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Review Article

Illicit Use of Gabapentin May Reveal More About the Drug's Benefits Than Its Liabilities

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Abstract: The anticonvulsant gabapentin is now one of the most commonly prescribed drugs in America. However, after nearly three decades of steady growth in popularity, the drug is becoming as controversial as it is popular. Although gabapentin was initially approved for the adjunctive treatment of partial seizures, its use has gradually expanded to an ever-increasingly number of disorders, including neuropathic pain, restless leg syndrome, generalized anxiety disorder, bipolar disorder, treatment-resistant depression, post-traumatic stress disorder, chronic insomnia, various substance use disorders, chronic insomnia, diabetic neuropathy, postoperative analgesia, tension headache, migraine headache, fibromyalgia, irritable bowel syndrome, hot flashes, essential tremor, nausea and vomiting, interstitial cystitis, overactive bladder, pruritus, chronic cough, and persistent hiccups. However, in addition to its prescription use, gabapentin is now becoming increasingly popular among illicit users, a phenomenon that appears to be the primary basis of the growing controversy around the drug. This article will explore both the benefits and liabilities of gabapentin in an effort to dispel the myths and clarify the facts about the drug. It will also compare the benefits of gabapentin to other anticonvulsants, analgesics, and psychotropic drugs in an effort to arrive at a more accurate risk-benefit assessment of gabapentin's use. With an ever-increasing amount of information being uploaded to the internet, it is especially important for those who have the most experience prescribing and researching gabapentin to tease out the misinformation and provide the medical community and the public with the most accurate possible understanding of the drug. Only then will we be able to take the greatest advantage and avoid the most harm in relation to this inexpensive and widely-prescribed pharmacological resource. Those interested in addition evidence-based information on gabapentin are directed to the article, Gabapentin: The Popular but Controversial Anticonvulsant Drug May Be Zeroing in on the Pathophysiology of Disease.

Keywords: Gabapentin, Neurontin®, Anxiety, Mood Swings, Chronic Pain, Drug Withdrawal, Neuronal Hyperexcitability, Mood Stabilizers

1. Introduction

After nearly 3 decades on the market as a safe, well-tolerated, and highly versatile anticonvulsant drug, gabapentin's safety and tolerability have, in recent years, been called into question. Some critics have raised concerns that the drug could be highly addictive; others fear that it could have serious respiratory depressant effects; and still others claim that it could be impairing brain function by preventing the formation of new connections between neurons. However, these concerns are inconsistent with gabapentin's long history of uneventful use; hence, they raise the question of whether the factors driving them could be related more to gabapentin's growing popularity among illicit users than any new facts about the safety of the drug itself.

In an effort to provide an unbiased assessment of gabapentin, this review will discuss the potential risks and benefits of the drug in conjunction with its proposed mechanism of action in treating the growing number of disorders for which it is currently being used. It will also discuss the potential role of gabapentin in helping to prevent

the development of those disorders.

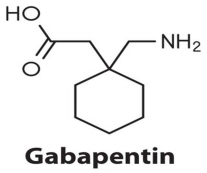

Figure 1. *Molecular structure of gabapentin.*

2. Therapeutic Effects of Gabapentin

2.1. Seizure Control

Normally, select neurons of the brain fire in a coordinated or "synchronous" pattern so as to regulate the various functions of the body. Neuronal firing also induces magnetic fields that stimulate specific thoughts, emotions, and sensations in the perceptual element (mind) of a human being [1]. However, when large clusters of neurons called "nests" fire simultaneously, they can overstimulate various muscles of the body, resulting in rhythmic muscular contractions called "convulsions." The so-called "hypersynchronous" firing can also induce abnormally large magnetic fields that exceed the normal range of human perception. As a result, a complete or partial breakdown in communication between the mind and the brain can occur resulting in a change in sensorium and, in some cases, a complete loss of consciousness.

