Potential for Pregabalin Abuse or Diversion After Past Drug-Seeking Behavior

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Pregabalin, primarily used to manage neuropathic pain and fibromyalgia, is categorized as a Schedule V drug (ie, lowest potential for abuse) in the US Drug Enforcement Administration’s Controlled Substances Act. Because pregabalin is not recognized as a drug with high-abuse potential, data on pregabalin abuse and addiction are lacking. The authors report a case of a 35-year-old woman with a history of opioid-seeking behavior who was prescribed pregabalin for pain control. The patient requested an increase in her medication 2 months after beginning treatment and, after her physician denied her request, subsequently obtained pregabalin from other sources. Over a 28-day period, the patient received a total of 88,500 mg of pregabalin. After learning of the other prescriptions, the patient’s physician became suspicious of pregabalin abuse or diversion. In accordance with state medical board guidelines, the patient was discharged from the practice and referred to a local detoxification center.

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S ubstance use disorder and diversion of controlled medications, a criminal act, are two problems that are prevalent and damaging to our society. The administrator of the US Drug Enforcement Administration (DEA) highlighted the dangers of nonmedical pharmaceutical use in 2004, stating that “the diversion and abuse of legal controlled substances poses a significant threat to the health and safety of Americans.” According to the 2007 National Survey on Drug Use and Health, 22.3 million people in the United States are classified with substance dependence or abuse, with the nonmedical use of prescription drugs ranking second only to marijuana as the most prevalent category of illicit drug abuse.

Pathways through which individuals obtain controlled substances vary. The 2007 survey revealed that individuals obtained prescription pain relievers through means including acquisition at no cost from a friend or relative (56.5%), prescription from a physician (18.1%), purchase from a friend or relative (8.9%), purchase from a drug dealer (4.1%), and purchase on the Internet (0.5%).

While the medical literature contains many reports that describe notable substance use disorders and diversion of controlled medication related to opiates and benzodiazepines, other medications that fall under the Controlled Substances Act may have the same potential for misuse. One example is pregabalin, which the DEA placed in Schedule V of the Controlled Substances Act. Although Schedule V drugs are defined as having a low potential for abuse relative to the drugs in Schedule IV (eg, benzodiazepines), abuse of Schedule V drugs (eg, cough medicines with codeine) may lead to limited physical dependence or psychological dependence.

Report of Case

A 35-year-old woman presented to an ambulatory family medicine office with a 2-year history of neuropathic abdominal pain syndrome resulting from a prior history of Guillain-Barré syndrome. Her medical history was remarkable for depression with comorbid anxiety managed with escitalopram. The patient denied tobacco use but admitted to consuming 2 to 3 alcoholic beverages per week. Her family history was notable for a mother with bronchogenic carcinoma and a brother with major depressive disorder.

The patient’s pain management regimen during the previous 2 years included oxycodone, hydrocodone bitartrate, hydromorphone hydrochloride, fentanyl (applied transdermally), and pregabalin. The patient was frequently admitted to the hospital because of her neuropathic pain syndrome, despite regularly scheduled outpatient follow-up and repeated use of opioid medications. Two years after the initiation of opioid medication treatment, the patient’s prescribing physician was made aware by the patient’s pharmacist that the patient had been receiving additional opioids that were prescribed by other local ambulatory care physicians during the same 2-year period. The physician also learned that the patient was diverting a portion of her opioids to a family member. All other ambulatory care physicians involved in her care were also notified of this behavior. The patient was referred for detoxification.

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CASE REPORT

Detoxification and her physician informed her that he would no longer prescribe opioid analgesics. The patient did not pursue detoxification and initiated care for her chronic pain with a different physician.

At the patient’s initial visit with her new physician, the physician ordered a urine drug screen, which was negative for amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, phencyclidine, and oxycodone. The patient voiced that she did not want to use opioid analgesics and questioned whether higher doses of pregabalin, which she had taken before, may be effective. A review of systems did not reveal symptoms of depression or anxiety. The patient and physician agreed to a treatment plan using nonopioid treatment with pregabalin. The dosage regimen of pregabalin was titrated over several weeks to the maximum dose of 200 mg, administered three times a day. The patient reported satisfactory pain relief for the first 2 months after the initiation of pregabalin treatment. However, 2 months after beginning treatment, the patient complained of worsening pain and requested increased amounts of pregabalin be added to her dosage regimen. Because the physician did not want to exceed the maximum recommended dose of pregabalin and could not identify the origin of her increased pain, he declined the patient’s request and the patient was maintained on her total daily dosage of 600 mg per day. In addition, the physician referred the patient to specialty pain management for further assessment.

During the 4 weeks after her last appointment with her new physician, the patient presented to 3 different hospitals, complaining of abdominal pain, nausea, headache, and diarrhea. Each visit led to a brief hospital stay, during which multi-specialty workup for the patient’s complaints resulted in discharge diagnoses of abdominal pain with uncertain origin. The patient was provided supportive care and discharged with a prescription for a 7-day supply of pregabalin on each occasion. Symptoms spontaneously resolved within 48 to 72 hours of each hospital admission.

At a follow-up appointment 2 weeks after her last hospitalization, the patient had no further complaints related to her hospitalization. In addition, she reported satisfactory control of her pain and cancelled her appointment for specialty pain management. The patient also refused to reschedule and ultimately declined specialty pain management despite continued recommendations by her physician. The patient was continued on the same dosage of pregabalin.

