U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Drug Safety Communications

FDA warns about serious breathing problems with seizure and nerve pain medicines gabapentin (Neurontin, Gralise, Horizant) and pregabalin (Lyrica, Lyrica CR)

When used with CNS depressants or in patients with lung problems

12-19-2019

What safety concern is FDA announcing?

The U.S. Food and Drug Administration (FDA) is warning that serious breathing difficulties may occur in patients using gabapentin (Neurontin, Gralise, Horizant) or pregabalin (Lyrica, Lyrica CR) who have respiratory risk factors. These include the use of opioid pain medicines and other drugs that depress the central nervous system, and conditions such as chronic obstructive pulmonary disease (COPD) that reduce lung function. The elderly are also at higher risk.

Gabapentin and pregabalin are FDA-approved for a variety of conditions, including seizures, nerve pain, and restless legs syndrome.

Our evaluation shows that the use of these medicines, often referred to as gabapentinoids, has been growing for prescribed medical use, as well as misuse and abuse. Gabapentinoids are often being combined with CNS depressants, which increases the risk of respiratory depression. CNS depressants include opioids, anti-anxiety medicines, antidepressants, and antihistamines. There is less evidence supporting the risk of serious breathing difficulties in healthy individuals taking gabapentinoids alone. We will continue to monitor these medicines as part of our routine monitoring of all FDA-approved drugs.

What is FDA doing?

We are requiring new warnings about the risk of respiratory depression to be added to the prescribing information of the gabapentinoids. We have also required the drug manufacturers to conduct clinical trials to further evaluate their abuse potential, particularly in combination with opioids, because misuse and abuse of these products together is increasing, and co-use may increase the risk of respiratory depression. Special attention will be paid to the respiratory depressant effects during this abuse potential evaluation.

What are gabapentinoids and how can they help me?

Gabapentinoids are FDA-approved to treat a variety of conditions including partial seizures and nerve pain from spinal cord injury, shingles, and diabetes. Other approved uses include fibromyalgia and restless legs syndrome. Gabapentin was first approved in

1993 and pregabalin was first approved in 2004. Gabapentin is marketed under the brand names Neurontin and Gralise, and also as generics. Gabapentin enacarbil is marketed under the brand name Horizant. Pregabalin is marketed under the brand names Lyrica and Lyrica CR, and also as generics. Pregabalin is a Schedule V controlled substance, which means it has a lower potential for abuse among the drugs scheduled by the Drug Enforcement Administration (DEA), but may lead to some physical or psychological dependence.

What should patients and caregivers do?
Patients and caregivers should seek medical attention immediately if you or someone you are caring for experiences symptoms of respiratory problems, because these can be life-threatening. Symptoms to watch for include:

- Confusion or disorientation
- Unusual dizziness or lightheadedness
- Extreme sleepiness or lethargy
- Slowed, shallow, or difficult breathing
- Unresponsiveness, which means a person doesn't answer or react normally or you can't wake them up
- Bluish-colored or tinted skin, especially on the lips, fingers, and toes

Always inform your health care professional about all the drugs you are taking, including prescription and over-the-counter (OTC) medicines and other substances such as alcohol.

What should health care professionals do?
Health care professionals should start gabapentinoids at the lowest dose and monitor patients for symptoms of respiratory depression and sedation when co-prescribing gabapentinoids with an opioid or other central nervous system (CNS) depressant such as a benzodiazepine. Patients with underlying respiratory disease and elderly patients are also at increased risk and should be managed similarly.

We recognize that incorporating one or more medications with non-drug therapies is the prevailing approach for optimizing analgesia. However, pairing an opioid with any CNS depressant – a gabapentinoid, benzodiazepine, sedating antidepressant, sedating antipsychotic, antihistamine, or other product – will increase the risk of respiratory depression. Shifting treatment from one CNS depressant to another may pose similar risks. Be aware of the potential additive effects of all these CNS depressants and plan accordingly, by starting with low doses, titrating carefully, and informing patients of the potential for CNS and respiratory depression and their symptoms. The gabapentinoid prescribing information already includes guidance for health care professionals to caution patients about dizziness, somnolence, and the potential for impaired ability to operate a car or complex machinery.

