

# High-Dose Gabapentin and Amitriptyline in the Treatment of Refractory Chemotherapy-Induced Peripheral Neuropathy in a Toddler

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## Abstract

Pharmacologic management of chemotherapy-induced peripheral neuropathy (CIPN) in pediatric patients remains a challenge. Without effective treatment to control pain from CIPN in children, reduction or discontinuation of life-saving chemotherapeutic medications may be required. Various combinations of medications are available, but none have been thoroughly evaluated for their effectiveness in managing CIPN in the pediatric population. We present the clinical management of severe CIPN in a 3-year-old child with pre-B acute lymphoblastic lymphoma that was refractory to a regimen that included high-dose gabapentin and opioids. Therapy was subsequently adjusted to include amitriptyline, eliminating the need for opioids with complete resolution of symptoms. The potential combination pharmacotherapies for pediatric CIPN are discussed and mechanisms accounting for inadequate response with monotherapy are presented.

**Keywords:** Chemotherapy-induced peripheral neuropathy; Pediatric cancer; Amitriptyline; Gabapentin

## Introduction

Chemotherapy is the mainstay of treatment for oncologic disorders in children. Effective chemotherapeutic regimens have led to a significant decline in mortality, with the overall 5-year childhood cancer survival reaching 80% for many types of cancer [1]. However, the longer survival rates may be complicated by the symptom burden associated with the prolonged use of chemotherapeutic medications. Chemotherapy-induced

peripheral neuropathy (CIPN) is one of the major complications associated with the chemotherapeutic agents used to treat pediatric cancer. CIPN is extremely challenging to treat and contributes to a significant impairment in the quality of life of affected patients. Most treatment options for CIPN include termination or dose reductions of the offending therapeutic agent, which limits the efficacy of treatment and may require the use of adjunctive therapies or alternative chemotherapy regimens. Although these options may result in CIPN remission, an estimated 30-40% of patients have persistent symptoms [2].

First-line therapies for CIPN include gabapentin, pregabalin, and duloxetine, in addition to traditional analgesic agents such as opioids and anti-inflammatory medications. Unfortunately, regardless of the medication combination that is chosen, no agent or combination of agents has proven to be universally effective, often resulting in inadequate symptom management. We present a 3-year-old boy with a history of Noonan syndrome and precursor B-cell acute lymphoblastic leukemia (pre-B ALL) whose clinical course was complicated by CIPN. Symptoms persisted despite treatment on a high-dose gabapentin and oxycodone regimen. The patient was in the maintenance phase of chemotherapy scheduled for the next 2 years, with CIPN significantly impacting his quality of life. Therapy was subsequently adjusted to include amitriptyline, eliminating the need for opioids with complete resolution of symptoms. Potential pharmacotherapy modalities for pediatric CIPN are discussed, and mechanisms accounting for inadequate response with monotherapy are presented.

## Case Report

### Investigations

Review and presentation in this format followed the guidelines of the Institutional Review Board at Nationwide Children's Hospital (Columbus, Ohio). A 3-year-old, 10-kg boy with a history of Noonan syndrome and pre-B ALL in remission, on maintenance chemotherapy with vincristine and weekly methotrexate presented with a 1-year history of pain in his hips and legs.

### Diagnosis

The pain was presumed to be neuropathic in origin after a

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negative workup with advanced radiologic imaging. Although peripheral neuropathic pain associated with vincristine is generally expected to improve during maintenance therapy as the dosing is spaced out, this patient's pain was worsening [3]. Treatment included gabapentin which was gradually titrated from initial 10 mg/kg/day to current dose of 52 mg/kg/day, divided three times per day, topical 5% lidocaine cream, and oxycodone (1 mg *per os*) as needed for breakthrough pain. Unfortunately, his neuropathic pain symptoms were refractory to this treatment regimen with a FLACC pain score ranging between 4 and 10, limiting his participation in physical therapy, playtime with friends, and poor sleep (waking 3 - 4 times per night). He was subsequently referred to the pediatric pain clinic for assistance with neuropathic pain management. Neurological examination was non-focal with no localization findings, although the sensory examination could not be performed due to his reduced developmental language capacity.

### Treatment

Amitriptyline (0.175 mg/kg/dose PO at bedtime) was added to the current regimen that included high-dose gabapentin and as needed oxycodone. Improvement in symptoms was observed within 7 days with a subjective reduction in pain complaints and scores, a decrease in nighttime awakening, and no need for supplemental oral opioids or topical lidocaine cream.

### Follow-up and outcomes

At 8 weeks of follow-up, his mother reported that he had some pain, especially at night. The amitriptyline dose was increased to 4 mg (0.3 mg/kg once a day), and the gabapentin dose was maintained at 52 mg/kg/day. Within a week of the dose increase, his mother reported a significant improvement in sleep with no nighttime awakenings and the ability to tolerate physical therapy without worsening pain. Additionally, there was no need to use topical lidocaine or oral opioids for breakthrough pain, and the FLACC pain score was reduced to 1 on his worse day. He continued to receive vincristine and methotrexate for maintenance chemotherapy and did not exhibit any neuropathic pain symptoms for the past 6 months.

### Discussion

With the advent of effective chemotherapeutic regimens, the survival rate of pediatric cancer has increased, but patients may also experience a symptom burden due to the prolonged use of chemotherapeutic agents. An estimated 30-40% of patients who receive neurotoxic chemotherapeutic agents experience CIPN [2, 3]. Clinical manifestations of CIPN are often dependent on the dose and the specific agent used. Susceptibility to CIPN is increased in patients with a history of CIPN or with preexisting neuropathic conditions or damage to peripheral nerves [4]. Although the neurotoxicity caused by the offending agent may involve multiple locations of the nervous system,

peripheral sensory nerves are most often affected, leading to sensory abnormalities and often pain. However, the pathological processes underlying neuropathic pain are complex, involving central, peripheral, and inflammatory mechanisms mediated by different neurons, ion channels, signaling pathways, and molecules. The clinical consequence is primarily pain that may persist long after cure or remission [5]. Although the symptoms may decrease or resolve with dose reductions or cessation of therapy, these interventions may impact long-term survival.

