

Key Points

1. Neurontin is one of the most widely prescribed drugs on the market with annual sales of over \$2 billion
2. Considered an anti-epilepsy drug (AED), is currently FDA approved for treating epilepsy and post-herpetic neuralgia
3. Widely prescribed 'off-label' for treating other types of pain and other disorders
4. Not approved as a pain treatment for children under 12
5. Rigorous studies have shown it offers some relief for some types of neuropathic pain
6. May be especially useful in helping allodynia
7. How it works is not known
8. Considered very safe with few medically serious side effects; very little of the drug is actually absorbed by the body
9. Some common side effects are sleepiness, dizziness, balance problems, numbness, skin problems
10. There is controversy around the alleged illegal promotion of Neurontin for off-label uses

Neurontin

- Manufactured by Pfizer, Inc.
- Generic name - gabapentin
- Formula is $C_9H_{17}NO_2$
- Formula is read as 1-(aminomethyl)cyclohexaneacetic acid
- Comes in capsules, tablets, and an oral slution in strengths of 100mg, 300mg, 400mg, 600mg, and 800mg
- Half-life (meaning how long before half the drug is eliminated from the body) is 5-7 hours
- Maximum recommended daily dose is 3600mg/day. Patients generally start at a low dose and increase the dosage over

Neurontin

Not many people are thrilled about taking medication on a daily basis, especially one with side effects. Yet for people suffering through daily, chronic pain the choices are limited. Is the relief worth the side effects? Will the drug even work? These are some of the issues that become part of daily living for many people.

The drug Neurontin - generically known as gabapentin - is one of the most widely prescribed drugs on the market. Bringing in more than \$2 billion in annual revenue for Pfizer, its manufacturer, it is a high-profile drug with a bit of a storied past. Originally designed - and approved - as an anti-epilepsy drug, it has since been FDA approved to treat post-herpetic neuralgia, a painful type of neuropathic pain that some people develop after having shingles. But with billions of dollars of sales, it is clear that Neurontin is being prescribed for more uses than just those two. In fact, a large portion of Neurontin sales are from what are known as off-label uses. Once a drug is approved by the FDA, doctors are allowed to prescribe the drug not only for the approved use, but for other uses for which they think the drug might be effective.

This is an important, and necessary, part of medicine. Many drug benefits were discovered by prescribing them off-label, including the heart related benefits of aspirin. Unfortunately, as will be discussed later, this is also where Neurontin's checkered past comes into play. Pfizer (actually Parke-Davis, a division of Warner-Lambert, which Pfizer acquired) is being accused of illegally marketing Neurontin and encouraging doctors to prescribe it off-label.

What Is Neurontin?

Neurontin was designed to look like a neurotransmitter known as GABA. GABA is an important neurotransmitter, and several types of drugs, including sedatives, work by affecting how GABA attaches to other chemicals at the molecular level. In addition, the role of GABA in spinal cord injuries is thought to be important and is being investigated by spinal cord injury researchers.

What is surprising is that no one knows how Neurontin works. No one can explain how it offers pain relief or acts as an anti-convulsant. Despite looking like GABA, it does not affect how GABA attaches - or binds - in the brain, it doesn't affect how GABA is processed, and it isn't converted into GABA by the body. In addition, gabapentin does not affect dopamine or serotonin, other common neurotransmitters. The substance was also tested to see if it would bind to many different types of sites at the molecular level, but it does not. In a study involving a rat brain, the drug was found to attach to certain areas, but the connection between those sites and how the drug might work is not clear. Adding to the mystery is the fact that gabapentin itself is barely absorbed by the human body and is fairly quickly eliminated through the kidneys and urine.

Does It Work?

Despite the unknowns, there is growing evidence that Neurontin does indeed offer some level of relief for some types of neuropathic pain. Setting aside the anti-epileptic effects of the drug, Pfizer's literature on Neurontin cites two randomized, double-blind, placebo controlled studies on the use of Neurontin for managing postherpetic neuralgia. The studies involved 563 patients who were experiencing pain at least 3 months after their bout with shingles. The patients were given either Neurontin or a placebo for a several week period (dosage was ramped up to 3600mg/day). Both studies showed a significant reduction in reported pain throughout the treatment for those receiving the drug. In fact, around 30% of the participants receiving the drug reported a 50% or greater improvement in their pain.

