Pennsylvania Overdose Reduction
Technical Assistance Center (TAC)

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Gabapentin Background Report

INTRODUCTION

In recent years, gabapentinoids have appeared in an increasing number of toxicology reports across Pennsylvania. To understand the rise in fatal overdoses, Pitt PERU's gabapentin working group conducted a literature review on gabapentin and pregabalin, two medications comprising the gabapentinoid drug classification. The aim of this report is to understand the increase in gabapentin prescription and overdose deaths, recognize the risks involved with co-prescriptions of gabapentin and opioids, and present considerations for next steps for providers, drug scheduling, and beyond regarding gabapentinoid medications.

GABAPENTIN

Gabapentin was first approved by the U.S. Food and Drug Administration (FDA) in 1993 for epilepsy.[11] In 2002, gabapentin was approved by the FDA for its use in the treatment of pain caused by shingles (post-herpetic neuralgia pain), making it one of the first-line medications used for the treatment of nerve pain following shingles, neuropathic pain (such as multiple sclerosis or phantom limb syndrome), and restless leg syndrome.[25,26] While gabapentin currently has two FDA-approved indications, it is one of the top ten most prescribed medications in the United States.[3] Since its introduction, gabapentin has been prescribed for several off-label uses and non-FDA-approved indications, including treating agitation in dementia, drug and alcohol withdrawal, bipolar disorder, nerve damage caused from diabetes, anxiety, fibromyalgia, migraines, and the list continues to grow.[26] In fact, a study that focused on the managed Medicaid population indicated that 95% of patients who were prescribed gabapentin were using this medication for off-label diagnoses.[22]

Gabapentin and its analogs are collectively referred to as gabapentinoids.[11] In particular, gabapentin is in a class of medications known as anticonvulsants, as this medication affects chemicals and nerves in the body that are involved in the cause of seizures and some types of pain. Gabapentin treats seizures by decreasing abnormal excitement in the brain. Gabapentin has a white, solid crystalline physical appearance and includes the following brand names: Neurontin®, Gralise®, Fanatrex®, and Horizant®.[11,28] Gabapentin can be commercially obtained as capsules or tablets of different doses, such as 100, 300, and 400 mg capsules or 300, 600, and 800 mg tablets. Particular patient groups that gabapentin may be useful for include cancer patients, HIV patients, transplant patients, and those on anticoagulant (i.e., blood thinner) treatments.[28]

The mechanism of action of gabapentin is currently unknown. Gabapentin is an amino acid related structurally to gamma-aminobutyric acid (GABA)—a neurotransmitter.[26] Neurotransmitters communicate messages from one brain cell to another. GABA tells neurons to slow down or to stop firing, causing a quietening effect on the brain. Approximately 40% of the brain's neurons are responsive to GABA, so the GABA neurotransmitter and related medications can have quite an impact on the brain.[35] Gabapentin appears to work by altering electrical activity in the brain and influencing the activity of the neurotransmitters that send pain messages between nerve cells. Clinical studies demonstrate that gabapentin relieves patients of their neuropathic conditions by changing the way the body senses pain.[14]

Gabapentin is known to have a diverse range of side effects, including drowsiness (somnolence), fatigue, dizziness, respiratory failure, slowed breathing (hypoventilation), involuntary coordination of muscle movements (ataxia), vision distortion, physical weakness (asthenia), self-harm behavior, and suicidal behavior. Additionally, gabapentin is also known to make the user become very friendly, talkative, and disinhibited.[28] Supratherapeutic doses (greater than that of medical recommendation) of gabapentinoids may have effects including sedation, dissociation, numbness, contentment, relaxation, uninhibited behavior,

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improved sociability and empathy, and audio/visual hallucinations.[11] Gabapentin use may include dissociations similar to that reported for dextromethorphan (i.e., cough syrup). More research is needed to specify and confirm all potential side effects, as there is a wide range; however, the route of administration of gabapentin is a relevant factor that influences its potential side effects.[28]

PREGABALIN

Another drug to consider when discussing gabapentin is one of its most comparable medications on the market, a gabapentin analog known as pregabalin. Pregabalin is sold under the brand name Lyrica® and was introduced into the market in 2004. Like gabapentin, pregabalin is also approved to treat seizures and shingles (post-herpetic neuralgia), as well as all FDA-approved indications that gabapentin is designed to treat. However, unlike gabapentin, pregabalin is FDA-approved to treat neuropathic nerve pain associated specifically with diabetes and pain associated with fibromyalgia.[27] In some cases, pregabalin is a suggested medication for drug and alcohol withdrawal symptoms, specifically for the treatment of opioid, benzodiazepine, nicotine, cannabinoid, and alcohol dependence. However, the role of pregabalin in substance use populations, particularly for opioids, is not sufficiently explored and more research is required.[33]

