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personal health

Chance Find Puts End to Hot Flashes

By Jane Brody

A widely used drug that has been mired in controversy for most of its decadelong life may now bring relief to postmenopausal women whose lives have been disrupted by unrelenting hot flashes. The relief may be especially welcome to women who have had breast cancer and cannot take estrogen.

The drug, best known by its trade name, Neurontin, but now prescribed generically as gabapentin, was approved by the Food and Drug Administration in 1994 to treat epileptic seizures. In 2002, it was approved to treat postherpetic neuralgia, horrific pain that sometimes follows shingles.

Aided by the Internet and, the government has said, an illegal marketing campaign by its parent company, Neurontin sales eventually exceeded \$2 billion a year before its patent expired and the generic gabapentin entered the market in 2004.

The parent company, WarnerLambert (since bought by Pfizer), was investigated after a whistle-blower said it had paid doctors to promote Neurontin to their colleagues for a host of additional symptoms not approved by the FDA. The whistle-blower also said the company had paid to have research articles prepared claiming benefits of a dubious nature.

As a result, Neurontin has been used for problems like migraines, social phobia, attentiondeficit disorder in children, gastric ulcers, restless leg syndrome, essential tremor, osteoarthritis, backache, insomnia, anxiety, bipolar disorder, panic attacks and withdrawal from cocaine and alcohol -- all known as off-label uses. Its most frequent off-label use is as an adjunct to drugs used to treat pain, especially pain thought to have nerve involvement.

Thus, gabapentin was part of the medication prescribed for my unrelenting pain after a double knee-replacement operation last year. It was prescribed again last fall when I developed debilitating back and leg pain caused by a pinched nerve in my back.

Between the two prescriptions, I made a discovery that changed my life for the better. While taking Neurontin three times a day for the knee pain, I had none of the hot flashes that had plagued me day and night after breast cancer in 1999 made me stop postmenopausal hormones. But when I weaned myself from gabapentin last May, the hot flashes returned, resulting in three sleepless nights in a row. I wondered whether it could be a factor and decided, with my doctor's approval, to try just one 300milligram capsule before bedtime. Voila! No hot flashes. No waking up damp and clammy and unable to go back to sleep.

I've stayed on the drug, and during the winter I was able to wear turtlenecks. I'm sleeping much better. On the dose that helps me -- 300 milligrams after breakfast and 300 or 600 milligrams at bedtime -- I've noticed no unusual effects beyond an ability to sleep comfortably for seven hours a night.

Last September, I found a report in The Lancet, the medical journal, by researchers from four medical centers who conducted a clinic trial using gabapentin to treat hot flashes in women with breast cancer. In the study, 420 women having two or more hot flashes a day were randomly assigned to take 300 or 900 milligrams of gabapentin or a lookalike placebo each day in three divided doses for eight weeks.

About one patient in five on the placebo reported a decline in hot flashes, while a third of those taking 300 milligrams of gabapentin did and nearly half of those on 900 milligrams reported a benefit.

The researchers, led by Dr. Kishan J. Pandya of the James P. Wilmot Cancer Center at the University of Rochester Medical Center, found that "only the higher dose of gabapentin was associated with significant decreases in hot flash frequency and severity." They recommended that the drug "be considered for treatment of

hot flashes in women with breast cancer."

Pandya undertook this study after Dr. Thomas J. Guttuso Jr., a neurologist then at the university's medical center, published findings in February 2003 in *Obstetrics & Gynecology*. Guttuso and his colleagues had randomly assigned 59 postmenopausal women who suffered from seven or more hot flashes a day to receive gabapentin or a placebo for 12 weeks.

Those who took 300 milligrams of gabapentin three times a day reported a 54 percent reduction in overall hot flash activity (frequency and severity) compared with a 31 percent drop in the placebo group.

In an interview, Guttuso, now at the Jacobs Neurological Institute at the University at Buffalo, discussed a soon-to-be-published study by Dr. Sireesha Y. Reddy and colleagues that pitted 2,400 milligrams of gabapentin daily against 0.625 milligram of estrogen, the gold standard for controlling hot flashes.

Participants suffered from moderate to severe hot flashes, defined as seven or more per day, accompanied by sweating. Gabapentin relieved hot flashes as effectively as estrogen, Guttuso said. Although about 40 percent of the women taking 2,400 milligrams of gabapentin daily reported side effects (sleepiness, dizziness and swelling of the feet), they felt that the benefit of the drug outweighed them, Guttuso said.

Gabapentin has other benefits. Guttuso, who has been studying it, said: "It does not interact with any other medications, which is very unique, so doctors don't have to worry about other drugs a patient might be taking. Also, gabapentin is not metabolized, so it has no effect on the liver. It's fully excreted in the urine." He said it works through a receptor on the membranes of brain and peripheral nerve cells.

Estrogen normally acts as a brake on cells in the brain's temperature-regulating center through pathways called calcium channels. Gabapentin binds to a channel.

Gabapentin was developed to help avoid the addictive quality of drugs called GABA analogues (Valium, Ativan and Xanax) used for anxiety and seizure disorders. The modified drug proved nonaddictive.

Properly designed clinical trials are needed to show just how helpful gabapentin is against various conditions and whether prolonged use may have unexpected adverse effects. At high doses, side effects like drowsiness, dizziness and weight gain from retained water can limit its usefulness.

Now that the drug is without patent protection, future FDA approvals will depend on studies by two companies. One, PharmaNova, has patented a sustained-release formulation of gabapentin and is studying its role in treating hot flashes. Meanwhile, Pfizer has introduced a chemical cousin of gabapentin, sold as Lyrica and approved for treating nerve pain caused by shingles and diabetes. It should control hot flashes, too.

Lyrica is being studied in patients with hot flashes under a licensing agreement with the University of Rochester, which has patented new uses of gabapentin and other drugs that use the same mechanism.

OTHER OPTIONS

Because gabapentin and Lyrica are already on the market, there is nothing to stop physicians from prescribing them for any use, including hot flashes.

But herbal and nutritional remedies like black cohosh and soy supplements have not withstood controlled clinical trials.

Here are some alternatives that may reduce the frequency and severity of hot flashes:

- Getting regular exercise.
- Avoiding highly spiced foods, large meals, hot drinks, caffeine and alcohol.
- Using stress-reduction techniques like yoga.
- Taking low doses of the antidepressants Effexor, Paxil or Prozac.
- Drinking lots of water.

- Wearing loose clothes (no turtlenecks) in easily removable layers.
- Sleeping in a cool room.

Jane Brody covers science and biology for The New York Times.
