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Case Report

Gabapentin-related suicide: Myth or fact?

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Abstract

Background: The opioid epidemic in America is real and is estimated to be the number one cause of death in adults under 50 years of age. Finding alternative analgesic medications is part of the effort to decrease the prescription of narcotics, with gabapentin being at the top of the list.

Case Description: In the present case, we discuss the side-effects of gabapentin, used as part of the multimodal treatment approach of painful spinal degenerative disease. The patient stated that he had noticed personality changes after gabapentin was initiated, and that he had become more depressed, frustrated, and aggressive. His uncontrolled pain and acute mood changes led him to attempt suicide by hanging himself. Gabapentin was discontinued and the patient's suicidal ideation completely subsided.

Conclusion: It is imperative to screen, identify, and appropriately manage patients with underlying psychiatric disorders prior to initiating pain management with gabapentin. Therefore, it is crucial to raise awareness of gabapentin as a potential cause of depression, aggressive behavior, and suicidal ideation.

Key Words: Chronic low back pain, gabapentin, suicide

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INTRODUCTION

Since the beginning of the new millennium, opioid-related deaths have increased five times in women and almost four times in men. More than half a million people died from drug overdoses between 2000 and 2015. It is estimated that 91 Americans die every day from an opioid overdose.[3] Studies conducted among postsurgical patients by Gugelmann *et al.* indicated that prescribing opioids within 7 days of surgery increased the likelihood of long-term opioid use at 1 year by about 44%.[10] Taking this into account and considering the side-effect profile of opioids, there has been an increasing interest in the potential use of gabapentin and other nonopioid medications for postoperative pain relief.[4]

Gabapentin is an antiepileptic medication, and is also frequently used for off-label purposes such as acute and chronic pain management in various neurological and neurosurgical disorders. Reported off-label uses are migraines, trigeminal neuralgia, complex regional pain syndrome, drug and alcohol withdrawal seizures, and bipolar disorder.[4] Recent articles have also shown

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that the anti-hyperalgesic properties of gabapentin are seen for postoperative pain management in surgeries including breast surgery, hysterectomy, cholecystectomy, and spinal and knee surgery.[1] Some clinical studies have demonstrated a reduction in postoperative opioid consumption when gabapentin was administered preoperatively and pre-emptively for pain control.[18]

However, despite its popularity, gabapentin is not free of side effects. The psychiatric side-effects of gabapentin have been infrequently discussed. In this article, we will report a case of a patient who demonstrated aggressive and suicidal behavior after initiation of gabapentin.

CASE DESCRIPTION

A 28-year-old male with a history of chronic low back pain described his pain as constantly present, 4–8/10 in intensity, shooting down both legs with any movement, and with associated tingling and numbness. His exercise tolerance had decreased to walking a quarter of a mile/day over a period of 6 months, and he ended up quitting his job due to his debilitating pain.

Besides the low back pain, for which the patient frequently visited the emergency room, he also had left testicular pain. He was diagnosed with orchitis, and was started on oral antibiotics. Despite the treatment, his testicular pain worsened, and he was prescribed additional antibiotics. The infection resulted in left groin pain that extended to his mid-back, buttock, and radiated down the hamstring and lateral aspect of leg, correlating with L5-S1 dermatomes.

His electromyography (EMG) showed decreased sural nerve signals. Magnetic resonance imaging (MRI) of his lumbar spine demonstrated central canal stenosis at the L3-4-5 levels and disc herniations at L3-4 and L4-5 levels. His hip X-ray, computed tomography (CT) of the abdomen, ultrasound of the testicles, and urinalysis were within normal limits.

He was first started on nonsteroidal anti-inflammatory drugs (NSAIDs), and then acetaminophen/hydrocodone and muscle relaxants were added to his treatment regimen without any relief. The next step was physical therapy and two lumbar epidural steroid injections, which provided no relief. He refused to get a third lumbar epidural steroid injection, and was referred to a neurologist for further evaluation. He was then started on gabapentin 300 mg three times per day, a dose that was gradually increased over 4 weeks to 1600 mg/day by his orthopedic surgeon in conjunction with muscle relaxants and NSAIDs.