Although pregabalin does interact with the same neurotransmitter and has a similar pharmacologic profile as gabapentin, its binding affinity to receptors in the brain and the potency of the medication is six times more than that of gabapentin.[18,23] Furthermore, orally administered pregabalin is absorbed more rapidly in the body than gabapentin and remains present in the bloodstream for longer periods of time. The increased potency and bioavailability allow for pregabalin to achieve the effects of gabapentin but at a lower dose.[7] Although pregabalin has shown to have formidable clinical efficacy and distinct advantages over gabapentin, these improved therapeutic effects also increase its potential for abuse. To address this, the U.S. Drug Enforcement Administration (DEA) has classified pregabalin as a controlled substance, listed as a Schedule V (defined as a low potential for misuse compared to Schedule IV drugs). Medications containing gabapentin are not currently scheduled as controlled substances by the DEA.

Pregabalin has euphoric and sedative properties like other substances that are frequently misused, and these properties may contribute to the misuse of pregabalin.[32] Pregabalin users can obtain their legitimate prescriptions through family doctors and/or psychiatrists. However, this medication is reported to be diverted for illegitimate use, much like gabapentin.[33] It is also important to note that if a user abruptly discontinues the use of a gabapentinoid medication, they may experience withdrawal symptoms that suggest physical dependence. There are also case reports describing intense mental cravings for gabapentinoid medications.[11] Due to the euphoric effect and potential cravings associated with gabapentinoids, these medications can be sold and consumed illicitly.

GABAPENTINOID ILLICIT USE

There is a street market demand for gabapentinoid medications, including both gabapentin and pregabalin. Due to its widespread off-label use, obtaining a gabapentin prescription is relatively easy. Misused gabapentinoid medications are most commonly obtained from a healthcare provider, given by family or friends, purchased online, or obtained abroad. Gabapentin is a relatively inexpensive medication, and individuals may receive a prescription at a low cost or nearly free of charge. As a result, the licit and illicit market has been flooded with gabapentin over the years.[11]

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Individuals may misuse their prescribed medication recreationally, or they may choose to obtain the medication illicitly for their recreational pursuits. The deception of gabapentinoid users are reported in the following ways: doctor shopping, fabricating symptoms to receive prescriptions or to obtain higher doses, requesting prescription refills early, and/or filling a prescription at multiple pharmacies in rapid succession.[11] Gabapentin is also sold on the Internet without the need for a medical prescription, and it is often distributed at a very low price.[28] The reported illicit market value for gabapentin ranges from less than one to seven dollars per pill, depending on strength, and it is known among the drug-using population as a "cheap man's high."[32] Gabapentin pills may be traded on the street for other drugs, which increases the likelihood of diversion.[11]

With the increased emphasis by providers and pharmacists on reducing the number of opioid and benzodiazepine prescriptions, patients may be substituting their drug use with other licit or illicit drugs in greater availability. Specifically, for some patients in substance use disorder (SUD) treatment, misusing gabapentinoids can potentiate the effects of methadone or Suboxone® (buprenorphine/naloxone).[28] A self-reported survey of a prison population supported the potentiation of methadone as an illicit use; 22% of the survey respondents reported that they had abused gabapentinoids, and of those, 38% abused gabapentinoids with the intention of potentiating their methadone high.[5] Using this medication type also may avoid detection during routine Urine Drug Screen (UDS) monitoring. Additionally, police reports have cited gabapentin as a potential cutting agent for heroin.[31] Patients with a tolerance after long-term opioid use may gravitate toward gabapentinoids to explore the euphoric effects of a new drug.[11]

POTENTIAL FOR MISUSE

Research suggests that there is a statistically significant difference in gabapentin misuse between patients with a history of opioid use disorder (OUD) and those without. According to the results of an assessment of former inmates, individuals with a history of OUD have a 22% higher chance of taking gabapentin alongside opioids.[6] Another study concluded similar results, reporting approximately 22% of the participants interviewed in regard to their substance use reported that they used non-prescription gabapentinoids to potentiate the effect of opioids, as well as to get high.[5] These numbers are consistent with the results of yet another study, which indicated that around 36% of the study participants seeking inpatient detoxification with a history of OUD were misusing prescription medications. Of the medications reported, gabapentin misuse was the second highest with a report of 22%.[37]

