# Gabapentin-Induced Neutropenia at Four Months Follow-up Post Initial Chemotherapy for the Treatment of Lymphoma

L Davenport, M Oswald, J Chin-Hon, T Prashad, J Londono

**Citation**

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**Abstract**

**Introduction:** Gabapentin belongs to a class of drugs known as gabapentinoids. Due to its potent inhibitary effect in neuropathic pain, gabapentin became an attractive non-opioid adjunt treatment option. Gabapentin shows a mild-side effect profile with common adverse effects being somnolence, dizziness, headaches and peripheral edema. Neutropenia induced by gabapentin is very rare and has only been recorded by one case report in 2004. This case will be a second case report on neutropenia associated with gabapentin use.

**Case presentation**: A 64-year-old white male with a past medical history significant for hypertension, hyperlipidemia, motor vehicle accident forty years ago that resulted in the right leg amputation below knee, prior pulmonary embolism as well as stage IV diffuse large B-cell lymphoma (DLBCL) diagnosed one year ago status-post 6 cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) initially presented with symptoms of neck pain and radicular pain in right arm due to cervical radiculopathy four months after his last chemotherapy cycle. He was started on gabapentin 300mg once a day at bedtime for symptom control. On day 1 of gabapentin therapy, his ANC was 2.7 K/uL (reference range 1.8-5.4 K/µL) and Lactate Dehydrogenase (LDH) was 149 IU/L (reference range 100-250 IU/L). On day 55 of gabapentin therapy, the patient denied any symptoms of pain, however, his ANC was significant for severe neutropenia (0.3 K/uL) and his LDH level stayed normal (205 IU/L). On day 62 of gabapentin therapy, the patient returned to the clinic after completion of levofloxacin prophylaxis therapy with worsening of severe neutropenia (ANC of 0.2 K/uL). At that time the decision was made to stop gabapentin. On day 8 of gabapentin-free period, his ANC increased to 0.7 K/uL, followed by additional increase to 1.7 K/uL on day 24 of gabapentin-free period at a follow-up visit.

**Discussion:** In line with Naranjo algorithm, our patient experienced a “probable” gabapentin-induced neutropenia with a total of six points scored: (1) Previous case reports of this ADR (1 point); (2) ADR appear after gabapentin was taken (2 points); (3) ADR improved when gabapentin was discontinued (1 point); (4) No other alternative causes of this ADR identified (2 points).

**Conclusion**: We have described a second case of gabapentin-induced neutropenia, classified as “probable” according to Naranjo algorithm. This side effect is very rare but serious and life-threatening, if not recognized on time. We hope this case report will emphasize on the importance of monitoring of complete blood count after initiation of new therapy and help healthcare providers recognize gabapentin-induced neutropenia early in the course of treatment.

## INTRODUCTION:

The Food and Drug Administration first approved gabapentin in the United States in 1993 for the treatment of neuropathic pain and epileptic disorders [1]. Neuropathic pain is a generalized term that can be divided into various subtypes, two of interest are cervical radiculopathy and peripheral neuropathy. Cervical radiculopathy results from the compression of cervical nerve roots in the neck while peripheral neuropathy occurs from damage to the nerves in the peripheral nervous system that prevents communication from the brain and spinal cord to the rest of the body [2]. Approximately 64 million prescriptions were filled in 2016, gabapentin was notably a commonly used medication [3]. Gabapentin is a structural analogue of gamma-aminobutyric acid (GABA) however it does not bind to GABA receptors nor demonstrate any influence for uptake or degradation. The exact mechanism of action for its analgesic and antiepileptic effects is currently unknown [4]. Gabapentin is thought to work by having a high affinity for binding sites

