PREGABALIN AS A TREATMENT FOR SEIZURES OR NEUROPATHIC PAIN

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Topic Overview

Pregabalin is a Schedule V controlled substance. It was discovered by Northwestern University chemistry professor Richard Silverman and visiting colleague Ryszard Andruszkiewicz in 1987. Pregabalin is a drug that has Food and Drug Administration approval for the treatment of neuropathic pain, including pain that is associated with spinal cord injury and diabetic peripheral neuropathy. It also has received FDA approval for fibromyalgia and postherpetic neuralgia. For patients with epilepsy, pregabalin is approved as an adjunctive treatment for partial-onset seizures in patients 1 month of age and older. Pregabalin also has off-label uses. Before prescribing pregabalin, a patient must be aware of contraindications, warnings, and adverse events.

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Learning Objectives: Upon completion of this educational activity, participants should be able to:

1. **Identify** the approved indications for pregabalin
2. **Describe** the different dosage forms and dosing frequencies for pregabalin
3. **Identify** the potential side effects associated with pregabalin
4. **List** some patient education points for patients who are prescribed pregabalin

Disclosures

The following individuals were involved in developing this activity: Steven Malen, PharmD, MBA, and Pamela Sardo, PharmD, BS. Pamela Sardo, Pharm.D., B.S., was an employee of Rhythm Pharmaceuticals until March 2022 and has no conflicts of interest or relationships regarding the subject matter discussed. There are no financial relationships relevant to this activity to report or disclose by any of the individuals involved in the development of this activity.

Introduction

Pregabalin is a drug that has Food and Drug Administration (FDA) approval for the treatment of neuropathic pain, including pain that is associated with spinal cord injury and diabetic peripheral neuropathy (DPN). It also has received FDA approval for fibromyalgia and postherpetic neuralgia. For patients with epilepsy, pregabalin is approved as an adjunctive treatment for partial-onset seizures in patients 1 month of age and older. This course provides insights into the various indications, potential adverse effects, and dosing in individuals suffering from diverse nervous system maladies that result in the prescribing of pregabalin.

History of Pregabalin

Pregabalin is an antiepileptic drug and a Schedule V controlled substance.[1,2] It was discovered by Northwestern University chemistry professor Richard Silverman and visiting colleague Ryszard Andruszkiewicz, resulting from a $681,764 grant from the National Institutes of Health in 1987.[3]

Pregabalin was researched to treat seizures, neuropathic pain, and generalized anxiety disorder.[4] It was in development as an improvement on gabapentin.[5] Pregabalin was approved by the FDA in 2004 for painful diabetic peripheral neuropathy and post-herpetic neuralgia.[6] In 2005, pregabalin was approved to treat partial-onset seizures in adults.[6] In 2007, it was the first drug FDA-approved to treat patients with fibromyalgia.[6] In 2012, the FDA approved its use, in capsule form, for managing neuropathic pain associated with spinal cord injury.[7] The controlled-release formulation, Lyrica CR was approved by the FDA in 2017 and is FDA-approved for neuropathic pain and postherpetic neuralgia.[8]

There are more pain syndromes for which pregabalin is prescribed; however, these are off-label uses. Other conditions for which pregabalin is prescribed off-label include alcohol use disorder, benzodiazepine use disorder, chronic sciatica, generalized anxiety disorder, pruritus, restless legs

syndrome, social anxiety disorder, and vasomotor symptoms associated with menopause.[2]

Clinical Pharmacology of Pregabalin

Mechanism of Action

Pregabalin binds with high affinity to the alpha$_2$-delta site (an auxiliary subunit of voltage-gated calcium channels) in the central nervous system (CNS) tissues.[1] The mechanism of action is not fully known, but the binding to the alpha$_2$-delta subunit may be involved in the anti-nociceptive and antiseizure effects.[1]

Pregabalin is categorized as a GABA analog, but it does not bind to GABA A or GABA B receptors; however, it does appear to increase the density of GABA transporters and increase the functional rate of GABA transport.[1,9] Some studies theorize that pregabalin can be neuroprotective and antioxidant in its effects, making it potentially useful in ischemia and preventing reperfusion injury in the brain when blood supply is restored.[10]

Pharmacokinetics

Pregabalin is mostly eliminated through the kidneys as the liver does not metabolize it. While it does not bind to plasma proteins, it does cross into the blood-brain barrier, placenta, and breast milk. Finally, the half-life is about six hours. The pharmacokinetics of pregabalin are not significantly affected by race (Caucasians, Blacks, and Hispanics).[1,8]

Dosage and Administration

Labeled Uses

Each FDA-approved indication for pregabalin is described in this section and includes dosing information as well as treatment efficacy. The dosing regimen and type of formulation differ by condition.