Factors that contribute to the appeal and prevalence of gabapentinoid misuse include their relative ease of obtaining large quantity prescriptions, low cost, misunderstanding of misuse potential by medical professionals, rapid-dose titration schedules, and frequent off-label use described as "good for what ails you."[11,36] Due to large dosages and the lack of scheduling, the supply of gabapentin is more readily available than opioids or other drugs of misuse. Overall, the maximum recommended dose of pregabalin and gabapentin are 600 and 3,600 mg per day, respectively, and these doses are divided throughout the individual's day in multiple pills or capsules.[32] Pills can be procured for "a dollar apiece for 800 milligrams," compared to more expensive pills of misuse such as Xanax® and Oxycontin®.[10] Gabapentinoids are typically taken orally; however, other routes of administration include smoking, injecting, inhaling crushed tablets, rectal plugging, or parachuting (emptying the tablet or capsule contents into a pouch such as toilet paper and swallowing).[11] There are also accounts of individuals snorting gabapentin powder to experience a similar high to that of cocaine.[32]

Motivations for misusing gabapentinoids are classified into three main categories: recreational (to get high), self-medication (for anxiety, pain, or withdrawal symptoms of other drugs such as cocaine, opioids, or

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alcohol), or self-harm.[11] One impetus for gabapentin misuse is to experience its sedative, relaxing, calming effects, which can be achieved in combination with other substances. Gabapentinoid misuse is often in combination with other drugs such as opioids, alcohol, benzodiazepines, zopiclone, amphetamines, marijuana, baclofen, selective serotonin reuptake inhibitors (SSRI), quetiapine, or LSD.[11] Studies suggest that buprenorphine and tramadol are among the most common drug combinations alongside gabapentinoids. Other desirable effects of gabapentin include sociability, disassociation, increased energy and focus, and improved quality of sleep.[32] Gabapentinoid misuse occurs at supratherapeutic doses, which are in clear excess of the recommendations provided by a clinician.[11] The feelings of calm can also be achieved with gabapentin alone with a dose range of 600 to 4,800 mg, and the euphoric effects of gabapentin can be achieved on high dosages of gabapentin, specifically 1,500 to 12,000 mg.[32] Individuals who misuse gabapentin have claimed that the euphoric effects are reminiscent of opioids, though not quite as strong.

In addition to the potential for misuse of gabapentin, there are specific concerns about misusing pregabalin, particularly among patients with former or current SUDs. Major motivations for using pregabalin include decreasing opioid withdrawal symptoms, increasing the effects of other psychotropic substances, and the psychotropic effects available with pregabalin in particular.[33] There is a growing recognition that combining heroin and specifically pregabalin may enhance the effects of the heroin. Gabapentin and pregabalin are both prescribed to opioid and/or heroin users directly, and they can also be purchased on the street with ease. Desired behavioral effects such as relaxation, euphoria, enhanced sociability, dissociation, and sedation are all reasons why an individual may choose to misuse gabapentinoid medications, particularly in conjunction with using heroin. This has its own risks, as the combination of pregabalin and heroin may cause blackouts or loss of control. Opioid and heroin users that misuse gabapentin or pregabalin are at an increased risk of acute overdose death due to the reversal of tolerance or due to decreased breathing.[25]

GABAPENTINOID CO-PRESCRIBING

Although gabapentinoids are generally perceived as safe medication options, respiratory depression is a serious and potentially fatal health outcome that may occur when gabapentinoids are used alone and/or in combination with other central nervous system (CNS) depressants, including benzodiazepines, muscle relaxants, and opioids.[4] Both gabapentinoids and opioids slow down the central nervous system leading to a slowing of breathing rate and heart rate. According to a population-based nested case-control study examining the risk of death when taking gabapentin and opioids, individuals who simultaneously used gabapentin and opioids have a 49% higher chance of experiencing a fatal opioid overdose compared to those that used opioids alone. This study indicates that the increased risk of a fatal overdose was due to the effect of slow, ineffective breathing caused by the combination of gabapentinoids and opioids.[20]

The dosage of gabapentin consumed also affects the danger of a fatal overdose in combination with CNS depressants. The nested case-control study compared the gabapentin dose for those individuals taking both opioids and gabapentinoids and concluded that the likelihood of a fatal overdose was increased by 60% in individuals taking a moderate (900 – 1,799 mg/day) to high (≥1,800 mg/day) dose of gabapentin.[20]