However, there are many types of pain, and is postherpetic neuralgia similar to SM pain? Fortunately, Neurontin has also been shown to help pain associated with spinal cord injuries. In a study published in 2003 (Spine 28(4):341-6), 31 patients with neuropathic pain due to spinal cord injury were given Neurontin over an 8 week period. The patients were divided into two groups based on whether they had been experiencing pain for less than or more than 6 months. Despite the fact that they tried other types of pain medicines to no avail, Neurontin did reduce the pain for both groups. On a scale of 0-10, the average pain score for the less than 6 month group dropped from 7.3 to 3 over the course of the treatment. While the other group also responded to the drug, the average score only dropped from 7.6 to 5. So while this study shows Neurontin can provide relief for SCI related pain, getting started early on the drug may be important.

Another study demonstrating the effects of Neurontin on a wide variety of neuropathic pain was published in the journal Pain in 2002 (Pain 99(3):557-66). This double-blind, randomized, placebo controlled study looked at over 300 people suffering from neuropathic pain due to a number of different causes. Over an 8-week period, the participants either received Neurontin or a placebo. The results showed a significant difference in the pain relief between the group receiving the drug and the placebo group.

Of special interest to the CMISM community is growing evidence which shows that Neurontin can reduce the brutal consequences of allodynia. This type of pain - feeling pain from things that shouldn't be painful - can be

time.

Definitions

allodynia - pain in response to something that should not cause pain, like a light touch

central nervous system - the brain and spinal cord

central pain - abnormal pain arising from damage to the central nervous system

chronic - long lasting, persistent

double blind - scientific technique used to eliminate bias in a study, where neither the study participant nor the experimenter (doctor) knows which of two treatments the participant is receiving

epilepsy - disorder of the nervous system in which abnormal electrical activity causes seizures

GABA - a neurotransmitter; thought to play a role in spinal cord injuries; some drugs work by affecting the transmission of GABA

narcotic - class of drugs derived from the opium plant - or created synthetically for the same effect; used as pain-killers

neuron - nerve cell

neuropathic - abnormal pain caused by damage to the nervous system

neurotransmitter - chemical that carries a message between neurons

opioid - narcotic

peripheral pain - pain arising from the outer - or peripheral - nervous system, the ends of the nerves

post-herpetic neuralgia - abnormal pain which results from nerve damage due to herpes zoster - also known as shingles

randomized - technique used in a scientific study where participants are randomly assigned to one of two groups; used to control the effects of age, gender, etc. on the study outcome

refractory - not responsive to treatment

retrospective study - scientific study which uses medical records

especially limiting and difficult to deal with. In well established rat models, gabapentin - along with other, similar drugs - has been shown to dramatically reduce allodynia. As more and more rigorous studies are published showing the beneficial effects of Neurontin, attention will likely turn to how it works. And once the exact mechanisms are understood, it should become clearer who the drug can benefit the most.

What About Side Effects?

A drug's effectiveness is only half the equation. In order to be useful, any side effects caused by the drug must be minor enough to be tolerated or the drug is essentially worthless. Narcotics are powerful pain relievers, but also have very strong side effects. In narcotic studies, it is not unusual for more than 20% of participants to drop out because of side effects. In addition, drug tolerance and addiction pose even bigger challenges to the effective use of a narcotics for pain relief. What are the side effects of Neurontin like, are they as bad as narcotics'?

In a postherpetic neuralgia study cited by Pfizer, the most common side effects of Neurontin were sleepiness, dizziness, numbness, and bruising. Twenty-eight percent of participants reported experiencing dizziness and 21% sleepiness. Because of this, more than 3% of participants experienced accidental injuries versus just 1% of the control group. In addition to the most common effects, there are a wide range of less common side effects which nonetheless did not occur in the placebo group. These range from dry mouth to rashes to blurred vision to stomach problems to cognitive impairment.

Similar side effects are listed in other published gabapentin studies but are usually characterized as mild to moderate. Overall, the drug is considered very safe with few and infrequent serious medical side effects. One reason for this is that the body metabolizes very little of the drug itself and the drug doesn't stay in the body for very long. Addiction to the drug has not been studied adequately to make a determination if it is a problem.