Fibromyalgia

Pregabalin immediate-release formulations are FDA-approved for treating fibromyalgia.[1] Fibromyalgia is a debilitating, often overlooked, chronic syndrome that is characterized by diffuse musculoskeletal pain, other somatic complaints, and cognitive, psychiatric, and sleep disturbances.[11-14]

Fibromyalgia is not associated with serious or life-threatening complications; however, it is not curable, and it can overlap with other functional chronic syndromes, including irritable bowel, chronic fatigue, and temporomandibular joint dysfunction. Overlapping chronic syndromes make it difficult to manage symptoms successfully.[11-14]

Pregabalin is one of three drugs (with duloxetine and milnacipran) that have FDA approval for treating fibromyalgia.[15-17] Pregabalin is proven to be effective in relieving pain, decreasing fatigue, and improving functional ability and quality of life in patients who have fibromyalgia.[15-17]

For initial dosing and titration, begin with 75 mg orally twice daily (150 mg/day) and may increase to 150 mg twice daily (300 mg/day) within 1 week, based on tolerability and efficiency.[1] The maximum daily dose is 450 mg.[1]

Nineteen percent of all patients taking pregabalin for the treatment of fibromyalgia stopped using the drug because of adverse effects such as dizziness, somnolence, and weight gain occurring at all three doses; 600, 450, and 300 mg daily.[1] A 2016 study showed that only 50% to 60% of patients had more than 30% pain reduction and a placebo response of 30%-40%; moreover, it found that there was a "major reduction in pain intensity … with tolerable adverse effects" only in a small proportion of patients, equivalent to about 10% more than those receiving a placebo. [18]

Pregabalin is comparable to other drugs commonly used to treat fibromyalgia, although there is some variability in symptom management.[11] Farag, *et al.* (2022) acknowledged that pregabalin is among the drugs commonly used for treating fibromyalgia pain. It can relieve signs and

symptoms and has a tolerable level and intensity of side effects.[20] However, the choice of medication to treat fibromyalgia should be made after considering the patient's age, medication cost, comorbidities, potential drug-drug interactions, and the risk of adverse effects for the patient.[20] In the end, clinicians should consider how treatments may be individualized or patient-centered, weighing the benefits and adverse effects for the patient.[20] Clinicians should also consider nonpharmacological approaches such as physical activity and coping skills.[20]

Neuropathic Pain: Diabetic Peripheral Neuropathy

Pregabalin immediate-release and extended-release formulations are FDA-approved for treating DPN.[1,8] Diabetic peripheral neuropathy is a common complication of type 1 and type 2 diabetes mellitus.[21-23] Diabetic peripheral neuropathy reportedly affects 28.85% of diabetic patients, and 88% of them have pain symptoms.[21]

Pregabalin is a first-line choice for treating painful DPN, and it is safe and efficacious for this purpose.[21-23] Clinical trials and a considerable amount of research dating from 2004 have proven that pregabalin can significantly decrease the severity of pain caused by DPN.[1,21-23] The maximum recommended dose of pregabalin immediate-release is 100 mg three times a day (300 mg/day) in patients with creatinine clearance of at least 60 mL/min.[1] Begin dosing at 50 mg three times a day (150 mg/day). The dose may be increased to 300 mg/day within 1 week based on efficacy and tolerability. The maximum recommended dose for pregabalin extended-release is 330 mg/day. Begin dosing of extended-release pregabalin at 165 mg/day. The dose may be increased within one week.[8] Many of the adverse effects usually resolve within the first few weeks after initiation of therapy.[1,21-23] The dosing range of pregabalin is 150 mg – 300 mg a day, and some patients may not respond to the lowest dose.[1] Pregabalin has been prescribed in combination with other medications, particularly duloxetine, and the results have been encouraging, but there is very little experience with this approach.[1]