Aside from opioids, gabapentin may have adverse drug interactions when taken with the following medications: morphine, naproxen, losartan, caffeine, sevelamer, cimetidine, magnesium oxide, mefloquine, phenytoin, and ethacrynic acid. On the other hand, studies suggest that gabapentin may interact synergistically with metamizole or tramadol for alleviating pain symptoms.[28]

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RISK FACTORS FOR GABAPENTINOID MISUSE

The factor most associated with gabapentinoid misuse is opioid misuse.[11] A systematic assessment of a public detoxification program suggests that among individuals treated for OUD, 22% reported gabapentin misuse and 7% reported pregabalin misuse, whereas 0% of those with non-opioid SUD reported gabapentinoid misuse.[37] Another study performed at a community correctional center's treatment program corroborated these findings.[6] Other drugs such as cocaine, concurrent cannabis use, and benzodiazepines are associated with gabapentin misuse, though alcohol does not appear to be a predictor. Psychiatric comorbidities (one or more conditions that occur alongside a primary condition) may also be associated with gabapentinoid misuse. While this comorbidity is common with drugs with misuse potential, gabapentin's numerous off-label uses and large quantity available in the community may provide further risk.[11] Prison populations may also be at additional risk of gabapentin misuse and diversion, especially individuals with prior substance misuse.[29]

GABAPENTINOID DRUG TRENDS IN OVERDOSE DEATHS

Overdose death toxicology reports demonstrate a statistically significant ($p<0.05$) increase in gabapentinoid-related overdose deaths in Pennsylvania between 2015 and 2018. In 2015, gabapentinoids comprised 4.17% of total overdose deaths in Pennsylvania, which increased to 4.31% of total overdose deaths in 2016, 4.66% of total overdose deaths in 2017, and 5.50% of total overdose deaths in 2018.[1] The increase in gabapentinoid presence in overdose deaths is also strongly correlated ($r = 0.887$) with the overall increase in overdose deaths from 2015 to 2018. There were a total of 4,491 overdose deaths across Pennsylvania in 2018, and gabapentinoids contributed to 247 of the overdose deaths.[1] While there has been an increase in overdose deaths involving gabapentinoids across Pennsylvania, examining the overdose death reports regionally gleans an understanding of the scope of the issue across the state.

The prevalence of overdose death reports that include gabapentinoid medications varies in range across the state. The region displaying the greatest percentage of gabapentinoid medications compared to the total overdose deaths reported is the north central region, where gabapentinoids accounted for an average of 12.5% of the total overdose deaths from 2015 to 2018. Between 2015 and 2018, gabapentinoid-related deaths comprised 8.75% of the total deaths for the south central region, 7.75% for the northeast region, 5.1% in the southwest region, 5% in the southeast region, and 2.25% average for the northwest region.

In addition to the percent of gabapentinoids found in aggregate overdose death reports from 2015 to 2018, examining the annual increase of gabapentinoid-related cases from 2015 to 2018 is also illuminating. Annual gabapentinoid-related cases increased in five of the six regions in Pennsylvania between 2015 and 2018, while the southwest region exhibited a decrease during this time frame. Of the regions with an increase, the southeast and northeast reported statistically significant ($p<0.05$) increases from 2015 to 2018, while the north central, northwest, and south central regions demonstrated non-significant ($p=0.32$, 0.85, 0.07, respectively) increases. The southeast region increased from 61 to 109 gabapentinoid-related deaths, while the northeast region increased from 27 to 55. In contrast, gabapentinoid-related overdose deaths in the southwest region decreased significantly ($p<0.05$) from 15 in 2015 to one in 2018.