What did FDA find?
We reviewed several sources of data, including case reports submitted to FDA or published in the medical literature, observational studies, clinical trials, and animal studies.

Reports submitted to FDA and data from the medical literature show that serious breathing difficulties can occur when gabapentinoids are taken by patients with pre-existing respiratory risk factors.[1-6, 8] Among 49 case reports submitted to FDA over the 5-year period from 2012 to 2017, 12 people died from respiratory depression with gabapentinoids, all of whom had at least one risk factor. This number includes only reports submitted to FDA,* so there may be additional cases about which we are unaware.

We also reviewed the results of two randomized, double-blind, placebo-controlled clinical trials in healthy people, three observational studies, and several studies in animals. One trial showed that using pregabalin alone and using it with an opioid pain reliever can depress breathing function.[7,8] The other trial showed gabapentin alone increased pauses in breathing during sleep. The three observational studies at one academic medical center showed a relationship between gabapentinoids given before surgery and respiratory depression occurring after different kinds of surgeries.[9-11] We also reviewed several animal studies that showed pregabalin alone and pregabalin plus opioids can depress respiratory function.[12-14]

*The cases were reported to the FDA Adverse Event Reporting System (FAERS) database.

What is my risk?

All medicines have side effects even when used correctly as prescribed, but in general the benefits of taking a medicine outweigh these risks. It is important to know that people respond differently to all medicines depending on their health, other medicines they are taking, the diseases they have, genetics, and many other factors. As a result, we cannot determine the likelihood that someone will experience these side effects when taking gabapentinoids. Your personal health care professional knows you best, so always tell them about all other medicines you are taking and if you experience any side effects while taking your medicines.

How do I report side effects from gabapentinoids?

To help FDA track safety issues with medicines, we urge patients and health care professionals to report side effects involving gabapentin, pregabalin, or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

Facts about Gabapentinoids

- Gabapentinoids include gabapentin and pregabalin. They are FDA-approved to treat a variety of conditions including partial seizures; pain from damaged nerves that follows spinal cord injury, healing of shingles, or diabetes; fibromyalgia; and moderate to severe primary restless legs syndrome.
- Gabapentin is marketed under the brand names Neurontin and Gralise, and as generics. Gabapentin enacarbil is a prodrug of gabapentin marketed under the brand name Horizant.

    - Gabapentin is not scheduled by the Drug Enforcement Administration (DEA) as a controlled substance. A human abuse liability evaluation was not conducted when gabapentin was developed in the 1980s and early 1990s.
    - Gabapentin is available as a tablet, capsule, solution, and extended-release tablet.
- Pregabalin is marketed under the brand names Lyrica and Lyrica CR, and as generics.
    - Pregabalin is a Schedule V controlled substance, which means that among the drugs scheduled by the DEA because of their abuse potential, it has a lower potential for abuse but may lead to some physical or psychological dependence.
    - Pregabalin is available as a capsule, solution, and extended-release tablet.
- Common side effects of gabapentinoids include drowsiness, dizziness, blurry or double vision, difficulty with coordination and concentration, and swelling of the hands, legs, and feet.

