

Medical News & Perspectives

Growing Role of Gabapentin in Opioid-Related Overdoses Highlights Misuse Potential and Off-label Prescribing Practices

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Growing evidence of misuse and overdoses involving gabapentin—often in conjunction with opioids—is drawing attention to substantial off-label prescribing of the anticonvulsant drug.

A recent report from the US Centers for Disease Control and Prevention (CDC) found that between 2019 and 2020, coroners and medical examiners detected gabapentin in 5687, or almost 10%, of the 58 362 overdose deaths in 23 states



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and the District of Columbia that had available toxicology results. Officials ruled that gabapentin was a cause of death in almost 3000 of these cases. The number of fatal overdoses in which gabapentin was detected or involved increased from 2019 to 2020, apparently tracking with the overall increase in overdose deaths during the COVID-19 pandemic.

In almost 90% of fatal overdoses in which gabapentin was detected, opioids also were involved. The US Food and Drug Administration (FDA) in 2019 warned that gabapentin can cause severe breathing difficulties, especially when used with other central nervous system depressants like opioids, anxiety medications, or antidepressants or when used by older adults and people with respiratory risk factors such as chronic obstructive pulmonary disease. At that time, the agency had received 49 reports of respiratory depression among patients taking gabapentin or pregabalin, including 12 deaths. The agency also reviewed evidence from clinical trials and animal studies that confirmed the risk.

“We think [gabapentin] overdoses are primarily being driven by people with opioid use disorders vs people accidentally taking too much or taking multiple medications that suppress breathing,” Mance Buttram, PhD, an associate professor of public health at the University of Arkansas in Fayetteville who tracks drug misuse trends, said in an interview with *JAMA*.



The CDC data implicate illicit opioids—particularly illicitly manufactured fentanyl—in a growing proportion of gabapentin-involved overdoses. Illicit opioids were involved in about 57% of fatal gabapentin overdoses in the first quarter of 2019 compared with about 69% in the fourth quarter of 2020. Between the same 2 time points, the share of gabapentin-implicated overdoses involving prescription opioids declined from about 42% to 33%.

Gabapentin can produce feelings of euphoria and intoxication and can potentiate opioids' effects. Individuals who misused the drug reported multiple reasons in a 2019 study, including a desire to enhance the effects of opioids; to achieve a “high” when preferred substances were unavailable, such as when they were living in a treatment facility or were incarcerated; or to self-treat withdrawal or pain.

Two years prior, a study of gabapentin users found that many began to misuse the drug after an initial prescription for a usually off-label medical indication, like pain, detoxification, or anxiety. The partici-

pants reported using gabapentin in combination with buprenorphine, other opioids, cocaine, and caffeine to produce effects such as feeling drunk or “high,” muscle relaxation, sleep initiation, or pain relief. They also noted gabapentin's rising popularity among people that use illicit or prescription drugs for nonmedical reasons and cited easy access to the drug and its low street costs as potential explanations.

Prescribing Patterns

That easy access isn't surprising. In the US, prescriptions for gabapentin more than doubled between 2004 and 2019 from about 18 million to about 45 million. It was the sixth most prescribed drug nationally in 2021. The drug has FDA approval for treating seizures and pain associated with shingles. Yet it's used off-label for many other conditions, including anxiety, postmenopausal hot flashes, essential tremor, migraines, and many nonindicated types of pain. A recent study found that in 2018, 1 in 5 adults with chronic pain were treated with gabapentin or the related drug pregabalin,

which is [approved](#) for postshingles pain, fibromyalgia, and neuropathic pain caused by diabetes or a spinal cord injury. Increased prescribing of gabapentin and other nonopioid pain medications like antidepressants has followed a decline in prescribing potentially riskier drugs like opioids, the study showed.

"People are trying to use things other than opioids, and there aren't a lot of options when it comes to medication for pain," Christopher Goodman, MD, a clinical associate professor of internal medicine at the University of South Carolina School of Medicine Columbia, said in an interview.

Yet data supporting such widespread off-label use of gabapentin for pain is [limited](#). Researchers also have found limited evidence to support other off-label uses such as treatment for [alcohol use disorder](#).

"Gabapentin, by some estimates, is more widely prescribed off-label than what it is indicated for," Matthew Ellis, PhD, MPE, a research faculty instructor of psychiatry at the Washington University School of Medicine in St Louis, said in an interview. "We really don't have data on what efficacy and dosages look like for this off-label use."

Experts say gabapentin's growing off-label prescribing is inextricably linked with efforts to curb the ongoing opioid epidemic and historical marketing practices for the drug.

In 2004, the Parke-Davis Division of Warner-Lambert Company [pleaded](#) guilty and agreed to pay more than \$430 million to resolve a lawsuit filed by a former employee of the company over off-label marketing of its brand-name gabapentin product Neurontin. The legal case revealed a trove of documents [showing](#) how the pharmaceutical firm used medical education and research publications to shape prescribing practices—similar tactics drug companies have [engaged in to promote opioid use](#).

"The elephant in the room is the role of the pharmaceutical industry in the growth of gabapentinoid prescribing," Goodman said. "We are living in the world created by that push for off-label use."

[National efforts](#) to curb opioid misuse and overdose also have led to a shift to gabapentin prescribing. "Physicians have been afraid to prescribe opioids for fear that they will be contributing toward opioid misuse and abuse or that the Drug Enforcement Administration will prosecute them for prescribing opioids," Lynn Webster, MD,

a board-certified pain medicine specialist and senior fellow at the Center for US Policy, said in an interview. "There's been a significant movement to nonopioids and gabapentin because it is believed by most physicians that it is not abused and that it is less harmful."