Neuropathic Pain: Spinal Cord Injury

Pregabalin immediate-release formulations are FDA-approved for treating neuropathic pain associated with spinal cord injuries.[1,8,24] Neuropathic pain is caused by a disease or an injury to the somatosensory nervous system. It is a very common complication of spinal cord injuries and has a tremendously negative impact on a patient's emotional, physical, and psychological well-being.[25] The effectiveness of pregabalin for this clinical situation was initially established by two clinical trials; a 12-week randomized, placebo-controlled study of 137 patients (70 given pregabalin, 67 given placebo) and a 17-week randomized, placebo-controlled study of 220 patients (108 received pregabalin, 112 given placebo).[1] In both studies, the patients in the pregabalin groups had a significantly greater degree of pain relief (a decrease in pain score of 1.92 versus 0.46), and pregabalin was superior to placebo in other study endpoints, as well. A re-examination of the data from these two trials found that the onset of beneficial effects occurred within two days of beginning therapy, and several literature reviews have confirmed that pregabalin is an effective analgesic for this patient population.[1]

The dosing for those individuals suffering from neuropathic pain associated with spinal cord injury begins with 150 mg a day in two divided doses. The dose can be increased to 300 mg a day in two divided doses within one week if needed. The maximum daily dose is 600 mg in two divided doses.[1]

Post-herpetic Neuralgia

Pregabalin immediate-release and extended-release formulations are FDA-approved for treating postherpetic neuralgia.[1,8] Post-herpetic neuralgia is the most common complication of herpes zoster infection.[26] Approximately 20% of people with or who have had a herpes zoster infection will develop post-herpetic neuralgia, and 80% of cases are in people > 50 years old.[26] The likelihood a person will get a herpes zoster infection is between 25% and 30%, but this increases to 50% for individuals older than 80 years.[27]

Post-herpetic neuralgia is characterized by intense, burning pain at the site of the original infection, most often on the thorax, and by allodynia, pain caused by stimuli that are normally not painful. It is unilateral in distribution, not crossing the midline along the dermatome associated with the site of infection.[27]

In most cases, post-herpetic neuralgia is a non-resolution of pain past the acute phase of infection; however, post-herpetic neuralgia can start months and years after the initial herpes zoster infection has resolved. For many people, post-herpetic neuralgia will stop within weeks or months, but it can persist for much longer or never resolve. Regardless of the duration of post-herpetic neuralgia, the ongoing symptoms are debilitating and difficult to treat effectively.[26,27] Pregabalin is a first-line drug for treating post-herpetic neuralgia, along with gabapentin and tricyclic antidepressants.[26,27] The clinical trials that established its efficacy evidenced that pregabalin significantly decreased pain and increased the number of patients with at least a 50% reduction in their baseline pain score.[1,7] Meta-analyses and more recent randomized, placebo-controlled studies have duplicated and confirmed these results. Most of the participants had 30% or 50% pain reductions from baseline compared to the controls.[21]

Partial-onset Seizures

Pregabalin immediate-release formulations are FDA-approved for adjunctive therapy for treating pediatric and adult patients weighing 30 kg or more with partial-onset seizures.[1] A seizure is defined as a paroxysmal (sudden, unexpected) change in neurologic brain function caused by an excessive, hypersynchronous discharge of neurons in the brain.[28] Hypersynchrony describes a decreased inhibition and enhanced excitation in neurologic brain function that causes a transient, intense, "hypersynchronous" neuronal activity.[29]

Seizures are classified as focal seizures, generalized seizures, or seizures of unknown onset.[30] Focal seizures are also referred to as localized or partial seizures. Although the term partial seizure is still commonly used,

the current and preferred term is *focal seizure*.[30] Epilepsy classification is key in evaluating a patient's seizures, and it guides the selection of antiepileptic therapies.[30]

A focal or partial seizure is unlike a generalized seizure in that only part of the cerebral cortex is involved. Focal seizures are typically divided into two types: 1) focal seizure with retained awareness and 2) focal seizure with impaired awareness.[31,32]

A focal seizure with *retained awareness* is characterized by full awareness during the seizure, but the patient experiences a wide variety of signs and symptoms that can be autonomic, motor, physical, or sensory; for example, a rapid heartbeat, abnormal involuntary and repetitive movement of a body part, incontinence, memory loss, or spatial perception distortion.[31,32] Tonic-clonic movements (convulsions) do not happen during a focal seizure.[31,32] When a patient has a focal seizure with *impaired awareness*, there is impaired consciousness, and the patient is unaware of his or her surroundings.[31,32] The changes in consciousness or awareness are complex in presentation, and the patient may have autonomic, motor, physical, or sensory signs and symptoms.[31,32]

