProof.



replaced by a better alternative tomorrow. Keeping up with the best choices poses an ongoing challenge for neurologists.

“That’s the major role of evidence-based medicine—to identify what we know and what we don’t know, and to determine where we have to use our judgment,” says Gary Gronseth, M.D., vice chairman of neurology at the University of Kansas Medical Center in Kansas City and a Fellow of the American Academy of Neurology. Since the mid-1990s, Dr. Gronseth has helped the AAN create evidence-based guidelines.

Before the rise of evidence-based medicine, first mentioned in the *Journal of the American Medical Association* in 1992, neurologists often practiced what Dr. Gronseth calls “eminence-based medicine.” In other words, they adopted the practices recommended by the most respected experts, combined with their own clinical judgment.

“If your professor said, ‘This is what you do,’ then that’s often what you did,” Dr. Gronseth says. “Even today if you ask a physician, ‘Why do you do it that way?’ they often say, ‘Where I trained, that’s what my professors did.’ We’re trying to get beyond that.”

Computers helped advance evidence-based medicine. The development of computer search engines has enabled physicians to find, quickly and easily, every study ever done on a particular topic.

“Before, we would have to spend weeks sifting through Index Medicus [an index of medical research papers published by the National Library of Medicine] trying to find a few articles dealing

with a particular topic,” says Michael Benatar, M.B.Ch.B., M.S., D.Phil., associate professor of neurology and epidemiology at Emory University in Atlanta, GA. “It was almost impossible to find all the available literature. Now you can look at everything relatively easily, synthesize a lot of information, and apply it to clinical judgments,” Dr. Benatar says.

NOT WRITTEN IN STONE

Some physicians remain concerned about how evidence-based medicine is applied. In a speech to the AAN in 2009, Louis Caplan, M.D., a stroke specialist at Beth Israel Deaconess Medical Center in Boston, MA, criticized over-reliance on evidence gathered from randomized trials of patients with general conditions. In the speech, Dr. Caplan argued that the best treatment must consider factors unique to the patient, such as other illnesses, risk factors, socio-economic status, family dynamics, and the person’s values.

Dr. Caplan embraces the importance of evidence and acknowledges that evidence-based guidelines can be an enormous help to emergency room physicians, family practitioners, and others who may not be experts in certain disorders. “A lot of strokes, for example, are handled by emergency room personnel, and having guidelines can help,” Dr. Caplan says.

However, he says, “The details of a case are not always captured by such guidelines.”

For example, the stroke treatment guidelines from the American Heart Association (AHA) originally said that what is called a “thrombolytic agent”—a drug for dissolving a blood clot blocking an artery in a stroke victim—must be administered within three hours.

“They picked three hours because that was the amount of time used in the trial,” observes Dr. Caplan. “They didn’t study patients after three hours, so they don’t know if the thrombolytics would help them.”

A recent article in the medical journal *Stroke* reported on a survey in which 93 percent of stroke specialists said they give intravenous thrombolytics more than three hours after the onset of stroke. Based on new evidence, the AHA guidelines expanded the window to four-and-a-half hours. Evidence-based medicine does not produce recommendations that are written in stone but remain flexible and open to new information.

THYMECTOMY FOR MYASTHENIA GRAVIS

The tension between evidence- and eminence-based medicine—and the determination of researchers to resolve that tension—is perhaps nowhere more clear than in the controversy over whether neurologists should recommend thymectomy for myasthenia gravis.

Good doctors use both individual clinical expertise and the best available external evidence.

Myasthenia gravis (MG) is an autoimmune disease in which a person's own antibodies attack receptors on muscle cells that receive signals from the brain.

For people with MG, neurologists often prescribe steroids, which help suppress autoimmune attacks, as well as thymectomy—a time-honored treatment that involves the removal of the thymus gland located just below the throat.

Neurologists believe that thymectomy works because the antibodies that attack the receptors on muscle cells are produced in the thymus gland. So removing the thymus should help reduce the attacks.