Additionally, examining the percent change of overdose deaths regionally can provide an understanding of the rise in overdoses at a local level. There is an increase of gabapentinoids in overdose death reports evident from 2015 to 2018 in the north central (3% increase), northeast (3% increase), south central (6% increase), and southeast (0.5% increase) regions. The cause of the increase could be due to more gabapentin

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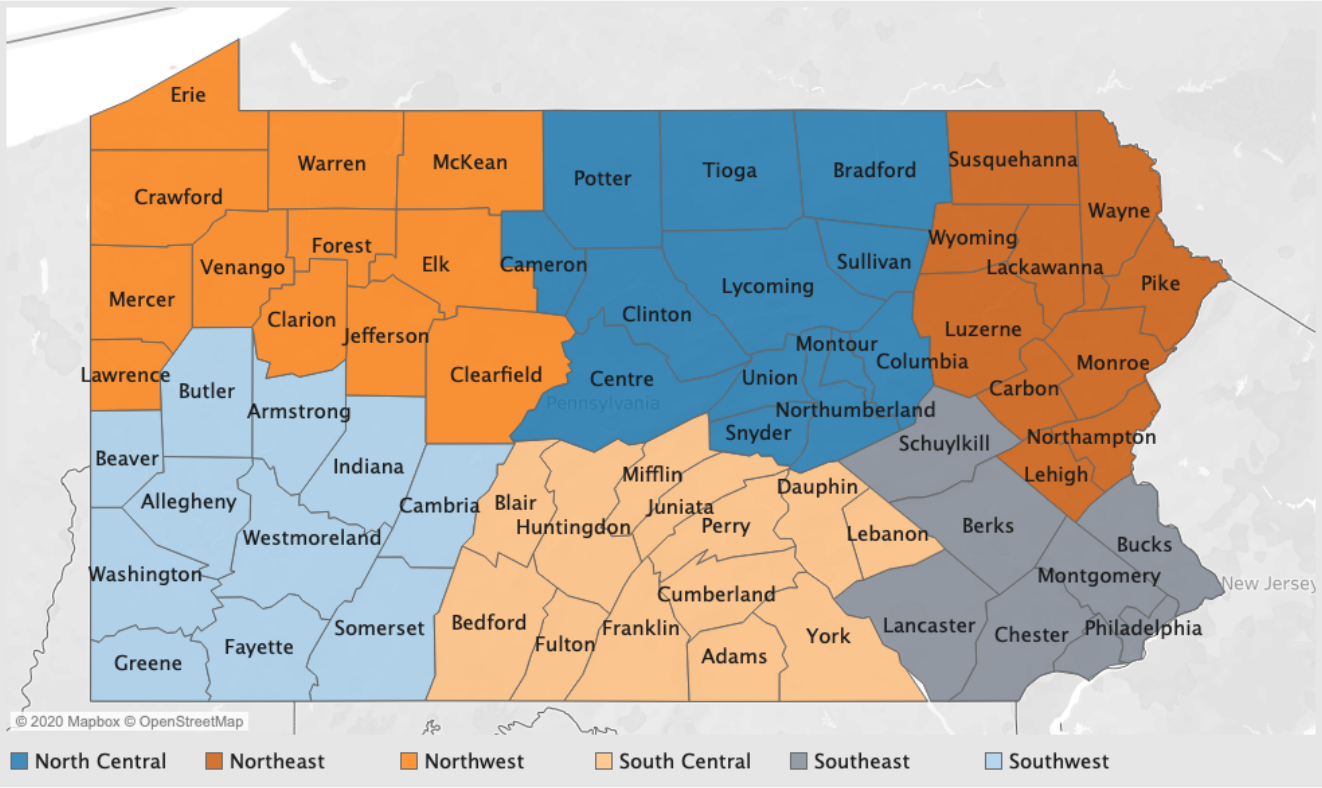
prescriptions available to individuals in the community or due to an increase in illicit gabapentin procurement. Both the southwest and northwest regions indicate a slight decrease in gabapentinoids found in overdose death reports from 2015 to 2018, a 1.97% decrease and 1% decrease, respectively.[1] This indicates that gabapentinoid use has increased in the central and eastern parts of the state, while the use of gabapentinoids in the western portion of Pennsylvania is slightly less prevalent.

While overdose death reports provide an understanding of the lethality of gabapentinoids for Pennsylvania in particular, it is difficult to infer the availability of gabapentinoids through overdose death data alone, as it does not account for the number of active prescriptions available licitly and illicitly. There are additional limitations to the way in which coroners report the overdose deaths that occur in their communities. Across the state, coroners do not follow a standardized protocol in terms of reporting their procedures for toxicology and autopsy reports, which may create inaccuracies in the total number of overdose deaths in which a gabapentinoid was present. For example, coroners may only report demographic information without including data on the drugs present in the toxicology report. Additionally, not all coroners use the same toxicology testing methods, which may not account for all gabapentinoid medications. These limitations should be kept in mind; however, the trends indicated by the overdose death data provide valuable insight into the use of gabapentinoids in Pennsylvania.