Focal seizures with retained awareness and impaired awareness may be preceded by an *aura,* which can be one of the autonomic, motor, physical, or sensory signs and symptoms of this type of seizure.[31,32] Both types of focal seizures are often followed by a postictal period, during which the patient's neurologic function has not returned to baseline.[31,32]

Pregabalin immediate-release is an effective adjunctive treatment for patients with focal (partial-onset) seizures.[1,33] In pediatric patients, the recommended dosing regimen is body weight dependent. Dosage may be increased weekly based on response and tolerability. Table 1 describes dosing in this indication.

Table 1: Recommended Dosage in Adults and Pediatric Patients with Focal (Partial Onset) Seizures[1]

Age and Body Weight	Recommended Initial Dosage	Recommended Maximum Dosage	Frequency of Administration
Adults (17 yr +)	150 mg/day	600 mg/day	2 or 3 divided doses
Pediatric patients (wt 30 kg +)	2.5 mg/kg/day	10 mg/kg/day (not to exceed 600 mg/day)	2 or 3 divided doses
Pediatric patients (wt < 30 kg)	3.5 mg/kg/day	14 mg/kg/day	1 month to less than 4 years of age: 3 divided doses 4 years +: 2 or 3 divided doses

Clinical trials using 50 mg, 150 mg, 300 mg, or 600 mg daily dose showed a median decrease in seizure frequency of 9%, 35%, 37%, and 51%, respectively.[1] French, *et al.* (2016) found that patients with focal seizures had a 58.65% decrease in seizure frequency.[33] French, *et al.* (2016) reported that in two separate studies, pregabalin was as effective for this purpose as gabapentin and levetiracetam.[33]

Off-Label Uses

Pregabalin is used off-label to treat a number of conditions, such as generalized anxiety disorder, trigeminal neuralgia, and social phobia.

Generalized Anxiety Disorder (GAD)

Pregabalin immediate-release formulations are used off-label for treating generalized anxiety disorder.[35] Despite being off-label in the U.S., it is approved in other countries and is recommended by organizations like The World Federation of Biological Psychiatry for this purpose.[35] A 2014 review including 89 clinical trials and 25,441 patients found that pregabalin was effective for GAD and comparable to other standard treatments such as duloxetine, venlafaxine, and escitalopram. Pregabalin actually had the second-highest score for effectiveness but also had the second-highest discontinuation rate due to side effects.[36]

The dosing for adults starts at 75 mg daily and increases to a maximum of 300 mg twice daily, gradually increasing the dose each week. To discontinue, gradually decrease the dose week by week. For geriatric adults, start at 50 mg daily for two days, increase to 50 mg twice daily for two days, then start with dosing above and the same maximum and discontinuing directions.[35,36]

Trigeminal Neuralgia

Pregabalin immediate-release formulations are used off-label for treating trigeminal neuralgia.[37] Since this is a relatively uncommon treatment, the studies are very small; however, they do show promise. One of the studies included 53 patients, and 39 of these patients (74%) had improvement in pain. An interesting note is that patients without facial pain had a better response than patients with facial pain; that being said, this study was not placebo controlled and was prospective.[37] Standard dosing is used to treat trigeminal neuralgia.

Social Phobia (Social Anxiety Disorder)

Pregabalin immediate-release formulations are used off-label for treating social phobia or social anxiety disorder.[38] There was one good double-blind RCT of 135 patients on 150 mg and 600 mg of pregabalin plus a placebo arm. The 600 mg group significantly improved; however, the 150 mg did not.[8] The target dose is 200 mg three times daily titrated over one week.

Administration

Pregabalin immediate-release formulas are given orally regardless of food.[1] The bioavailability of pregabalin extended-release is reduced if taken on an empty stomach; therefore, it should be taken after the evening meal.[8]

Dosage Forms and Strengths

The brand name is Lyrica, and its generic form is pregabalin.

- Oral capsule: Lyrica, 25 mg, 50 mg, 75 mg, 150 mg, 200 mg, 225 mg, 300 mg. (Immediate Release or IR)
- Extended-release tablet: Lyrica CR (pregabalin ER) 82.5 mg, 165 mg, 330 mg.
- Oral solution: Lyrica, 20 mg/mL.