One week after the follow-up appointment, the patient’s physician was informed by the patient’s pharmacist that the patient had received prescriptions for pregabalin from 3 other physicians. Calls to other local pharmacies further revealed that there were additional prescribers. The patient often paid cash for the pregabalin despite having prescription coverage insurance. Over a 28-day period, the patient had received a total of 88,500 mg of pregabalin. At this time, the physician became suspicious of pregabalin abuse or diversion and, in accordance with state medical board guidelines, the patient was discharged from the practice and referred to a local detoxification center. It was later determined that the patient did not enter a detoxification program.

Comment

The present report highlights the potential for patient abuse and diversion of pregabalin. Pregabalin was approved in the United States in 2004 and received regulatory approval in 40 countries in 2005. In the United States, pregabalin is indicated for the treatment of neuropathic pain associated with diabetic neuropathy, postherpetic neuralgia, adjunctive therapy for adult patients with partial onset seizures, and fibromyalgia. In Europe, the drug also has been approved for the treatment of generalized anxiety disorder and central neuropathic pain. Studies have shown that pregabalin may also be effective in the treatment of benzodiazepine dependence, posttraumatic stress disorder, alcohol dependence, and posttraumatic peripheral neuropathic pain. However, pregabalin is not currently approved for the treatment of these conditions. The maximum dose of pregabalin depends on its indication but should not exceed 600 mg/d.

Pregabalin is an analog of γ-aminobutyric acid, a major inhibitory neurotransmitter in the brain. It does not bind at γ-aminobutyric acid, benzodiazepine, or opioid receptors. Rather, pregabalin binds to the α2-δ receptor site in the central nervous system, which may account for its therapeutic effect on neuropathic pain, anxiety, and seizure.

Pregabalin has also been shown to produce psychoactive effects similar to other controlled substances. In a study with recreational users of sedative or hypnotic drugs, the subjective ratings provided by study participants after taking a 450-mg dose of pregabalin were similar to the ratings given by participants after taking a 30-mg dose of diazepam. In another study, up to 12% of patients taking pregabalin reported feeling euphoria, compared to 1% of placebo-treated patients. However, these psychoactive effects are likely transient and not sustained with continued pregabalin use.

As stated earlier, pregabalin has been studied as a replacement for benzodiazepines and therefore may be sought and misused by abusers of benzodiazepines to reduce the anxiety and sleep problems related to sudden withdrawal. Clinical studies show that while pregabalin may be abused for its immediate effects, the risk of dependency is less than that of benzodiazepines. The development of tolerance for the pain-relieving effect of pregabalin has not been proven; therefore, it is unlikely for patients to escalate doses for better pain control. Abrupt or rapid discontinuation of pregabalin may produce symptoms suggestive of physical dependence including insomnia, nausea, headache, or diarrhea.

Although pregabalin has been labeled a Schedule V drug (ie, the lowest potential for abuse compared to other controlled substances), it is evident that pregabalin may be a
readily available substitute for drugs with higher abuse potential, such as opioids and benzodiazepines. The patient in the present report, who had a history of opioid-seeking behavior, was suspected of substance use disorder after she showed similar drug-seeking behavior with pregabalin. In retrospect, when one considers the patient’s presenting complaints at her three hospitalizations, the patient’s symptoms may have been related to sudden withdrawal of pregabalin each time her supply was exhausted. Pseudoaddiction, defined as drug-seeking behavior due to inadequate analgesia, not substance abuse, may also have been considered in this case.17 An assessment by a chronic pain specialist—as recommended by the patient’s physician—may have further differentiated substance use disorder from potential pseudoaddiction. However, the patient’s cancellation and avoidance of a comprehensive pain assessment may make pseudoaddiction less likely, since patients with pseudoaddiction would want to pursue opportunities for improved pain relief with specialty pain management. In addition, the patient’s history of mood disorder placed her at greater risk for both alterations in chronic pain magnitude and substance use disorder.18 As previously mentioned, drug diversion was another possibility in the present case, based on the quantity of pregabalin obtained in a 28-day period and prior history of opioid diversion to a family member.

Conclusion
It is standard for healthcare professionals to be vigilant when prescribing opioids, benzodiazepines, and other commonly known drugs of abuse. However, it is also important for clinicians to use similar prescribing vigilance related to dose escalation, identification of multiple prescribers, and misuse with newer drugs, especially those with lower reported abuse potential. Past history supports such a recommendation: federal noncontrolled drugs such as cyclobenzaprine and carisoprodol that historically were not considered by clinicians or the DEA to be drugs with abuse potential are now on the DEA Office of Diversion Control’s list of most commonly abused drugs.19 In fact, the DEA has recently scheduled hearings to make carisoprodol, a muscle relaxer, a Schedule IV drug.20

Although current data and opinion suggest that pregabalin has a very low potential for abuse, the case presented shows that physicians should exercise caution when prescribing pregabalin, particularly in a patient with past substance abuse or drug-seeking behavior. The current case also demonstrates the importance of a comprehensive approach to chronic pain management, including psychological assessment, especially in a patient with a history of depression and anxiety contributing to aberrant drug-related behaviors. Further epidemiologic research regarding the incidence of pregabalin abuse should be considered in an effort to more accurately assess its incidence.

References