throughout the brain, associated with voltage-gated Ca2+ channels, specifically alpha-2-delta-1 subunit (2-1), resulting in a decrease in neuronal excitability [3]. Gabapentin elimination half life is 5-7 hours and generally takes two days for complete elimination from the body. Patients commonly reach steady-state plasma levels within 1-2 days with no clinical significance with administration of food [4]. Primarily excreted by the kidneys, with no active metabolites, gabapentin is renally adjusted using creatinine clearance (CrCl) below 60 milliliters per minute (mL/min), thus dose is generally reduced in the elderly or those with impaired renal function [5]. Gabapentin exhibits a mild-side effect profile with common adverse effects being somnolence, dizziness, headaches and peripheral edema. However close monitoring should be considered for the presents of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), anaphylaxis, angioedema, suicidal behavioral or ideation and pediatric neuropsychiatric adverse reactions. Comparing gabapentin to placebo, in a randomized, double-blind trial conducted in the United States, found a side effect profile of drowsiness (36%), dizziness (24%), ataxia (26%), fatigue (11%) and headaches (9%). The incidence of purpuric rash was found at 0.5% and neutropenia at 0.2% [6]. This case highlights the serious, life threatening rare adverse events of gabapentin. Gabapentin is a widely preferred anticonvulsant/nerve pain medication with a favorable side-effect profile; however it still has serious but atypical adverse effects such as neutropenia. Research has demonstrated that other anticonvulsants such as sodium valproate and carbamazepine which are also use for neuropathic pain can induce neutropenia as well.

White blood cells are predominantly made up of neutrophils, accounting for 50 to 70% of all circulating leukocytes. As the most predominant leukocytes, neutrophils are the first line of defense against foreign infectious pathogens [7]. Neutropenia is characterized as a reduction in neutrophils below normal counts (reference range 1.8-5.4 K/ μL). Neutrophils play an essential role in the body's immune defense mechanism by ingesting, digesting and terminating foreign microorganisms [8]. Neutropenia is a common side effect of oncologic medications which puts patients at an increased risk of contracting infections. Absolute Neutrophil Count (ANC, band forms and neutrophils combined) is the value evaluating neutropenia and when the ANC falls below <1 K/μL infectious diseases are more prevalent. When ANC levels fall <0.5 K/μL endogenous microbial flora in the gastrointestinal tract become impaired; when the ANC <0.2 K/μL, local inflammatory responses are absent, and the patient becomes susceptible to opportunistic infections [9]. Due to the nature of neutropenia, it is often considered an oncological emergency that can result in serious complications such an increase in hospitalizations, sepsis and even death [10].

The case described a 53-year-old male with adenocarcinoma that received chemotherapy (mitomycin, vinblastine, cisplatin) and seven months later initiated gabapentin 300mg three times daily (900mg/day) for neuropathic pain. About 4 months into therapy, the patient presented to the hospital with neutropenic sepsis and gabapentin was thought to be the cause of neutropenia. Three other case reports described gabapentinoids (pregabalin and microgabalin) associated with the development of neutropenia [11, 12, 13]. This case will be a second case report on neutropenia associated with gabapentin use.

## CASE PRESENTATION:

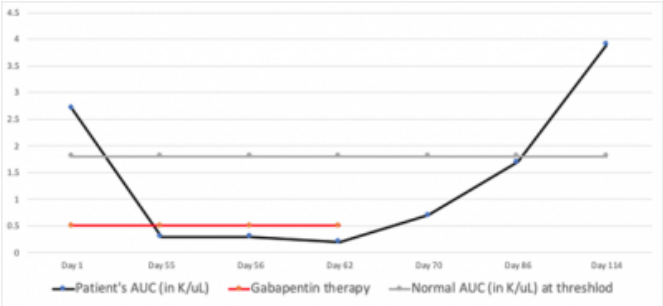
A 64-year-old white male with a past medical history significant for hypertension for three years, hyperlipidemia for seven years, motor vehicle accident forty years ago that resulted in a right below the knee amputation, prior pulmonary embolism three years ago as well as stage IV diffuse large B-cell lymphoma (DLBCL) diagnosed one year ago status-post 6 cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) initially presented with symptoms of neck pain and radicular pain in right arm due to cervical radiculopathy four months after his last chemotherapy cycle. He was started on gabapentin 300mg once a day at bedtime for symptom control. Home medications included oxycodone-acetaminophen, methocarbamol, amlodipine, valsartan, furosemide, loratadine, aspirin and atorvastatin that the patient has been taking for at least 6 months before this presentation.