Contraindications, Warnings, and Adverse Reactions

The most common adverse effects, ≥5%, reported in the premarketing controlled trials for all labeled uses but not necessarily resulting in drug discontinuation, were cognitive difficulties (primarily with concentration or attention), blurred vision, dizziness, dry mouth edema, somnolence, and weight gain.[1] In addition, these and other adverse events, contraindications, and warnings are described in the prescribing information. Patients must be aware of these issues before they are prescribed pregabalin. If a patient has a history of any of the following, it is best to avoid taking pregabalin: Known

hypersensitivity to pregabalin or any of the components of the specific products; ethanol use; pregnancy or breast-feeding.[1,8]

Angioedema

This is a vascular reaction in the deep dermis, subcutaneous, or submucosal tissues that causes localized edema, typically in the face and in and around the mouth.[1] Drug-induced angioedema is relatively common. Although it is uncomfortable and frightening, it is seldom dangerous; however, in rare cases, airway obstruction and death can occur from drug-induced angioedema, and serious cases have been reported after the use of pregabalin.[1] This has been reported as occurring during initial therapy and with chronic use; in some cases, angioedema caused airway compromise requiring emergency care.[1] Patients should be educated about the signs and symptoms of drug-induced angioedema, advised that it can reoccur, and if angioedema develops, treatment with the drug should be stopped. The prescribing information recommends using pregabalin cautiously if a patient has developed angioedema from another drug. Also, other medications may cause angioedema, such as angiotensin-converting enzyme inhibitors, so pregabalin should only be cautiously prescribed if a patient is taking medications with this potential adverse reaction.[1]

Cardiovascular

Treatment with pregabalin has been associated with PR interval prolongation (indicating a slowing of conduction between the atria and ventricles). At doses of 300 mg a day, the mean PR interval increase was 3-6 msec. There is one case report of PR interval prolongation caused by pregabalin in a patient with a normal heart and normal renal function. Other reported cases of this adverse effect have occurred in patients with cardiovascular and/or renal diseases.[1]

Central Nervous System

Mild CNS effects caused by pregabalin are common but especially noted as dizziness (31%) and somnolence (22%). When these symptoms occur either separately or in combination, there can be safety concerns about performing certain activities, such as driving a car. Dizziness and somnolence are the two most common reasons patients give as adverse reactions causing them to discontinue taking the medication.[1]

Creatine Kinase (CK) Levels

Creatine kinase is important in cell energy and muscle cell metabolism. Higher CK levels are associated with a greater burden on the kidneys. An increase in CK levels has been reported in patients taking pregabalin, but progression to rhabdomyolysis is rare.[1] The mean change in CK level in patients receiving pregabalin was 60 U/L and for patients receiving placebo, 28 U/L. Controlled trials of pregabalin found that 1.7% of patients taking the drug had CK elevations ≥ three times the upper limit of normal versus 0.7% of the patients taking a placebo. If myopathy occurs, the patient should immediately stop taking pregabalin.[1] A rare case of pregabalin-induced myopathy was reported by Hegde, *et al.* (2020) in a patient who was a double-lung transplant recipient.[39]

Hematologic

The full prescribing information advises that pregabalin has been associated with decreased platelet count.[1] Ongoing monitoring is suggested.[1]

Ophthalmologic

Amblyopia, blurred vision, diplopia, fundoscopic changes, and reduced visual acuity have been reported as adverse effects of pregabalin.[1] No reports of serious and/or irreversible ophthalmic adverse reactions caused by pregabalin were located. Interestingly, an ophthalmic microemulsion of pregabalin is being used by some in an off-label capacity for the reduction of

intraocular pressure. Elevated pressure is a risk factor for the loss of visual field from glaucoma. Although adverse effects are cited above, there are some indications where pregabalin optic drops are being used.[40]

Peripheral Edema

During controlled clinical trials, 6% of the patients receiving pregabalin developed peripheral edema, with an occurrence of only 2% of the patients receiving a placebo.[1] This adverse effect was not associated with laboratory test changes that are indicative of hepatic or renal disease. In patients without heart or peripheral vascular disease, congestive heart failure and hypertension did not occur. Patients taking pregabalin and a thiazolidinedione antidiabetic drug (also known as "glitazones") were more likely to develop peripheral edema and weight gain.[1]

Suicidal Behavior and Ideation

The use of antiepileptics, including pregabalin, is associated with an increased risk for suicidal behavior and ideation. The increase can begin one week after starting therapy with the drug. Patients taking an antiepileptic should be closely monitored for signs and symptoms of depression and suicidal behavior and thoughts.[1]

In 2008, a warning was issued by the FDA regarding a self-harm risk in patients taking antiepileptics. This issuance was after a meta-analysis of controlled trials of the use of antiepileptics (multiple uses), reporting that people taking an antiepileptic had an increased risk for suicidal behavior and thoughts.[41] Later, in 2008, the FDA published the details of its investigation.[42]

- Data was collected from 11 controlled trials involving 27,863 patients.
- The drugs involved were carbamazepine, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, valproate, and zonisamide.