Gabapentin (and other anticonvulsant drugs) reduce the risk of hypersynchrony by reducing the excitability of neurons throughout the brain. Gabapentin is thought to reduce neuronal excitability by several mechanisms [2]. It binds to the alpha-2-delta type 1 subunit of voltage-sensitive calcium channels, which inhibits calcium-mediated membrane depolarization [3, 4]. It also has the dual effect of decreasing the release of the main excitatory neurotransmitter glutamate [5] and increasing the concentration of the main inhibitory neurotransmitter gamma-aminobutyric acid (GABA) [6]. Gabapentin also modulates the activity of glutamate synthesizing enzyme and glutamic acid decarboxylase, the latter of which is involved in the synthesis of GABA. These actions have the effect of decreasing glutamate signaling and increasing GABA signaling, respectively [4]. Finally, by blocking excitatory neurotransmission, gabapentin may indirectly increase the concentration of GABA in the central nervous system [4, 5]. These brain-calming effects combine to make gabapentin highly effective in the prevention of seizure activity.

2.2. Postherpetic Neuralgia

Postherpetic neuralgia is neuropathic pain caused by irritation of a peripheral nerve in association with the reactivation of the varicella zoster virus. The condition, which is more commonly known as "shingles," is typically confined to an area of skin innervated by a single sensory nerve. The nerve pain, which must persist for at least 90 days to qualify for the diagnosis, typically begins after the herpes zoster vesicles have crusted over. The types of pain that may occur during a shingles outbreak include stinging, burning, or electric shock-like pain together with a heightened sensitivity to touch. Although there is no known antidote for the condition, topical pain relievers, such as capsaicin and lidocaine, may be helpful, as can anticonvulsant drugs, such as gabapentin and pregabalin [6]. The mechanism by which anticonvulsants can help reduce the pain of shingles is thought to be the same as that by which they prevent seizures; namely, by quieting the nervous system [7, 8]. Various anticonvulsants appear to be equally effective for the condition [9], but among them only gabapentin and pregabalin are FDA approved for the condition [10].

2.3. Restless Leg Syndrome (RLS) and Periodic Limb Movement Disorder (PLMD)

RLS, also known as "Willis-Ekbom disease," is an irresistible urge to move the arms or legs while at rest. The sensation can occur during the day or night, and the movements are voluntary. PLMD, also known as "nocturnal myoclonus," is a frequently associated condition characterized by limb movements that occur involuntarily and only during sleep. In both disorders, the movements can range from mild to severe, and both can be a significant source of sleep disruption because of the proclivity of the movements to occur when the individual is at rest. In addition to being closely related in their symptomatology, the two disorders commonly co-occur; approximately 80% of those with RLS also have PLMD. The two disorders also tend to co-occur with various psychiatric disorders, thus suggesting that the underlying cause of the two disorders could be related to the underlying cause of mental illness.

The initial evaluation of RLS and PLMD involves a search for readily reversible causes, such as excessive intake of caffeine, alcohol, or nicotine. It also involves a search for possible underlying medical causes, such as nutritional deficiencies, anemia, thyroid disease, renal disease, varicose veins, diabetes, and Parkinson's disease. If this work-up is negative and symptoms occur at least three nights per week, a trial of medication is indicated. Based on the idea that RLS and PLMD are caused by dopaminergic dysfunction, first-line medical therapy typically involves dopaminergic drugs. However, anticonvulsants and other drugs that quiet the nervous system have also been found to be helpful. The proposed mechanism by which anticonvulsants may help relieve the symptoms of RLS and PLMD is the same as that by which they are thought to relieve the symptoms of the various psychiatric disorders with which RLS and PLMD are commonly associated; namely, by reducing the excitability of the neurological system [8]. Although any of the currently available anticonvulsants, including the benzodiazepine anticonvulsants, could potentially reduce the symptoms of RLS and PLMD, gabapentin is the only one that is FDA-approved for this use.