On day 1 of gabapentin therapy, his ANC was 2.7 K/uL and Lactate Dehydrogenase (LDH) was 149 IU/L (reference range 100-250 IU/L). On day 55 of gabapentin therapy, the patient denied any symptoms of pain, however, his ANC was significant for severe neutropenia (0.3 K/uL) and his LDH level stayed normal (205 IU/L). Levofloxacin 500mg daily for 7 days was initiated for prophylactic bacterial infection prevention. On day 62 of gabapentin therapy, the patient returned to the clinic after completion of levofloxacin prophylaxis therapy with worsening of severe neutropenia (ANC of 0.2 K/uL). At that time the decision was made to

stop gabapentin. On day 8 of gabapentin-free period, his ANC increased to 0.7 K/uL, followed by additional increase to 1.7 K/uL on day 24 of gabapentin-free period at a follow-up visit [Figure 1].

**Figure 1**

Changes of absolute neutrophil count after initiation and discontinuation of gabapentin therapy




## DISCUSSION

The incidence of cervical radiculopathy seems to peak in the fourth and fifth decades in life. Risk factors for cervical radiculopathy include white race, cigarette smoking, and prior lumbar radiculopathy [14]. In our case report, gabapentin was started for symptomatic neck and arm radiculopathy. Gabapentin can be useful as an adjunct treatment.

Gabapentin works by binding to 2-1, commonly known as a voltage-activated Ca2+ channel subunit on NMDA receptors. Gabapentinoids reduce neuropathic pain by inhibiting forward trafficking of 2-1-NMDAR complexes [15].

It is not clear how gabapentin can cause neutropenia. It is not appreciably metabolized in the liver to associate this toxicity with active metabolites. Yet, there are a few case reports of gabapentin-induced hepatotoxicity [16,17]. Possibly, gabapentin scarce toxic metabolites bind to either mature neutrophils or the myeloid precursors causing neutropenia.

With respect to other pathologies that may cause neutropenia in our patient: PET/CT scan did not show any FDG uptake in the head and neck or hepatosplenomegaly; patient's LDH level stayed normal throughout the course of gabapentin therapy and after [Figure 2]; which signified that the patient remained in remission from their lymphoma; myelodysplastic syndrome is unlikely because the complete blood count is within normal range; the patient was unlikely to have had aplastic anemia [Table 1]; the patient did not have any symptoms of infectious disease process; the patient did not take any other medications that could have caused neutropenia; the patient did not have any history of immunosuppressive conditions.

In our case report, gabapentin was discontinued 2 months after initiation of therapy during a follow-up visit for DLBCL status-post chemotherapy. Thankfully, our patient no longer experienced cervical radiculopathy by that time. Because our patient was on a low dose of gabapentin, tapering was not necessary, the patient did not experience any withdrawal symptoms.

In line with Naranjo algorithm, our patient experienced a "probable" gabapentin-induced neutropenia with a total of six points scored: (1) Previous case reports of this ADR (1 point); (2) ADR appear after gabapentin was taken (2 points); (3) ADR improved when gabapentin was discontinued (1 point); (4) No other alternative causes of this ADR identified (2 points) [Table 2] [18].