The symptoms of CIPN are varied and generally subjective in nature which may make a definitive clinical diagnosis challenging. Neurophysiological studies such as nerve conduction studies and quantitative sensory testing (which allows for identification of the fiber type involved) may help confirm the diagnosis, but do not reflect the clinical severity of CIPN [6]. Currently, there is no objective method of assessing and quantifying CIPN in children even with severity grading tools such as the National Cancer Institute of Cancer Common Terminology Criteria for Adverse Events (CTCAE), WHO Common Toxicity Criteria for Peripheral Neuropathy, and The Pediatric-modified Total Neuropathy Score (ped-mTNS) [7, 8].

Various chemotherapeutic agents, including vinca alkaloids, platins, taxanes, and newer biological agents such as bortezomib, cause neuropathic pain via different pathways. Vincristine, a naturally occurring vinca alkaloid and an essential component of various combination chemotherapeutic regimens for children, inhibits the assembly of microtubules, an important integrant of nerve fiber axons, causing disruption of nutrient transport and distal axonopathy, which ultimately results in the classic jaw pain (with cranial nerve involvement) and the glove and stocking distribution of pain [9]. While the majority of children who receive vincristine will experience CIPN, the peripheral neuropathic pain associated with vincristine is dose-related and typically improves with dose reduction, treatment interruption, or entry into maintenance therapy as the dosing is spaced out [4].

The majority of the literature surrounds the adult population and recommendations regarding the treatment of neuropathic pain in children are extrapolated from adult studies [10]. Furthermore, although various preventive and therapeutic strategies have been implemented to reduce CIPN, studies evaluating the efficacy of such treatments have produced conflicting results. For instance, gabapentin has been used to treat neuropathic pain in various co-morbid conditions including diabetes, post-amputation phantom pain, and postherpetic neuralgia [4, 11]. Tsavaris et al reported that all 75 adult patients with painful CIPN had a significant improvement in pain with gabapentin monotherapy compared to the 35 patients in the control group who refused gabapentin [12]. In contrast, a placebo-controlled, multicenter, double-blinded, cross-over study of 115 patients with CIPN showed no difference in symptom severity between the patients who received gabapentin and placebo [13]. Likewise, a randomized, double-blind placebo-controlled single-center study comparing the analgesic efficacy of gabapentin in the treatment of vincristine-induced neuropathic pain in children with ALL reported a higher opioid consumption and pain scores in the gabapentin group compared to the placebo group [14]. Although the failure of the analgesic benefit of gabapentin may be multifactorial, the authors reported

that the use of a conservative low-dose regimen of gabapentin (20 mg/kg/day) without an upward titration based on clinical response may have impacted the study outcomes [14]. For that reason, it is generally recommended that dose adjustments with an upward titration based on symptom control as well as the addition of other medications be considered to enhance the efficacy of gabapentin in treating CIPN [15].

Agents including non-opioid analgesics, anticonvulsants, opioids, membrane stabilizers, vitamins, and antidepressants have been proposed and studied as adjuncts to gabapentin in managing CIPN [4, 11, 15, 16]. Amitriptyline is commonly prescribed for CIPN in adults, although multiple studies have shown either limited or no improvement in CIPN symptoms when it is used as the sole agent [17]. In the pediatric population, a prospective randomized trial comparing the efficacy of amitriptyline and gabapentin in neuropathic pain showed a significant and similar decrease in pain scores and improved sleep in both groups [10]. Despite the lack of evidence-based medicine to demonstrate the efficacy of dual therapy with the use of both gabapentin and amitriptyline in CIPN, as these two medications act via different pathways, it is possible that the synergistic effect of gabapentin and amitriptyline produced the therapeutic effect noted in our patient. When adding amitriptyline to monotherapy with high-dose gabapentin and then titrating up the dose, we noted decreased pain scores, improved sleep pattern, increased ability to tolerate activity, and decreased need for supplemental oral opioids and pain adjuncts, including topical lidocaine cream. Per clinical practice, dosing of amitriptyline for chronic pain management in the pediatric population ranges from 0.1 to 0.4 mg/kg, with preoperative electrocardiogram (EKG) performed to rule out concerns for any underlying arrhythmia [18].

### Learning points

This case illustrates the complexity of treating CIPN in patients on maintenance chemotherapy as clinicians must balance the benefits of the therapeutic agents used with their inherent adverse effects, including CIPN. Though the search for effective CIPN prevention and treatment in children continues, this case report suggests that combination therapy of high-dose gabapentin and daily low-dose amitriptyline may effectively and safely relieve refractory CIPN in pediatric patients on long-term vincristine-based chemotherapy. Future prospective research is needed to evaluate the therapeutic effect of the combination of gabapentin and amitriptyline in pediatric patients with refractory CIPN.

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None to declare.

### Financial Disclosure

None to declare.

### Conflict of Interest

None to declare.

### Informed Consent

Informed consent was obtained from a parent for clinical care and use of patient data for publication purposes. The patient information was de-identified for publication.

### Author Contributions

KOB performed the initial case review and manuscript preparation, literature review, and editing of subsequent revisions. EA provided care for the patient and was involved in the initial draft and subsequent revisions. JT contributed to literature review, manuscript writing, and editing of the manuscript.

### Data Availability

The data supporting the findings of this case report are available from the corresponding author upon reasonable request.

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