2.4. Psychiatric and Functional Physical Symptoms and Disorders

The use of gabapentin in the treatment of various

psychiatric and functional physical symptoms and disorders is rapidly expanding. Initially, gabapentin showed promise in the treatment of generalized anxiety disorder [11, 12]; however, it is becoming increasingly clear that gabapentin can also be of benefit in the treatment of panic disorder [13], social phobia [14], post-traumatic stress disorder [15], bipolar disorder [16], schizophrenia [17], treatment-resistant depression [18], chronic insomnia [15], tension headache [19], migraine headache [19, 20], fibromyalgia [21], irritable bowel syndrome [22], chronic pain [23], hot flashes [24], essential tremor [25], nausea and vomiting [26], interstitial cystitis [27], overactive bladder [28], pruritus [29], chronic cough [30], and persistent hiccups [31].

The advantages of gabapentin over other drugs that are commonly used to treat the aforementioned symptoms and disorders are its safety, tolerability, speed of action, long-term effectiveness, and low addiction potential. For example, when gabapentin is used to treat anxiety disorders, its therapeutic effects are much more rapid than those of antidepressants, and it is less likely to cause weight gain, insomnia, or sexual side effects. In comparison to benzodiazepines, gabapentin's anxiolytic effects are equally rapid but with less sedation and psychomotor impairment. Gabapentin also has less of a proclivity than benzodiazepines to cause tolerance and withdrawal.

When used as a mood stabilizer, gabapentin is generally safer and more tolerable than other anticonvulsants, such as carbamazepine, oxcarbazepine, depakote, lamotrigine, topiramate, and levetiracetam. No laboratory monitoring is needed and, due to its lack of hepatic metabolism, gabapentin may be favorable to benzodiazepines in the management of alcohol use disorders.

When used as an adjunct in the treatment of schizophrenia, gabapentin has fewer side effects than antipsychotics drugs because, like clozapine, it appears to act by mechanisms other than dopamine blockade [32, 33]. This can help spare patients the extrapyramidal side effects that are induced by antipsychotic drugs; in fact, there is some evidence that gabapentin can be used to actually reduce antipsychotic-induced akathisia [34].

When used for treatment-resistant depression, gabapentin is far less likely to cause bipolar switching than increasing the dosage of an antidepressant or adding another antidepressant. Actually, gabapentin tends to stabilize mood; hence its classification as a "mood stabilizer." Also, because gabapentin lacks the stimulatory effects of other antidepressant augmentation strategies, such as adding a psychostimulant or thyroid supplement, it is less likely to exacerbate the underlying cause of depression, which is thought to be an inherent hyperexcitability of the neurological system [7]. This, together with gabapentin's low potential for tolerance, helps explain why it tends to be more continuously effective. Another advantage of gabapentin is its beneficial effects on sleep. This is in contrast to some antidepressants, which can further exacerbate the insomnia that is often associated with and tends to perpetuate clinical depression.

In the treatment of the aforementioned functional physical symptoms and disorders, such as migraine headache, fibromyalgia, irritable bowel, and chronic cough, the advantage of gabapentin is that it is generally safer and better tolerated than the agents that have traditionally been used, such as triptans, antidepressants, benzodiazepines, opioids, anti-inflammatories, antihistamines, and decongestants.

The mechanism by which gabapentin reduces symptoms in the aforementioned psychiatric and functional physical ailments appears to be the same as that by which it prevents seizures—it reduces neuronal excitability. This idea is the premise of an emerging hypothesis that contends that all of the most common psychiatric and functional physical symptoms and disorders are rooted in an inherent hyperexcitability of the neurological system [7]. According to the multi-circuit neuronal hyperexcitability (MCNH) hypothesis of psychiatric disorders, psychiatric symptoms are driven by pathological hyperactivity in symptom-related circuits in the brain [7]. Thus, for example, pathological hyperactivity in anxiety circuits causes persistent feelings of anxiety; pathological hyperactivity in depressive circuits causes persistent feelings of depression; pathological hyperactivity in cognitive circuits causes ruminative and obsessive thoughts; etc... Similarly, pathological hyperactivity in various other circuits, such as those that control the skeletal muscles, those that control the intestinal muscles, and those that control the urinary muscles, could help explain the various physical symptoms that are often associated with psychiatric symptoms and why gabapentin can be effective in reducing all such symptoms [35]. Additionally, the chronic activating effects of neuronal hyperexcitability on the autonomic, the endocrine, the metabolic, and the immunologic systems could help explain why persons with mental illness are at increased risk of developing any of a wide range of general medication conditions, such as high blood pressure, diabetes, heart disease, autoimmune disease, cancer, and dementia [35]. It suggests that by reducing neuronal excitability, gabapentin (and other anticonvulsant drugs) could be used not only to treat mental and functional physical symptoms but also to *prevent* those symptoms and the various chronic medical conditions that tend to be associated with those symptoms [35].

