Gabapentin

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Gabapentin (brand name **Neurontin**) is a medication originally developed for the treatment of epilepsy. Currently, gabapentin is widely used to relieve pain, especially neuropathic pain.

Gabapentin was initially synthesized to mimic the chemical structure of the neurotransmitter gamma-aminobutyric acid (**GABA**), but is not believed to act on the same brain receptors. Its exact mechanism of action is unknown, but its therapeutic action on neuropathic pain is thought to involve voltage-gated N-type calcium ion channels. It is thought to bind to the α2δ subunit of the voltage-dependent calcium channel in the central nervous system.[2]

Contents

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[edit] Indications

A capsule of gabapentin

Bioavailability	Rapid, in part by saturable carrier-mediated L-amino acid transport system 60% for 0.9 g daily to 27% for 4.8 g daily dose Food increases absorption by 14%
Protein binding	Less than 3%
Metabolism	Not appreciably metabolized
Half life	5 to 7 hours
Excretion	Renal
Therapeutic considerations	
Pregnancy cat.	D(AU) D(US) Benefit of treatment may outweigh risk to fetus. Risk of teratogenicity greater if more than one drug used [1]
Legal status	POM(UK) ℞ Prescription only
Routes	Oral
PubChem	3446
DrugBank	APRD00015
Chemical data	
Formula	$C_9H_{17}NO_2$
Mol. mass	171.237 g/mol
Pharmacokinetic data	

Gabapentin was originally approved in the U.S. by the Food and Drug Administration (FDA) in 1994 for use as an adjunctive medication to control partial seizures (effective when added to other antiseizure drugs). In 2002, an indication was added for treating postherpetic neuralgia (neuropathic pain following shingles, other painful neuropathies, and nerve related pain).[3]

has been found to be effective in prevention of frequent migraine headaches,[4] neuropathic pain[5] and nystagmus,[6] and is prescribed off-label (that is, without formal regulatory agreement) for these conditions.

Gabapentin has also been used in the treatment of bipolar disorder. However, its off-label use for this purpose is increasingly controversial.[7] Some claim gabapentin acts as a mood stabilizer and has the advantage of having fewer side-effects than more conventional bipolar drugs such as lithium and valproic acid. Some small, non-controlled studies in the 1990s, most sponsored by gabapentin's manufacturer, suggested that gabapentin treatment for bipolar disorder may be promising.[7] However, more recently, several larger, controlled, and double-blind studies have found that gabapentin was no more effective (and in one study, slightly less effective) than placebo.[8] Despite this scientific evidence that gabapentin is not an optimal treatment for bipolar disorder, many psychiatrists continue to prescribe it for this purpose.

Gabapentin has limited usefulness in the treatment of anxiety disorders such as social anxiety disorder and obsessive-compulsive disorder, in treatment-resistant depression, and for insomnia.[9][10] Gabapentin may be effective in reducing pain and spasticity in multiple sclerosis.[7] Gabapentin has also had success in treating certain instances of Complex Regional Pain Syndrome.[11][12]

Gabapentin has also been found to help patients with post-operative chronic pain (usually caused by nerves that have been severed accidentally in an operation and when grown back, have reconnected incorrectly). Symptoms of this include a tingling sensation near or around the area where the operation was performed, sharp shooting pains, severe aches after much movement, constant 'low ache' all day and sometimes a general 'weak' feeling. These symptoms can appear many months after an operation, and therefore the condition can go unnoticed.[*citation needed*]

Gabapentin is also prescribed to patients being treated with anti-androgenic compounds to reduce the incidence and intensity of the accompanying hot flushes.[13]

Gabapentin (administered orally) is one of two medications (the other being flumazenil, which is administered intravenously) used in the expensive Prometa Treatment Protocol for methamphetamine, cocaine and alcohol addiction. Gabapentin is administered at a dosage of 1200 mg taken at bedtime for 40–60 days. Though the combination of flumazenil infusions and gabapentin tablets is a licensed treatment, there is no prohibition against a physician prescribing gabapentin outside the Prometa protocol. There have been reports by methamphetamine addicts that gabapentin alone in doses of 1200 mg at

bedtime taken for 40–60 days has been effective in reducing the withdrawal symptoms and almost eliminating cravings or desire to use methamphetamine.[14]

Gabapentin has occasionally been prescribed for treatment of idiopathic subjective tinnitus, but a double blind, randomized controlled trial found it ineffective.[15]

Gabapentin is also often used to treat nerve pain associated with spinal cord injury.[*citation needed*]

[edit] Adverse effects

Gabapentin's most common side effects in adult patients include dizziness, drowsiness, and peripheral edema (swelling of extremities)[16]; these mainly occur at higher doses, in the elderly. Also, children 3–12 years of age were observed to be susceptible to mild-to-moderate mood swings, hostility, concentration problems, and hyperactivity. Although rare, there are several cases of hepatotoxicity reported in the literature.[17] Gabapentin should be used carefully in patients with renal impairment due to possible accumulation and toxicity.[18][19]

An increase in formation of adenocarcinomas was observed in rats during preclinical trials, however the clinical significance of these results remains undetermined. Gabapentin is also known to induce pancreatic acinar cell carcinomas in rats through an unknown mechanism, perhaps by stimulation of DNA synthesis; these tumors did not affect the lifespan of the rats and did not metastasize. [20]

[edit] Recreational use

Though gabapentin is not a controlled substance, it does produce psychoactive effects that could lead to recreational use of the drug. However, it is widely regarded as having little or no potential for misuse. Pregabalin, a gabapentinoid with higher potency marketed for neuropathic pain, is a controlled substance, under Schedule V of the United States' Controlled Substances Act.

[edit] Sales

Gabapentin is best known under the brand name Neurontin manufactured by Pfizer subsidiary Parke-Davis. A Pfizer subsidiary named Greenstone markets generic gabapentin.

In December 2004, the FDA granted final approval to a generic equivalent to Neurontin made by Israeli firm Teva.

Neurontin is one of Pfizer’s best-selling drugs, and was one of the 50 most-prescribed drugs in the United States in 2003. However, in recent years, Pfizer has come under heavy criticism for its marketing of Neurontin, facing allegations that, behind the scenes,

Parke-Davis marketed the drug for at least a dozen supposed uses for which the drug had not been FDA approved.

By some estimates, so-called *off-label* prescriptions account for roughly 90% of Neurontin sales.[21] While off-label prescriptions are common for a number of drugs and are perfectly legal (if not always appropriate), marketing of off-label uses of a drug is strictly illegal.[22] In 2004, Warner-Lambert agreed to plead guilty and pay $430 million in fines to settle civil and criminal charges regarding the illegal marketing of Neurontin for off-label purposes, and further legal action is pending. The courts of New York State, for example, have refused to certify a class of injured parties who took Neurontin for off-label use, finding that they had failed to state that they had any injury.[23]

The University of California, San Francisco (UCSF) has archived[24] and studied[25] the documents made public by this case, which opens a unique window into pharmaceutical marketing and their illegal promotion. However, Pfizer maintains that the illegal activity originated in 1996, well before it acquired Parke-Davis (through its acquisition of Warner-Lambert) in 2000. Several lawsuits are underway after people prescribed gabapentin for off-label treatment of bipolar disorder attempted or committed suicide.

[edit] Related drugs

Pfizer has developed a successor to gabapentin, called pregabalin (being marketed as **Lyrica**). Related in structure to gabapentin, pregabalin is effective for neuropathic pain associated with diabetes, fibromyalgia, and shingles, as well as for the treatment of epilepsy and seizures.

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