The patient and his fiancé stated that they noticed personality changes in him; he became more depressed and aggressive. They attributed the changes in his behavior to gabapentin. His pain and mood had progressively deteriorated to the point where he attempted to commit suicide by hanging himself by the neck using his belt and a door jam. He was immediately found by his fiancé who emergently took him to the hospital. While he was hospitalized, all his medications were stopped, including gabapentin, and he was started on mood stabilizers. He noticed that his personality had changed back to normal and his suicidal ideation had subsided, after which he was discharged home.

At this point, after being on a multimodal pain medication regimen including lumbar epidural steroid injections without significant relief, the patient visited our clinic for a second opinion about his back pain. On examination, his vital signs were normal. However, he had an antalgic gait with a forward leaning posture of 15–20 degree, and was unable to stand on his toes or heels without support. Palpation also elicited mild tenderness over the lower lumbar region. His motor strength was 5/5 in both upper extremities and 4/5 in both lower extremities. Extension of the lower extremities was limited to 0 degrees, whereas range of flexion was 70 degrees with improvement in pain. Patellar reflexes were absent bilaterally, ankle reflexes were 1(+) bilaterally, Babinski's sign was negative, and the straight leg raise test was positive, left > right, 1(+) at 60 degrees. The remainder of the examination, including cranial nerve examination, respiratory, cardiovascular and abdominal was normal. Based on the clinical picture, he was recommended conservative treatment in a tertiary center.

DISCUSSION

Since its introduction in the market in 1993, gabapentin has consistently gained in popularity. A significant proportion of this use has been for non-FDA approved pain conditions. Besides its use in treating refractory partial seizures, the FDA also approved it in 2002 for the treatment of postherpetic neuralgia. Gabapentin is a structural analogue of the neurotransmitter γ-aminobutyric acid (GABA), but it does not bind to GABA receptors nor does it block uptake or metabolism of GABA. Although the mechanism of action of gabapentin is unclear, it does block voltage-gated Ca^{++} channels by binding to the α2-delta subunit in the dorsal horn, producing a reduced calcium influx, thereby reducing release of glutamate and substance P from primary nociceptive afferents and diminishing propagation of pain signals.[7,13] Other mechanisms contributing to the analgesic effects of gabapentin include a reduction in the release of dopamine, serotonin, and norepinephrine from the brain, as well as limitation of firing of Na^{+} dependant action potentials in the spinal cord and neocortical neurons.[24,28]

The recommended starting dose for neuropathic pain is 300 mg on day 1, followed by 300 mg twice daily on

day 2, and then 300 mg three times a day thereafter. This dose can be gradually increased to 1800 mg/day as 300 mg oftentimes is not sufficient. The most common side effects of gabapentin in therapeutic doses are drowsiness, somnolence, dizziness, movement disorders, diarrhea, and weight gain.[27]

In addition, cases have been reported of gabapentin-related suicidal acts and aggressive behavior [Table 1].

The mechanism of suicide linked to antiepileptic drugs (AEDs) is not very well understood, however, there is a possibility that AEDs lower the threshold for manifesting psychiatric symptoms in individuals who are susceptible because of genetic or historical predisposition to psychiatric disorders.[12] A combination of neurobiological and psychological factors could contribute to changes in people's behavior. It is thought that antiepileptic drugs lead to disinhibition and impulsiveness, which can subsequently influence and promote suicidal acts instead of having a direct effect on behavior.