Growing Misuse

However, misuse of gabapentin among individuals with opioid use disorders is common. In a recently published [survey](#) of almost 13 000 people seeking treatment for opioid use, about 9% reported nonmedical use of gabapentin during the past month.

"As prescriptions have drastically increased, [gabapentin] has become more readily accessible," Ellis said. About half of 49 individuals who [reported](#) past-year abuse of gabapentin and opioids in a 2020 study said they accessed them by sharing the drugs or trading for them with people they knew. Of the remaining participants, about 27% received a prescription for gabapentin, 20% bought it on the street, and 4% stole it. Forty-four percent of the prescriptions were for neuropathic pain, 25% were for withdrawal symptoms, 18% were for physical pain, 18% were for mental distress, and about 4% were for seizures.

Lack of access to substance use care could be 1 explanation for increased gabapentin misuse, Buttram said. He noted that insurance often covers only 1 month of such care. Based on conversations with patients, he has found that many leave care with a prescription for gabapentin and may try to continue using it without a prescription to avoid resuming opioid use. Longer-term treatment has been [shown](#) to lead to better outcomes, he said.

Ellis noted that lack of adequate chronic pain or mental health treatment in addiction care might also contribute to relapse to substance misuse. "If you just deal with addiction, it is just one piece of the puzzle," he said.

In some cases, gabapentin may be the best choice for both substance use and pain, according to Meg Chaplin, MD, an addiction psychiatrist in New Britain, Connecticut, who is board-certified in psychiatry and addiction medicine. The drug may be beneficial for treating alcohol use disorder symptoms and may also help with neuropathic pain resulting from chronic alcohol use. "[Gabapentin] does seem to be less risky than opioids, but we just don't have the data on whether it pro-

vides really good pain control," she said in an interview.

As concerns about misuse have grown, at least 11 states and the District of Columbia have added gabapentin to their [prescription drug monitoring programs](#) while at least 7 states have made it a controlled substance. The US Drug Enforcement Administration already classifies [pregabalin](#) as a schedule V controlled substance, indicating that it has some potential for abuse. The advocacy group Public Citizen [filed a petition](#) this February asking the agency to schedule gabapentin, too.

But these developments have been met with mixed reactions. Ellis explained that some clinicians support states taking steps to regulate gabapentin prescribing to help prevent a repeat of the misuse and overdose trends linked with opioid prescribing. For example, Chaplin said that prescription drug monitoring programs and drug scheduling can help remind prescribers that a drug has abuse potential. Others, however, worry that state or federal restrictions could limit access to gabapentin for patients who need it.

Individualizing Care

Buttram cautioned that research on gabapentin diversion and misuse is in early stages and that it's important not to "demonize gabapentin" or take an all-or-nothing approach. Instead, he and other experts argue for a personalized approach to care.

Chaplin recommended that physicians who are considering prescribing the drug off-label to approach it as an n-of-1 study, with a clear plan for how long they'll try the therapy, how they'll determine if it's helping, what will cause them to stop treatment, and what safeguards and monitoring will be in place.

Physicians should be particularly mindful of the risk of gabapentin misuse among patients with an opioid use disorder or a history of one. Chaplin advised using precautions like writing smaller and more frequent prescriptions, requiring urine tests, monitoring for early refills, and measuring evidence of benefit.

Pain and substance use disorders frequently co-occur. Ellis encouraged clinicians to treat both simultaneously because untreated pain can contribute to relapse. He suggested new approaches to ensure that patients receive the interdisciplinary care they need, such as locating pain and

addiction treatment services together or partnering with other clinicians across disciplines. "They're so significantly intertwined you can't address one without the other," he said. "We need to think about holistic care and treating the individual."

Webster pointed out that gabapentin has a significant adverse effect profile, which according to the FDA's 2019 warning may include drowsiness, dizziness, blurry or double vision, difficulty with coordination and concentration, and swelling of the hands, legs, and feet. Yet he asked physicians to also consider the potential harms of no pain treatment or inadequate treatment, such as depression or suicide. "We need to acknowledge that [pain medicine] is a difficult field, and a lot of research needs to be done to help us find safer and more effective therapies," he said. "That's going to take time."

Going forward, Goodman wants to see better regulation of pharmaceutical marketing practices, including direct-to-consumer advertising and the use of *seeding trials*, small industry-funded pilot studies for off-label indications that have been described as marketing ruses. These exploratory studies without follow-up confirmatory trials may contribute to potentially harmful off-label use, one *analysis* suggested.

Unless such changes are made, Goodman said, "We are just going to keep living in these boom-and-bust prescribing cycles with the current relationship between health care and the pharmaceutical industry." ■

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Health and Hospital Authority and the National Institute on Drug Abuse; consulting for the United Way of Broward County Commission on Behavioral Health and Drug Prevention; and receiving an honorarium to speak at the Researched Abuse, Diversion and Addiction-Related Surveillance System annual meeting. Dr Ellis reported that he is a member of the Scientific Advisory Group for the National Drug Early Warning System. Dr Webster reported receiving payments from pharmaceutical and technology companies BDSI, CognifiSense, Ensysce, Neurana, Pharmacom, Salix, Kempfarm, Elysium, and Shinogi for consulting fees, honoraria for CME presentations or other speaking engagements, travel expense reimbursement, expert testimony, and clinical research. Dr Webster also reported that he is associate editor of the special populations section of *Pain Medicine*; chief medical officer of PainScript, a company that makes a digital tool for managing patients with pain and addiction; and author of a book and coproducer of a documentary, both about pain. No other disclosures were reported.

Note: Source references are available through embedded hyperlinks in the article text online.