- These antiepileptics were being used to treat epilepsy (25% of the patients), psychiatric conditions (27% of the patients), and other conditions (48% of the patients).
- There were 4 completed suicides in the treated patients, and none in the placebo group.
- The conclusion was that patients taking an antiepileptic were significantly more likely to have suicidal behavior and thoughts (odds ratio 1.8, confidence interval 1.24 - 2.66).
- The incidence rate for suicidal behavior and thoughts was 0.43% for the treated patients and 0.24% for patients receiving a placebo.
- The relative risk was highest for patients who had epilepsy; the relative risk for patients with other conditions was not considered to be significant.

The risk for suicidal behavior and thoughts was observed to begin as soon as one week after treatment with the drug had begun. Based on this information, the FDA required manufacturers to include a warning in their prescribing information stating that studies of the antiepileptics have shown that there is an increased risk of suicidal thoughts or behavior in patients who are taking these drugs. In 2013 the International League Against Epilepsy published an expert consensus statement on antiepileptic drugs and suicide.[43]

The true risk of suicide associated with these drugs is unknown but appears to be very low. Pregabalin is listed in the low-risk category of antiepileptics concerning mood disorders.[43] Stopping antiepileptic drugs or not giving them to people who need them can cause serious harm and death. Suicidality in epilepsy is multifactorial.

Tumorigenic Potential

A high incidence of hemangiosarcoma was seen in animal studies.[1] In clinical studies involving humans > 12 years of age, new or worsening preexisting tumors were reported in 57 patients.[1] Cause and effect remain unknown.

Weight Gain

During controlled clinical trials, 9% of patients receiving pregabalin had a weight gain of ≥ 7%. This occurred in 2% of patients who were receiving a placebo.[1] For patients taking pregabalin and having a diabetes diagnosis, the link between weight gain and glycemic control remains uncertain.[1]

Recreational Drug Use and Substance Use Disorder

Pregabalin has been reported to cause euphoria in recreational drug users similar to that produced by diazepam.[1] In clinical trials, 4% reported euphoria when taking pregabalin, but some patient populations had higher reported rates, up to 12%.[1] In addition, discontinuing pregabalin can cause diarrhea, headache, insomnia, and other signs and symptoms often seen in patients who have a physical dependence on a drug.[1] Abrupt discontinuations have caused some to experience syndromes like those of benzodiazepine or alcohol withdrawal. Signs and symptoms of substance use disorder like craving, addictive behavior, tolerance, and withdrawal, have been reported in patients taking pregabalin, primarily in patients who have or have had a substance use disorder.[1] If the patient has a history of a substance use disorder, particularly involving benzodiazepines, or alcoholism, pregabalin prescribing must be carefully monitored for potential misuse.[1]

Withdrawal

As was previously described, treatment with pregabalin should not be abruptly stopped as this could cause seizures; the dose should be gradually reduced. Tapering doses of antiepileptics and avoiding abrupt discontinuation of these drugs are standard recommendations, but there is very little information about tapering antiepileptics, and there are no standard guidelines for doing so.[44] The prescribing information recommends that if therapy with pregabalin is to be stopped, the drug should be tapered over a minimum of one week.[1]

Post-marketing Experience

Patients reported dizziness and somnolence, nervousness, diarrhea, gynecomastia, headache, and gait imbalance primarily. There were also reports of constipation, intestinal obstruction, and paralytic ileus when pregabalin and opioids were used together and of coma and respiratory failure when pregabalin and a CNS depressant drug were used together.[1]

Drug Interactions

Pregabalin is excreted in the urine with virtually no metabolism nor plasma protein binding, so there are no drug interactions regarding metabolism.[1]