One of the factors that could impact patient's suicide intent is their chronic pain. Suicide rate among chronic pain patients was found to be significantly greater than the general population. Literature review concludes that suicidal ideation, suicide attempts, and suicide completions appeared to be common in chronic pain patients. As a result of research conducted in 2003, the American Psychiatric Association included chronic pain as a risk factor for suicidal ideation in their guidelines for the assessment and treatment of patients with suicidal behavior. Two approaches have been recommended – routinely measuring depression and suicidality in any chronic pain patient with tools such as the Beck Depression Inventory or monitoring pain and depression with the Brief Pain Inventory at every visit. High scores on pain or depression rating scales should stimulate the physician to inquire about suicidality.[8]

Based on the most recent systematic review, gabapentin was tested in nine different chronic pain conditions considered to be neuropathic in origin. Numbers needed to treat for an additional beneficial outcome were between 5 and 7 in postherpetic neuralgia and peripheral diabetic neuropathy. Evidence for other types of neuropathic pain was very limited. More than half of the patients treated with gabapentin will not have a justifiable pain relief.[29]

As part of the program for decreasing opioid prescriptions, the U.S. Centers for Disease Control and Prevention lists gabapentin as an appropriate nonopioid treatment for chronic pain, recommending the drug as a first-line agent for neuropathic pain. More recently, the American Pain Society recommended that gabapentin be included in the Clinical Practice Guideline in the management of postoperative pain.[5]

We noticed a 23% decrease in opioid dispensed prescriptions in the last 7 years while concomitantly witnessing a total of 153% increase in gabapentin prescriptions over the same period of time [Figure 1]. As an alternative to narcotic medications, gabapentin could

Table 1: Gabapentin - related suicide and near suicidal cases

Source reported	Case description
Cantrell F.L., *et al*.[2]	A 47-year-old female without any psychiatric history, who was dependent on acetaminophen/hydromorphine. She was found unresponsive after an overdose of gabapentin. Toxicology findings linked gabapentin overdose as her immediate cause of death.
Middleton O.[17]	A 62-year-old female with a history of intractable major depression, renal disease, obesity, and diabetes was found unresponsive with empty bottles of gabapentin and hand written notes stating her intent to commit suicide through overdose. Toxicology report certified gabapentin toxicity as her cause of death.
http://www.huffingtonpost.com /martha-rosenberg/ pfizer-neurontin-suicide_b_875603. html[32]	A 52-year-old male with past medical history of bipolar disorder and back pain was prescribed narcotics for pain control. While being on gabapentin he developed behavioral changes, agitation, nervousness and insomnia. He committed suicide by stabbing himself. After obtaining the pharmacy records, the wife noticed that an increase in the dosage of gabapentin correlated with his symptoms and personality changes.
http://www.huffingtonpost.com /martha-rosenberg/ pfizer-neurontin-suicide_b_875603. html[32]	A 54-year-old male was placed on Gabapentin for pain control after he suffered a surgical intervention for spinal cord. After a few months of therapy, he was noticed to have behavioral changes, developed akathisia and suicidal thoughts. He committed suicide by hanging himself, after 10 months of gabapentin therapy.
Pinninti N.R.[20]	A 38-year-old male was admitted for bipolar disorder, manic phase with psychotic symptoms. His symptoms were partially controlled by lithium carbonate, olanzapine, and lorazepam. On the day 4 of being on Gabapentin, the patient became very irritable and physically aggressive. Gabapentin was stopped while all other medications were continued, and within a day, his irritability and aggressive behavior ceased.
Pinninti N.R.[20]	A 51-year-old male was admitted with a diagnosis of bipolar disorder in a manic phase, with no history of psychotic symptoms, substance abuse, or aggression. Gabapentin was prescribed as a mood stabilizer, and sodium valproate was stopped. Within 48 hours the patient developed new symptoms of hostility, verbal aggression, and command auditory hallucinations. Gabapentin was stopped, sodium valproate reinstated, and in 48 hours hostility, aggressive behavior, and hallucinations stopped.

be considered to have a reasonable impact on decreasing the dispensed opioid prescriptions. However, the expense in this scenario would indicate that gabapentin would become another drug of abuse, with potential serious side effects, which were not investigated enough. It is crucial to raise awareness of the dangers that gabapentin use entails, and suggest it be added to the controlled substances list.