2.5. Substance Use Disorders

The first clear evidence that gabapentin could be of benefit in the treatment of substance use disorders came from a double-blind, placebo-controlled trial of gabapentin for alcohol dependence. In a study of 150 men and women, gabapentin was found to nearly triple the rates of sustained abstinence and double the rates of no heavy drinking [36]. It also decreased relapse-related insomnia, dysphoria, and craving without causing the sedation, psychomotor impairment, and withdrawal symptoms of benzodiazepines [2]. There is now evidence that gabapentin can also be of benefit in the management of opioid [37-39], cannabis [40, 41], cocaine [42, 43], and other substance use disorders [44, 45]. These emerging applications help explain why gabapentin is rising in popularity among prescribers, and it may also explain why gabapentin is rising in popularity among illicit users.

3. Potential Liabilities of Gabapentin

Although gabapentin has long-been thought to have a very favorable tolerability and safety profile, the drug has, in recent years, come under increasing scrutiny as a possible drug of abuse. After a steady growth in popularity among prescribers, gabapentin is now growing in popularity among illicit users. With increasing frequency, gabapentin is being found together with traditional drugs of abuse at drug raids, and a review of postmortem toxicology reports from fatal drug overdoses found traces of gabapentin in approximately 20% of the cases [46]. Most illicit users of gabapentin say that it relieves symptoms of drug withdrawal and helps prevent various psychiatric symptoms, such as anxiety, depression, and insomnia. Others say that it enhances the psychoactive effects of other drugs that they use illicitly. For example, among a cohort of 503 prescription opioid misusers in Appalachian Kentucky, 15% reported using gabapentin "to get high" [2]. Those who reported misusing gabapentin were 6 times more likely than nonusers to be abusing opioids and benzodiazepines, thus raising important questions about how to interpret the misuse of gabapentin. Another concern that has been raised by the positive toxicology reports is the possibility that gabapentin might contribute to the respiratory depressant effects of opioids, benzodiazepines, alcohol, and other drugs that have been detected along with gabapentin. Yet, as of this writing, neither the DEA nor the CDC have issued any warnings about gabapentin. However, in December 2019, out of an abundance of caution, the FDA warned that gabapentinoids (gabapentin and pregabalin) could cause serious breathing problems in persons who have concurrent respiratory conditions or who use gabapentinoids in conjunction with other CNS depressants.

Another concern that has been raised about gabapentin comes from a study in which the drug was found to inhibit the growth of new neuronal connections. According to Eroglu, et al. [47], gabapentin exerts its therapeutic effects by inhibiting the formation of new synapses in the brain. Although such an effect could potentially help explain gabapentin's anticonvulsant activity, the effect would be expected to develop gradually in conjunction with a gradual loss of neurotransmission throughout the brain. However, that is not what is observed in actual practice; clinically, gabapentin exerts its brain-calming effects within minutes of ingestion. Although this rapid action is difficult to observe in epilepsy management, it is very apparent in the management of generalized anxiety, sleep disorders, chronic pain, and other disorders that are thought to be driven by a hyperexcitability of the neurological system. Also, synaptogenesis is relatively inactive in the adult brain [48]; and even in the infant brain, where the formation of new synapses occurs more frequently, gabapentin does not appear to have any negative effects on neurological function. A study of pregnancy outcomes found that only 2 out of 223 infants born to mothers who took gabapentin during pregnancy demonstrated any evidence of neonatal adaptation syndrome [49]. Moreover, even this low incidence is questionable, as the authors indicated that the two infants who had neonatal symptoms were exposed to other psychotropic drugs in addition to gabapentin.