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ROLE OF HEALTHCARE PROVIDERS

Physicians and pharmacists should be aware that there is potential to misuse gabapentinoids, and this potential is greater for individuals who have an SUD. Gabapentinoids are often used for treating conditions that are measured on subjective means, which may allow patients to exaggerate or fabricate symptoms to obtain a new prescription or receive a higher dose. As such, prescribers and pharmacists must be aware of the high risk of gabapentinoid misuse.[11] Healthcare providers should monitor their patients' conditions for signs of misuse and/or diversion. Indicators of gabapentinoid misuse include claiming a medication was lost or stolen, filling prescriptions at multiple pharmacies, requesting to pay out-of-pocket rather than billing insurance, asking for a particular drug or a higher dosage, receiving prescriptions from multiple providers, or requesting refills early. Negative urine drug screens may signal diversion of the medications. In addition, healthcare providers can tailor their efforts to limit the quantities of gabapentinoids prescribed, use caution when prescribing for off-label use, prevent withdrawal by tapering the dosage, and manage the patient's pain adequately (such as referring to a specialist).[11]

It is also advised that clinicians use great caution for co-prescribing gabapentin, pregabalin, and/or opioids, especially when the dose of any drug is high. A fatal overdose may occur due to depressed respiration or from reversing the patient's tolerance.[24] Physicians and pharmacists may be aware of the dangers of co-prescribing gabapentin and pregabalin, though fewer warnings are released on the deadly risk of co-prescribing gabapentinoids and opioids.[19] When the clinician deems it necessary to combine these medications, the clinician should inform the patient of the risks of taking both medications, closely monitor the patient, and adjust the dose of both medications accordingly. Pharmacists can provide a second touchpoint to educate the patient on the risks of taking both medications simultaneously. Some strategies clinicians can use to minimize the risk of overdose for patients that they deem both medications necessary include dose titration, dose adjustment in the setting of comorbid lung and kidney disease, and avoidance of other CNS depressants.[20] Healthcare providers should also exercise the same caution of co-prescribing gabapentinoids, opioids, and benzodiazepines as they may result in a fatal combination.[11]

GABAPENTINOID DRUG SCHEDULING

Pregabalin is classified as a Schedule V drug by the DEA (defined as a low potential for misuse compared to Schedule IV drugs), though gabapentin is not a federally controlled substance at this time.[10] However, several states have scheduled gabapentin, including West Virginia, Kentucky, Tennessee, Michigan, North Dakota, and Virginia.[2,9,12,15,20,34] Additionally, several states, including Minnesota, Massachusetts, and Wyoming, are requiring gabapentin monitoring in their statewide prescription drug monitoring programs (PDMP).[8,13,16,28] Reasons for these actions include an increase in gabapentin prescription early refills, increase in risk of respiratory depression when combined with opioids, increased presence of gabapentin in postmortem toxicology, and off-label and illicit usage.

While there is a growing body of evidence suggesting gabapentinoid misuse over recent years, gabapentin has an important role in pain management and treatment of chronic conditions, such as epilepsy. Therefore, it is necessary to consider these benefits when determining whether Gabapentin should be re-classified.[32] Alternatives to re-classification include a greater emphasis on identifying misuse and encouraging safe prescribing guidelines, particularly when other CNS suppressant medications are co-prescribed.[11]

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COMMUNITY CONSIDERATIONS

Community members, including family, friends, and peers, should be aware of the growing number of reports on the potential misuse of gabapentinoids, especially for those with a history of SUD. Due to the high volume of gabapentin dispensed in a single prescription combined with the increasing number of gabapentin prescriptions, the supply in communities makes the risk of abuse and diversion a serious threat. Community members and providers alike should provide information and encourage the usage of medication take-back events, permanent drop-off locations, and other safe medication disposal options. The less unused medication in the community, the less chance of misuse and potential overdose. Several states have already begun requiring PDMP monitoring of gabapentin, so training prescribing providers to expand their usage of PDMP to include gabapentin monitoring can help reduce the possibility of duplicative prescriptions and diversion. There is also a need for healthcare providers to be more cautious about the number of gabapentinoid prescriptions they are prescribing and to use their best clinical judgment when increasing the dosage units for a patient's prescription and when prescribing for any off-label indications. Gabapentin's reputation as a catch-all pain remedy that is less dangerous than opioids has provided benefits for many individuals, but this medication is not without risk, and continued off-label and illicit usage has sparked concern around the country.

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