While it may be legal for medical practitioners to prescribe medications for off-label uses, in the United States it is illegal for manufacturers to market medications for off-label uses, which is one reason why Pfizer was fined $420 million after it was acquired from Warner-Lambert.[19]

After a recent survey in the USA, gabapentin had the highest proportion of off-label prescriptions (83%) among 160 commonly prescribed drugs; and only 20% of its off-label use had strong scientific evidence of clinical efficacy. This accounted for more than 90% of its sales.[14,21]

Numerous cases have been reported supporting the evidence of the abuse potential of gabapentin, in which individuals with a history of opioid abuse were the most susceptible. Prescribers should be aware of high-risk populations and monitor for signs of abuse because gabapentin is often co-prescribed with opioids and pain patients often receive prescription for benzodiazepines due to concomitant anxiety and/or difficulty sleeping.[6,15,16,22,23,25]

In a recent study performed in Central Appalachian region, a near 3,000% increase was found in the use of gabapentin "to get high" from 2008 to 2014 in a cohort of 503 prescription drug users. When compared to the previous year reports, a 165% increase was observed. The major sources of gabapentin were physicians (52%) and drug dealers (36%).[26]

From the data presented in Figures 2 and 3, it is noticeable that the number of patients exposed to gabapentin dramatically increased in 2012; however, it was not mentioned in the American Association of Poison Control Centers (AAPCC) annual reports prior to 2011. In addition, the number of those taking gabapentin intentionally with the purpose of overdosing has been exceeding the unintentional poisonings.

Antiepileptic drugs and suicidality

Numerous studies have been published to confirm or deny the role that antiepileptic drugs play in increasing the risk of suicidal behavior; however, so far they lack concordance and are limited by various methodological limitations.

The FDA issued a warning regarding the increased risk of suicide in patients taking AEDs based on a study

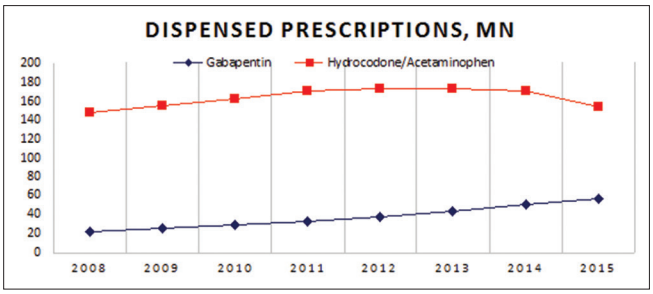

Figure 1: IMS Health data, Gabapentin dispensed prescriptions, in millions[33]

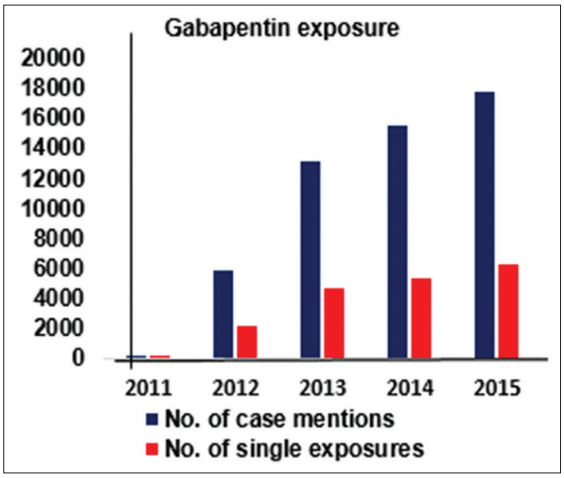

Figure 2: Clinical Toxicology report for Gabapentin exposure. American Association of Poison Control Centers Annual reports[30]