There is no drug-drug interaction between pregabalin and these commonly used antiepileptics: carbamazepine, lamotrigine, phenobarbital, phenytoin, topiramate, and valproic acid.[1]

The only drug interactions to be cautious of include additive "cognitive and gross motor function," which occur with any CNS depressants such as opioids, benzodiazepines, or alcohol.[1]

Specific Populations

Pregnancy

There are no adequate and well-controlled studies of pregabalin use during pregnancy. Animal studies have found evidence of congenital abnormalities and developmental abnormalities when pregabalin was used during pregnancy.[1] A recently published (2017) cohort population study examined data from 1,323,432 pregnancies. There were 477 infants in the study group who had first-trimester exposure to pregabalin, and 5.9% of these infants had congenital malformations; the rate in infants not exposed was 3.3%.[45] The authors concluded that the data do not confirm that pregabalin was teratogenic, but they noted the risk of a small effect could not

be ruled out.[45] The North American Antiepileptic Drug (NAAED) Pregnancy Registry collects information about the use of antiepileptic drugs during pregnancy, and pregnant women who are taking pregabalin or the clinicians caring for them should consider contacting NAAED. 1-888-233-2334, or through the website, www.aedpregnancyregistry.org/.

Lactation

Pregabalin has been detected in breast milk, and the estimated average daily intake of a nursing infant whose mother was taking 150 mg a day of pregabalin is 7% of the maternal dose.[1] Animal studies showed the potential for tumorigenicity with exposure to pregabalin in breast milk. The importance of pregabalin exposure in nursing infants is not clear, but the prescribing information recommends that pregabalin not be used by nursing mothers.[1]

LactMed is a database maintained by the U.S. National Library of Medicine that collects and summarizes information about drugs and breastfeeding. The LactMed Summary of pregabalin provides that data is very limited, but it does indicate that the amounts of pregabalin in breast milk are low. If the mother of an older infant requires pregabalin, this is not a reason to discontinue breastfeeding, but until more data become available, an alternate drug may be preferred, especially while nursing a newborn or preterm infant.[46]

Pediatric Use

Lyrica is approved as an adjunctive therapy for partial-onset seizures. During a 12-week randomized controlled trial in patients between 4 and 17 years of age, there was a 21% greater reduction in partial-onset seizures compared to placebo.[1,8]

Geriatric Use

There are dosing considerations to be evaluated when prescribing pregabalin to the elderly and to those with renal impairment. There have been

no recommendations for dosing adjustments of pregabalin for patients who have hepatic impairment.[1,8]

Clinicians should follow the adult dosing schedule but use pregabalin cautiously, being watchful for possible renal impairment in this population and dosing accordingly. (1) During controlled clinical studies that included 538 patients who were 65 years of age and older, there was no difference in the efficacy or safety of pregabalin when compared to younger patients.[1,8] In other clinical studies that included 106 patients of ages 65 years and older, there was a higher incidence of balance disorder, blurred vision, confusion, coordination difficulties, dizziness, and lethargy.[1,8] In the geriatric population, a decrease in renal function is not uncommon, and pregabalin is primarily excreted by the kidney. This may account for some of the findings in these studies.

Renal Impairment

Metabolism of pregabalin is minimal, and it is primarily excreted in the urine.[1,8] Patients who have impaired renal function as evidenced by a creatinine clearance (CrCl) of 30 – 60 mL/min do not tolerate pregabalin as well as patients who have a CrCl that is > 60 mL/minute, so dosing adjustments based on CrCl are necessary.[1,8] Table 2 provides doses associated with creatinine clearance values.

Table 2: CrCl and Pregabalin Dosing

CrCl ≥ 60 mL/minute: The dose should be 150 mg, 300 mg, 450 mg, or 600 mg a day, divided into two or three doses.
CrCl 30-60 mL/minute: The dose should be 75 mg, 150 mg, 225 mg, or 300 mg a day, divided into two or three doses.
CrCl 15-30 mL/minute: The dose should be 25-50 mg, 75 mg, 100-150 mg, or 150 mg, divided into two or four doses.
CrCL < 15 mL/minute: The dose should be 25 mg, 25-50 mg, 50-75 mg, or 75 mg, given once a day.

Table 2 is taken from reference 1.