Additional Information for Patients and Caregivers

- FDA is warning that serious breathing difficulties may occur when gabapentin (Neurontin, Gralise, Horizant) or pregabalin (Lyrica, Lyrica CR) is taken with other medicines that depress the central nervous system (CNS) such as opioids, in those patients who have underlying respiratory problems, or in the elderly. There is less evidence supporting the risk of serious breathing difficulties with gabapentinoids alone in otherwise healthy individuals, and we will continue to monitor this population for additional evidence.
- Respiratory problems can be life-threatening, so seek medical attention immediately if you or someone you are caring for experiences the following symptoms:
    - Confusion or disorientation
    - Unusual dizziness or lightheadedness
    - Extreme sleepiness
    - Slowed, shallow, or difficult breathing
    - Unresponsiveness, which means the person doesn't answer or react normally or you can't wake them up
    - Bluish-colored or tinted skin, especially on the lips, fingers, and toes
- Always take gabapentinoids as prescribed. Do not take more of the medicine or take it more often than prescribed because doing so can cause serious problems or death.
- Always tell all your health care professionals about all the medicines you are taking, including prescription and over-the-counter (OTC) medicines. It is helpful to keep a list of all your current medicines in your wallet or another location where it is easily retrieved. You can fill out and print a copy of My Medicine Record.
- Read the patient Medication Guide every time you receive a prescription for a gabapentinoid. The Medication Guide will be updated with new or other important information about your medicine. The Medication Guide explains the important things that you need to know. These include the side effects, what the medicine is used for, interactions with other medicines, how to take and store it properly, and other things to watch out for when you are taking the medicine.
- Talk to your health care professional if you have any questions or concerns.

- To help FDA track safety issues with medicines, report side effects from gabapentin, pregabalin, or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Additional Information for Health Care Professionals

- FDA is warning that serious, life-threatening, and fatal respiratory depression has been reported with the gabapentinoids, gabapentin (Neurontin, Gralise, Horizant) and pregabalin (Lyrica, Lyrica CR). Most cases occurred in association with co-administered central nervous system (CNS) depressants, especially opioids, in the setting of underlying respiratory impairment, or in the elderly.
- Our evaluation of respiratory depression with the gabapentinoids provides some evidence contrary to the widely held belief that gabapentinoids lack drug interactions and have wide therapeutic indices. Published studies demonstrate these drugs can behave in an additive way to potentiate central nervous system (CNS) and respiratory depression.
- When co-prescribing gabapentinoids with another CNS depressant, particularly an opioid, or in patients with underlying respiratory impairment, initiate the gabapentinoid at the lowest dose.
- Adjust the dose of both gabapentin and pregabalin in patients with renal impairment and patients undergoing hemodialysis, because both drugs are excreted by the kidneys.
- Monitor for symptoms of respiratory depression and sedation, especially when co-prescribing gabapentinoids with an opioid or other CNS depressant such as a benzodiazepine or when prescribing to patients with underlying respiratory impairment, or elderly patients.
- The management of respiratory depression may include close observation, supportive measures, and reduction or withdrawal of CNS depressants, including the gabapentinoid. Gabapentinoids used for analgesia or seizure control should be tapered prior to discontinuation. See the prescribing information for specific tapering guidance.
- Encourage patients to read the Medication Guide they receive with each gabapentinoid prescription, which explains the safety risks and provides other important information.
- To help FDA track safety issues with medicines, report adverse events involving gabapentin, pregabalin, or other medicines to the FDA MedWatch program, using the information in the "Contact Us" box at the bottom of this page.

Data Summary

We reviewed several sources of data including case reports submitted to FDA or published in the medical literature, observational studies, human trials, and animal studies.

Gabapentinoids are increasingly being prescribed for medical uses, and misuse and abuse of these medications are growing. Between 2012 and 2016, the number of patients who filled a gabapentin prescription increased from 8.3 million to 13.1 million annually, and the number of patients who filled a pregabalin prescription increased from 1.9 million to

2.1 million annually.[16] Gabapentinoids are commonly co-administered with opioids for prescribed medical uses and abused in combination with opioids. Data collected in 2016 from an office-based physician survey showed that 14 percent and 19 percent of patient encounters involving gabapentin and pregabalin, respectively, also involved opioids.[17] Several small cross-sectional studies suggest that in the U.S. and Europe, approximately 15 percent to 26 percent of patients with opioid use disorder (OUD) concomitantly misuse or abuse gabapentin, and approximately 7 percent to 21 percent of patients with OUD concomitantly misuse or abuse pregabalin. However, these studies were small, so the prevalence estimates may not be generalizable to all populations of patients with OUD.[17-22]