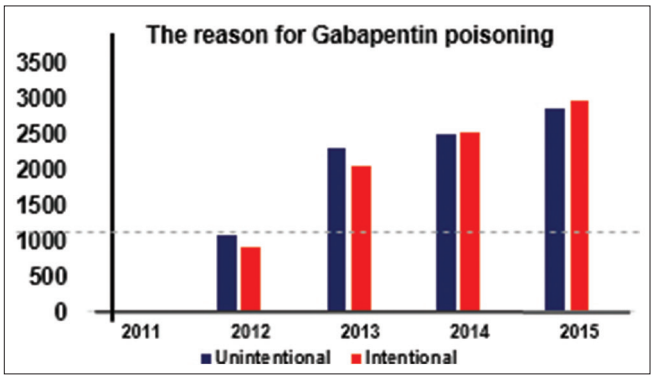

Figure 3: The reason for Gabapentin poisoning. American Association of Poison Control Centres AAPCC[30]

performed among 28,000 people taking AEDs and 16,000 people taking placebo. Four completed suicides were registered in the group that was taking AED and none in the placebo group. The odds ratio for the association between AEDs and suicidal behavior or ideation was 1.8 (95% CI, 1.24–2.66) and 1.45 (95% CI, 0.93–2.3) for ideation alone, which did not reach statistical significance.[31]

The validity of this meta-analysis was questioned after careful review of the data based on several methodological

problems, including the source of outcome data on suicidality, statistical methodologies used, heterogeneity of the trials, and the difference in mechanism of action of the 11 AEDs evaluated.[11]

The suicide attempt rates before and after gabapentin was prescribed were investigated in a cohort of 131,178 patients. The investigators found no significant differences in suicide attempt rates before (3.45/1000 patient years) versus after gabapentin prescription (3.45/1000 patient years).

While no differences were identified before and after gabapentin in the nonpsychiatric population, up to a 5 times post-prescription reduction in suicide-attempts rate were seen for bipolar disorder, major depressive disorder, and other psychiatric conditions. The pre-prescription suicide-attempts rate for patients with bipolar disorder was 48 per 1000 person years (PY); following prescription, the SAs rate decreased to 32 per 1000 PY (a 33% decrease). In patients with pain disorders, the SAs rate was 3 per 1000 PY before gabapentin prescription, and remained unchanged after gabapentin prescription. These findings suggest that gabapentin may have a protective effect among patients at an increased risk of SAs. The absence of a significant association between gabapentin and SAs in patients receiving a prescription for a pain disorder suggests that having comorbid psychiatric and pain disorders may significantly increase SA risk, which greatly decreases if the pain disorder is successfully treated with gabapentin. Their investigation also showed that patients who are on gabapentin monotherapy for pain only are at a lower risk of suicide in comparison to patients who are on multiple medications. The rationale behind this is that patients who are on multiple medications have multiple comorbidities that are difficult to treat and are already at an increased risk for suicide at baseline.[9]

CONCLUSION

With the increase in opioid misuse and overdose-related deaths nationwide, health care providers are encouraged to find a nonopioid analgesic. Application of gabapentin for treatment is not without side-effects, especially in patients with an undiagnosed psychiatric disorder or who are at risk of suicidality. It is imperative to screen, identify, and appropriately manage patients with underlying psychiatric disorders prior to initiating pain management with gabapentin. The recommended strategy is to perform more studies to identify the group at high risk of suicide between patients taking gabapentin and those who are not. Therefore, it is crucial to raise awareness of gabapentin as a potential cause of depression, aggressive behavior, and suicidal ideation.

Recommendations for Patients Taking Gabapentin

Recommendations	Rule out organic causes of pain; Psychological evaluation prior to initiation of GBP; Use caution in patients with a history of psychiatric disorder or aggressive behavior; Inform patients and their families of potential side effects; Monitor for response to treatment; Early psychiatry involvement; Consider early hospitalization if any acute mood or behavior changes occur in patients on GBP; Screening for abuse potential.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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