When taken at recommended doses, the most commonly reported side effects of gabapentin are dizziness or spaciness, which occur in approximately 20% of cases. These effects generally resolve after a few days at a steady dosage. Tiredness can also occur, but this can be avoided by limiting the dosage, and the risk of suicidal thoughts or behaviors is estimated to be around 1 in 200 cases [50]. Gabapentin rarely causes any sexual side effects, and weight gain is reported in less than 10% of cases. Other possible side effects, also reported rarely, include nausea, muscle spasm, and peripheral edema. There is generally no need for laboratory monitoring, and gabapentin is conspicuous among anticonvulsants for its lack of clinically relevant drug interactions, an advantage that is made possible by its lack of hepatic metabolism. Gabapentin is rapidly eliminated through the kidney, having a half-life of approximately 4.8 to 8.7 hours [51]. The U.S. Federal government does not categorize gabapentin as a controlled substance, as it is not considered to be addictive, and as of the date of this writing, only two deaths related to gabapentin overdose have been reported since the drug first became available commercially nearly thirty years ago [52, 53]. In comparison, more than 3,000 deaths annually have been linked to daily aspirin use [54]; approximately 500 deaths annually to acetaminophen toxicity [55]; and approximately 90 deaths annually to over-the-counter antihistamines [56].

4. Discussion

The purpose of this review was to examine the potential benefits and liabilities of the widely prescribed, inexpensive, and generally effective anticonvulsant drug gabapentin. As would be predicted by gabapentin's long track record of safety and tolerability together with its increasingly wide range of uses, gabapentin is now the sixth most commonly prescribed drug in America [57]. Yet, as of late, some have started to vilify gabapentin as a highly addictive, potentially lethal drug on the level of benzodiazepines and opioids. The development of these concerns in conjunction with the increasing illicit use of gabapentin suggests that it is primarily a matter of guilty-by-association—gabapentin is becoming associated with other drugs that are used illicitly, such as benzodiazepines, opioids, and sedative hypnotics. As more and more states are moving to institute regulatory requirements on gabapentin, there is a growing implication that the drug is somehow less safe than it had been in the past. Though gabapentin is arguably safer than most over-the-counter pain relievers and decongestants, the status of the drug as prescription-only is naturally giving cause for its unprescribed use to be viewed negatively, and this in turn is creating controversy around the drug that would otherwise appear to be unwarranted.

Based on gabapentin's putative mechanism of action, it is likely that most illicit users of gabapentin are using it successfully, albeit illegally, to treat a variety of psychiatric and functionally-related ailments, such as anxiety, depression,

insomnia, chronic pain, and drug withdrawal. Also, it is likely that most illicit users are using gabapentin at normal therapeutic doses, as clinical experience has shown that when gabapentin is prescribed at higher than recommended doses, common side effects, such as spaciness, dizziness, and sedation, tend to outweigh the drug's therapeutic effects. Then again, those who do attempt to use gabapentin at higher than recommended doses could easily confuse the mixture of gabapentin's therapeutic and side effects with the relief of dysphoria, clouding of sensorium, and sedative effects that they experience from substances like benzodiazepines, opioids, cannabinoids, and alcohol.