**Table 1**

Patient's complete blood count

| | Before therapy | During therapy | | | After therapy | |
|---|---|---|---|---|---|---|
| **Days** | Baseline | Day 1 | Day 55 | Day 62 | Day 70 | Day 86 |
| **Red Blood cells** (reference range 4.63-6.08 m/uL) | 3.56 | 3.97 | 3.66 | 3.69 | 3.86 | 3.93 |
| **White Blood Cells** (reference range 4.2-9.1 k/ul) | 3.1 | 4 | 1.8 | 1.4 | 1.8 | 3.1 |
| **Platelets** (reference range 150-400 k/ul) | 163 | 177 | 156 | 160 | 162 | 156 |
| **Hemoglobin** (reference range 13.7-17.5 g/dl) | 11.4 | 12.4 | 11.6 | 11.7 | 12.2 | 12.7 |
| **Hematocrit** (reference range 40-51%) | 32.8 | 35.9 | 33.0 | 33.4 | 36.9 | 35.2 |

**Figure 2**

Lactate Dehydrogenase level after initiation and discontinuation of gabapentin therapy

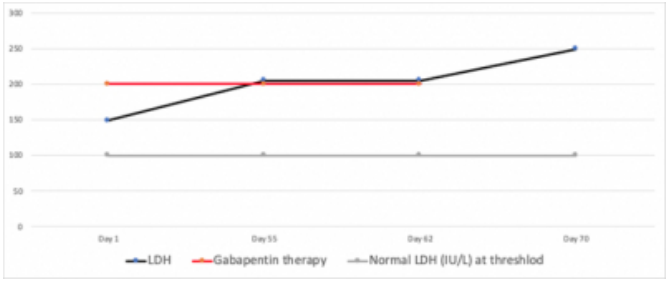


**Table 2**

Naranjo Algorithm

| | Question | YES | NO | UNKNOWN |
|---|---|---|---|---|
| 1 | Are there previous conclusive reports on this reaction? | 1 | 0 | 0 |
| 2 | Did the event appear after the suspected drug was administered | 2 | -1 | 0 |
| 3 | Did the adverse reaction improve when the drug was discontinued? | 1 | 0 | 0 |
| 4 | Did the adverse reaction reappear when the drug was readministered? | 2 | -1 | 0 |
| 5 | Are there alternative causes that could on their own have caused the reaction? | -1 | 2 | 0 |
| 6 | Did the reaction reappear when a placebo was given? | -1 | 1 | 0 |
| 7 | Was the drug detected in the blood in concentrations known to be toxic? | 1 | 0 | 0 |
| 8 | Was the reaction more severe when the dose was increased, or less severe when the dose was decreased? | 1 | 0 | 0 |
| 9 | Did the patient have a similar reaction to the same or similar drugs in any previous exposure? | 1 | 0 | 0 |
| 10 | Was the adverse event confirmed by any objective evidence? | 1 | 0 | 0 |

**Interpretation:** ≥ 9 – definite ADR; 5-8 – probable ADR 1-4 – possible ADR; 0 – doubtful ADR

**Total = 7 (probable ADR)**

## CONCLUSION

To the best of our knowledge, we have exemplified a second case of gabapentin-induced neutropenia, classified as “probable” according to Naranjo algorithm. This side effect is very rare but serious and life-threatening, if not recognized on time. We hope this case report will emphasize on the importance of monitoring of complete blood count after initiation of new therapy and help healthcare providers recognize gabapentin-induced neutropenia early in the course of treatment.

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## Author Information

**Lilia Davenport, PharmD**
NYU Langone Hospital - Long Island Department of Pharmacy
New York, USA

**Matthew Oswald, PharmD Candidate 2021**
Arnold and Marie Schwartz College of Pharmacy and Health Sciences
New York, USA

**Jamie Chin-Hon, PharmD, BCOP**
NYU Langone Hospital - Long Island Department of Pharmacy; NYU Langone Hospital - Long Island Department of Oncology
New York, USA

**Thaleshravi Prashad, NP**
NYU Langone Hospital - Long Island Department of Oncology
New York, USA

**Jaime Suarez Londono, MD**
NYU Long Island School of Medicine; NYU Langone Hospital - Long Island Department of Oncology
New York, USA