Anecdotally, people contacted by this publication with experience taking Neurontin present a mixed view. Most encountered some side effects with sleepiness and cognitive impairment being most prominent. Several people stopped taking the drug because of the side effects, but one person who stayed on it for awhile became used to the side effects and after a period of time was able to function normally.

Things To Be Aware Of

As with any drug, there are a number of precautions, or things to be aware of, when either taking or considering Neurontin:

- *Naproxen* - Studies show that when gabapentin is taken with Naproxen (the active ingredient in Alleve), the amount of gabapentin absorbed is 12%-15% higher than usual.
- *Morphine* - A study showed that morphine given 2 hours before gabapentin increased the absorption of gabapentin by 44%. The morphine absorption was not effected.
- *Antacids* - Maalox has been shown to inhibit the action of gabapentin. It is recommended that gabapentin be taken at least 2 hours after Maalox.
- *Oral Contraceptives* - Studies have shown that gabapentin does not interfere with the effectiveness of two common oral contraceptives.
- *Pregnancy* - Rat studies have shown that gabapentin is toxic to fetuses. Effects were seen at dosage levels of 1-4 times the daily maximum dose of 3600 mg/day. No effect was seen at 1/2 the daily dose level (for people). In addition, when rats were given the drug before and during mating, there were adverse effects at doses 1-5 times the daily human dose. There are no studies involving pregnant women.
- *Nursing* - Gabapentin is secreted into breast milk. The effects on a nursing baby are unknown.
- *Pediatric* - The drug is not FDA approved as a pain treatment for children under 12. In a study of children between the age of 3-12 (with epilepsy), behavioral problems were seen, including hostility, aggression, and other emotional problems
- *Dosage* - People with kidney problems may need to take a lower dose of the drug

Please note the above is not an inclusive list. More information about precautions can be found from the manufacturer or a doctor or pharmacist.

The Controversy

Despite it's apparent effectiveness, Neurontin is a controversial drug. The controversy stems from a highly publicized whistleblower lawsuit filed by a former employee, David Franklin, Ph.D.

Franklin - who has since been joined by the Justice Department - claims that Parke-Davis (later acquired by Pfizer in a merger with Warner Lambert) broke the law by marketing Neurontin for off-label uses. While such prescriptions are allowed, drug companies are not allowed to promote them.

Franklin was employed as a medical liaison, someone with scientific credentials who is supposed to answer doctor's medical and technical questions. Franklin claims that there was a company wide campaign to push

to look at events that occurred in the past

Sources

Pfizer, Inc. web site and drug literature

Serpell, MG. Gabapentin in neuropathic pain syndromes. Pain Oct, 2002 99(3): 557-66.

Ahn SH et.al. Gabapentin effect on neuropathic pain compared among patients with spinal cord injury and different duration of symptoms. Spine Feb, 15 2003 28(4): 341-6.

FDA web site

MSNBC web site, Dateline interview with David Franklin

Theo Emery (AP), Whistleblower's lawsuit could shake up the drug industry, 8/9/03

Neurontin for uses - such as treating bipolar disorder - for which there was no evidence that the drug worked. In addition, he claims that doctors were paid money to put their names on articles they didn't write, and were often flown to vacation-style getaway locations for 'education' sessions.

NBC's Dateline show conducted a year long investigation and aired an extensive interview with Franklin. Dateline was able to obtain internal Parke-Davis documents which they claim show a systematic push to promote Neurontin for off-label uses. During the interview, recorded voice messages were played that certainly seem incriminating. Franklin claims that the evidence shows that the company put sales ahead of good medicine.

Pfizer denies the claim and it should be pointed out that as a whistleblower, Franklin stands to gain financially from a successful lawsuit. Pfizer did not return a request to comment on any aspect of Neurontin, the controversy, or their new drug application.

The Bottom Line

Despite the controversy, Neurontin does appear to be effective in helping some people deal with neuropathic pain. The side effects are not severe from a medical perspective, but can still be too much from a patient's perspective. Like so many aspects of Daily Living for people with Chiari and syringomyelia, there are no easy answers when it comes to Neurontin. For some it may be a blessing, for some yet another waste of time, but for everyone, it is at least worth knowing about.

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