Another factor to consider is the route of administration. In addition to using larger amounts of gabapentin than would normally be prescribed, some illicit users may pulverize and snort the drug [58]. Reccoppa et al. [59] provided case reports of inmates in the Florida State Department of Corrections who described achieving an altered mental state or "high" by snorting gabapentin. However, gabapentin is not the only historically safe drug with a history of misuse in the prison system. Pierre et al. [60] described inmates in the Los Angeles County Jail who either snorted or used quetiapine intravenously to obtain its potent sedative and anxiolytic effects. Inmates across the United States refer to quetiapine as "quell," "Susie Q," or "baby heroin" [61, 62]. Quetiapine is also sold on the street at a cost of $3.00-$8.00 per pill [63]. Like gabapentin, quetiapine relieves symptoms by calming the brain; but unlike gabapentin, it blocks dopamine transmission, thus making it somewhat less attractive to illicit users. Other prescription drugs that have developed a reputation for misuse in the correctional system include olanzapine, benztropine, trihexyphenidyl, buspirone, bupropion, and tricyclic antidepressants [64]. Again, these relatively non-addictive drugs are purportedly misused for their sedative effects, mind-altering effects, and potential to induce a "high" [64]. Considering the attraction that illicit users have to these widely-prescribed medications, it becomes more apparent that gabapentin, like these other drugs, may simply be a good drug in the wrong hands or perhaps desperate hands. Statistics show that at least 50% of prison inmates have some form of mental illness [65], and so it is not surprising that they would try anything to relieve their anxiety, depression, insomnia, and other psychiatric symptoms. It is likewise not surprising that, in a desperate attempt to optimize a drug's effects, they are willing to experiment with different ways of self-administering the drug. Considering that most of gabapentin's illicit use is likely driven by a desperate effort to relieve psychiatric and functional physical symptoms, a more important focus than regulating gabapentin's illicit use might be to use the attraction to gabapentin as an opportunity to educate a captive audience. For example, what prescribers of gabapentin call a "therapeutic effect," illicit users call a "high"; and what prescribers call "a need to stay on the medication," illicit users call "a need to avoid losing the high." What we need to do is help illicit users reframe the way they conceptualize gabapentin. We need to help them see it as a drug that reveals something important about what may be wrong with them mentally or emotionally. Raising that awareness could help bring them into formal treatment.

This process should begin with the medical establishment. It should begin with guarding against the natural tendency for gabapentin's illicit use to jade the way we conceptualize the drug. We need to disentangle our concerns about gabapentin's illicit use from our valuation of the drug itself, keeping in mind its long history of uneventful use and demonstrated benefits for an increasingly wide range of health conditions.

Far from being a drug to vilify, there is mounting evidence from gabapentin's broad utility and putative mechanism of action that the drug is zeroing in on the pathophysiology of disease [66, 67]. It has been proposed that nearly all chronic illnesses are rooted in an inherent hyperexcitability of the neurological system [8, 35, 68-71]. Hence, for those who inherit the genes for neuronal hyperexcitability, early treatment with gabapentin (and other anticonvulsant drugs) could actually be protective against the development of chronic disease. Gabapentin is the most popular of the anticonvulsants because, with relatively few side effects or withdrawal effects, it has proven to be effective for such a high percentage of the population [72]. As the drug continues to grow in popularity, it is unlikely that regulatory efforts will be successful in curbing gabapentin's illicit use. It is more likely that such use will continue to increase as users, like prescribers, become increasingly aware of gabapentin's broad utility. Thus, rather than focusing exclusively on regulating gabapentin's distribution, consideration should be given to helping illicit users understand what their attraction to the drug is saying about their healthcare needs. This would help them reframe their attraction to the drug and perhaps incentivize more of them to seek formal evaluation for what they are self-medicating with the drug.

5. Conclusion

After nearly three decades on the market as a safe, effective, and well-tolerated anticonvulsant drug, gabapentin's safety is now being called into question. However, the growing controversy around the drug appears to be driven more by its growing popularity among illicit users than by any new findings about the drug's actual safety profile. Regulators argue that the illicit use of a drug can itself change its safety profile, as illicit users may administer the drug at doses and in ways that deviate from normal prescribing. However, the focus on gabapentin's illicit use may be obscuring a more salient issue: that illicit users, like licensed prescribers, may be finding gabapentin to be therapeutic for an expanding range of conditions. This raises the question of whether illicit users would be better served if the focus on gabapentin's illicit use were to shift toward helping users understand what their attraction to the drug might be saying about their treatment needs. Raising that awareness could incentivize illicit users to seek formal evaluation. It could also preserve gabapentin's safety even among illicit users by helping them understand that gabapentin's appropriate use is likely to be more beneficial than its inappropriate use.

Conflicts of Interests

The author declares that he has no competing interests.

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