We reviewed data from the FDA Adverse Event Reporting System (FAERS) database and the medical literature[1-6] which show that respiratory depression can occur when gabapentinoids are administered in combination with opioids or other central nervous system (CNS) depressants or in patients with underlying respiratory impairment. A small number of reports were in patients only on gabapentinoids. A search of FAERS from January 1, 2012, to October 26, 2017, identified 49 cases of respiratory depression with gabapentinoids. Fifteen cases were reported with gabapentin and 34 cases with pregabalin. Ninety-two percent of the cases reported either a respiratory risk factor, including age-related loss of lung function, or the use of a CNS depressant. Twenty-four percent of the cases resulted in death (n=12). All 12 death cases reported at least one risk factor for developing respiratory depression or concomitant use of a CNS depressant.

Several small randomized trials of healthy volunteers showed that gabapentinoids alone and in combination with opioids depress respiratory function. Myhre et al.[7] conducted a small randomized, double-blind, placebo-controlled cross-over trial in 12 healthy volunteers exposed to placebo, pregabalin alone, the opioid remifentanil alone, or a combination of pregabalin plus remifentanil. End-tidal CO_2 rose with exposure to the drugs together in an additive way. Piovezan and colleagues[8] carried out a small randomized, double-blind, placebo-controlled cross-over trial of eight healthy volunteers. The subjects were older non-obese men without sleep complaints or sleep apnea. Subjects were given a single dose of gabapentin or placebo followed by a sleep study. After a washout period, subjects were again given a single dose of treatment (crossing over to the alternate treatment) followed by another sleep study. The number of hourly apneic episodes during gabapentin exposure exceeded those during placebo exposure.

Observational studies suggest that patients exposed to preoperative gabapentinoids have an increased risk of postoperative respiratory depression compared to those not exposed to gabapentinoids preoperatively. A Mayo Clinic research group published a case-control study describing the relationship between preoperative gabapentin exposure and the risk of postoperative respiratory depression in more than 11,000 arthroplasty patients.[9] They defined respiratory depression as apnea, hypopnea, oxyhemoglobin desaturation, or an episode of severe pain despite moderate to profound sedation (i.e., “pain-sedation” mismatch) during recovery in the postanesthesia care unit. In this study, when compared to patients not exposed to preoperative gabapentin, the risk of respiratory depression was increased 60 percent for patients using regional anesthesia (odds ratio [OR] 1.60, 95%

confidence interval [CI] 1.27, 2.02) and 47 percent for those using general anesthesia (OR 1.47, 95% CI 1.26, 1.70) when the preoperative anesthesia regimen included gabapentin doses greater than 300 mg. This same research group conducted another case-control study describing the relationship between preoperative gabapentin exposure and the risk of postoperative respiratory depression in more than 8,000 laparoscopy patients.[10] Respiratory depression was defined as apnea, hypopnea, oxyhemoglobin desaturation, pain-sedation mismatch, naloxone administration, failure to extubate, need to reintubate, or non-invasive positive pressure ventilation (NIPPV) use in patients who were not previously prescribed such a device. In this study, preoperative gabapentin increased the risk of postoperative respiratory depression by 26 percent (OR 1.26, 95% CI 1.02, 1.58) compared to those not exposed to preoperative gabapentin.

Animal studies have shown that gabapentinoids can cause respiratory depression alone and in combination with opioids.[12-14] Kozer and colleagues[12] showed that rabbits given morphine after gabapentin had greater CO_2 retention than rabbits given saline after gabapentin. Lyndon and colleagues[13] studied the respiratory depressant effects of a high intraperitoneal dose of pregabalin with and without medium dose morphine in six mice. Pregabalin produced a dose-dependent decrease in respiration rate. A pregabalin bolus given alone depressed mouse minute ventilation to the same extent as a morphine bolus given alone. The respiratory depressant effects of morphine and pregabalin were additive, not multiplicative. Collectively, the published animal studies suggest that gabapentinoids have an independent dose-dependent depressive effect on respiration and can augment the respiratory depression caused by opioids.

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Related Information

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