That sounds logical, and some anecdotal evidence suggests that thymectomy works. In 1939 a surgeon named Alfred Blalock removed a tumor from the thymus of a young woman suffering from MG, and the disease went into remission. About half of subsequent MG patients who received a thymectomy also improved, so the surgery became the standard treatment for MG.

According to the principles of evidence-based medicine, neurologists should be able to point to trials demonstrating that MG patients who receive thymectomy do better than those who receive only steroids.

However, no such clinical trials have ever been done. Thymectomy became the standard treatment *based on the premise* that it *should* help, and anecdotal evidence suggests it *does* help, but no one has ever tested it rigorously. The situation was complicated in the 1970s when steroids such as prednisone proved very effective at suppressing the inflammation caused by autoimmune disorders, including MG. After that it became difficult to determine what was helping MG patients: thymectomy, steroids, or both.

In 2000 Gary Gronseth, M.D., and Richard Barohn, M.D., wrote a report for the AAN that found serious flaws in all the studies published about thymectomy. They called for a clinical trial to settle the question, but dividing MG patients into two groups and denying thymectomy to patients in one of the groups was considered unethical by many doctors who believed thymectomy was an effective treatment. Also, since thymectomy leaves a surgical scar, it would be obvious which patients had not received the surgery, and this knowledge might cause bias—for example, pro-thymectomy physicians might tend to perceive greater improvement in MG patients who received the surgery.

In an elegant solution, a trial sponsored by the National Institute of Neurological Diseases and Stroke (NINDS) has divided patients into two groups. One group is receiving thymectomy and steroids, the other is receiving prednisone only. The study will try to determine if those who have surgery can get by with a lower dose of prednisone than those who received the steroid alone. If so, the surgery apparently contributes to the improve-

ment; if not, the surgery contributes little if anything.

The only problem has been finding patients to include in the study. Patients have to relinquish their right to choose whether they receive surgery or not and accept assignment into one of the two groups—surgery plus prednisone, or prednisone only. Some physicians who still believe that thymectomy helps may have been reluctant to enroll their patients, knowing they might end up in the prednisone-only group.

But physicians are coming around. Enrollment recently passed 100—the two-thirds mark—and an extension of funding from NINDS will enable recruitment to continue through late 2010.

“We are trying to answer a longstanding question in the treatment of MG with this trial, using evidence-based medicine,” says one of the investigators, Gil I. Wolfe, M.D., of the University of Texas Southwestern Medical School.

THE ART AND SCIENCE OF NEUROLOGY

Douglas J. Lanska, M.D., a staff neurologist at the VA Medical Center in Tomah, WI, has been a member of the AAN's Quality Standard's Subcommittee, which generates evidence-based guidelines for the AAN. He believes that guidelines are meant to be used in two ways: to help individual patients and to expand overall knowledge.

“One approach is microscopic and focused on the patient,” Dr. Lanska says. “The other is telescopic—it views huge areas of knowledge but produces a coarser image that overlooks the details of individual patients. The evidence-based medicine approach is supposed to combine the best available scientific evidence with the expertise of the physician, who must consider the unique characteristics of each patient.”

Even ardent supporters of evidence-based medicine recognize that applying guidelines to a specific case is a bit like translating poetry from one language to another: While a word-by-word substitution may be possible, such a literal translation will almost certainly lose some of the subtle meaning and music.

In 1996 commenting on “Evidence-based medicine: What it is and what it isn't,” the *British Medical Journal* summarized the tension this way: “Good doctors use both individual clinical expertise and the best available external evidence, and neither alone is enough. ... Evidence-based medicine is not ‘cookbook’ medicine.”

Dr. Gronseth recognizes the tremendous advantages as well as the limitations of evidence-based medicine.

“The evidence is never sufficient,” Dr. Gronseth says. “Evidence is just one tool a physician uses. You always have to rely on basic principles of medicine and neurology that you've learned, and you always have to rely on your judgment.” NN