Lookalike/Soundalike Concerns

The Institute for Safe Medication Practices (ISMP) is concerned about possible drug name mix-ups: Lyrica and Lopressor.[47] That being said, Lyrica and pregabalin do not require "tall man letters."[48]

Storage and Handling

For immediate-release formulas, store at 77°F (25°C); excursions permitted to 59°F to 86°F (15°C to 30°C).[1] For extended-release formulas, store at 68°F to 77°F (20°C to 25°C), excursions permitted between 59°F and 86°F (15°C and 30°C) in the original package.[8]

Patient Education Pearls

Pharmacy team members are ideally positioned to provide patient education for pregabalin.

- Do not operate heavy equipment
- If a drug interaction question arises, refer the patient to the pharmacist
- Do not share this medication with others
- Tell your healthcare provider about any troubling side effects that do not go away
- Do not drink alcohol while taking this medicine
- Tell your doctor if you are pregnant or breastfeeding or plan to.
- This medicine works in the central nervous system. Please tell your doctor if any new symptoms occur or if you feel worse in any way.
- A Medication Guide is provided with this prescription. Please read it.
- When starting or increasing the dose of pregabalin, do not drive, operate complex machinery or engage in hazardous activities, as dizziness and somnolence may occur.
- Pregabalin is a controlled substance. Keep it and all medicines out of the reach of children.

Summary

Healthcare team members have an ideal opportunity to educate patients and other team members regarding pregabalin effects. Providing patient support and education is important in complex conditions such as fibromyalgia, neuropathic pain associated with spinal cord injury, diabetic peripheral neuropathy, and post-herpetic neuralgia.

Researchers are continuing to explore pregabalin for new indications. On ClinicalTrials.gov, studies are listed that will investigate pregabalin for postoperative pain control after total knee arthroplasty. It is also being explored for postoperative pain after spine surgery.

Course Test

1. **Pregabalin is _____ drug.**

    a. an antidepressant
    b. an antiepileptic
    c. a mood stabilizer
    d. an antipsychotic

2. **Which of the following labeled uses of pregabalin may be treated using immediate-release *and* extended-release forms of the drug?**

    a. Fibromyalgia
    b. Neuropathic pain associated with diabetic peripheral neuropathy
    c. Neuropathic pain associated with spinal cord injury
    d. Partial-onset seizures, adjunctive therapy for patients 4 and over

3. **Pregabalin has been used off-label to treat**

    a. generalized anxiety disorder.
    b. fibromyalgia.
    c. neuropathic pain associated with spinal cord injury.
    d. postherpetic neuralgia.

4. **When pregabalin is used to treat neuropathic pain associated with diabetic peripheral neuropathy, which dose is most likely to be prescribed?**

    a. 30 mg dosed orally, once a day
    b. 400 mg dosed four times a day
    c. 300 mg daily, dosed in 3 divided doses
    d. 300 mg weekly dosed by infusion

5. **Patients taking pregabalin who have impaired renal function**

    a. must stop using the drug and switch to opioids.
    b. require dosing adjustments and monitoring.
    c. may continue their dose since there are no recommendations.
    d. require dose adjustment only if consuming alcohol.

6. _____ has been reported during therapy with pregabalin, and in some cases, this condition caused airway compromise that required emergency care.

a. Peripheral edema
b. PR interval prolongation
c. Angioedema
d. Somnolence

7. The most common adverse effects, ≥5%, reported in premarketing controlled trials associated with pregabalin were reported to be

a. cognitive difficulties and blurred vision.
b. diarrhea and somnolence.
c. gynecomastia and seizures.
d. pregnancy and neuropathic pain.

8. The prescribing information and LactMed database discuss breastfeeding in mothers who take pregabalin and say that it is *preferable* for nursing mothers not to use pregabalin

a. for more than 6 months when nursing.
b. while breastfeeding but find an alternative drug.
c. with a daily dose over 150 mg.
d. if the patient has type 2 diabetes.

9. Patient education regarding pregabalin should include

a. call 911 if you are experiencing drowsiness and sleepiness.
b. troubling side effects will diminish after 2 days.
c. if a baby is premature, breastfeeding is recommended.
d. do not drive or operate machinery while increasing the dose.

10. Patients taking pregabalin should be counseled that

a. pregabalin is a controlled substance, so keep it and all medicines out of the reach of children.
b. you may consume up to 24 ounces of alcohol daily when taking pregabalin.
c. it is not necessary to inform your doctor about pregnancy if you are taking pregabalin.
d. the patient Medication Guide for pregabalin is optional. Would you like one?

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