# Improving Neuropathic Pain Due to Cancer Using Gabapentin

*Caraceni A, Zecca E, Bonezzi C, et al. Gabapentin for neuropathic cancer pain: a randomized controlled trial from the Gabapentin Cancer Pain Study Group. J Clin Oncol 2004;22:2909–17.*

## Study Overview

Objective. To determine the analgesic benefit and safety of the addition of gabapentin to opioids in the management of neuropathic cancer pain.

Design. Randomized, placebo-controlled, double-blind, multicenter, parallel-design trial.

Setting and participants. From August 1999 to May 2002, consecutive patients in Italy and Spain with neuropathic pain from cancer partially controlled with opioids were enrolled. Neuropathic pain was defined as pain secondary to infiltration or compression, confirmed by imaging, and having ≥ 1 of the following symptoms/signs: burning pain, shooting/lancinating pain, dysesthesias, or allodynia. Pain intensity had to be rated ≥ 5 on a numeric scale from 0 to 10 in the 24-hour period preceding the screening visit. Patients were randomized 2:1 to receive gabapentin or placebo over a 10-day period. Gabapentin was titrated from 600 mg/day to 1800 mg/day in addition to a stable opioid dose. Extra opioid doses were available as needed. Patients needing more than one daily opioid dose during the trial were withdrawn from the study. A 0 to 10 numeric scale was used to rate daily pain, and a daily pain diary was kept. If chemotherapy, radiotherapy, or surgery was needed during the treatment phase for disease control, the patient was withdrawn from the study.

Main outcome measures. The average pain score over the entire follow-up period. Secondary outcomes included intensity of burning pain, shooting/lancinating pain, dysesthesias, number of episodes of lancinating pain, allodynia, and extra doses of opiates.

Main results. 79 patients received gabapentin and 41 patients received placebo. The placebo and gabapentin groups were comparable with regards to age, sex, performance status, stabilized opioid daily dose, while baseline global pain intensity was higher in the placebo group. The presence of shooting pain, burning pain, and dysesthesias was similar for the 2 treatment groups, and allodynia and the number of daily shooting pain episodes were more frequent in the placebo group Analysis of covariance (ANCOVA) in the intention-to-treat population showed a significant difference of average pain intensity between the gabapentin and placebo groups (4.6 versus 5.4; $P = 0.025$). Dysesthesia scoring also showed a statistically significant benefit for gabapentin ($P = 0.0077$) on the modified intention-to-treat population ($n = 115$, patients with ≥ 3 days of pain assessments). The difference between the 2 groups was evident early in the study through day 5, while results tended to overlap thereafter. Adverse events were minimal and similar between arms, although gabapentin was associated with increased somnolence.

Conclusion. Gabapentin is effective in improving analgesia in patients with neuropathic cancer pain already treated with opioids.

## Commentary

Opiates are a mainstay in the treatment of pain due to cancer. Adjuvant therapies are often required to help maximize pain control and include acetaminophen, nonsteroidal anti-inflammatory drugs, steroids, bisphosphonates, antidepressants, and anticonvulsants. Gabapentin is an anticonvulsant that has emerged as a preferred adjunctive therapy for patients with neuropathic pain because of its excellent safety profile (relative to other pain medications and anticonvulsants) and efficacy demonstrated in phase 2 and 3 studies in patients with diabetic neuropathy [1,2]. However, there are limited data regarding the role of gabapentin in patients with neuropathic pain and cancer.

Caraceni et al conducted a randomized trial comparing gabapentin and placebo in patients with neuropathic pain due to cancer that was not well-controlled with opiates alone. This is a unique study because it represents one of a few trials with gabapentin in patients with cancer, and the only published randomized study. This distinction is in part due to the fact that pain studies are difficult to conduct because they are often resource-consuming for both researcher and patient and fraught with methodologic dilemmas. Pain is subjective, individual, and influenced by a host of variables including disease, treatment, and other medications. Caraceni et al attempt to mitigate many of these variables through randomization and by using a succinct, close-

ly monitored 10-day treatment plan. The results may be valid, but potential confounding must be considered. It is worth noting that a greater percentage of patients in the treatment group were already receiving antidepressant and bisphosphonate therapies—modalities with proven benefits in pain control. It is not clear how long patients had been treatedwith these modalities prior to enrolling. Moreover, prior chemotherapies were not described (some of which may be more likely to have neuropathy as a side effect), and patients could have received a new treatment as recently as 4 days prior to enrollment (and radiation 16 days prior to enrollment), which are modalities that could have affected pain scores in this 10-day interval. Ideally, randomization would adjust for these potential biases, but with a trial involving so few patients (placebo group, $n$ = 41), these issues should be considered. A larger trial and of longer duration could help reduce many of these potential biases.

Although gabapentin was originally developed as an anticonvulsant and has been criticized for off-label promotion, the weight of evidence for its use in patients with neuropathic pain due to surgery, spinal cord injury, diabetes, and now cancer confirms it has a role in patient care.

## Applications for Clinical Practice

Gabapentin is an important adjunctive therapy to narcotics in the treatment of pain due to cancer.

*–Review by David R. Spigel, MD*

## References

1. Backonja M, Beydoun A, Edwards KR, et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. JAMA 1998;280:1831–6.

2. Morello CM, Leckband SG, Stoner CP, et al. Randomized double-blind study comparing the efficacy of gabapentin with amitriptyline on diabetic peripheral neuropathy pain. Arch Intern Med 1999;159:1931–7.