Intrathecal Gabapentin to Treat Chronic Intractable Noncancer Pain

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ABSTRACT

Background: Oral gabapentin is approved as an anticonvulsant medication and to treat postherpetic neuralgia. Its nonopioid properties and presumed spinal site of analgesic action made the study on intrathecal gabapentin attractive to establish the minimum effective dose for a later, pivotal trial.
Methods: The authors examined the safety and efficacy of intrathecal gabapentin in a randomized, blinded, placebo-controlled, multicenter trial in a heterogeneous cohort of candidates with chronic pain for intrathecal drug therapy.
Results: Patients (N = 170) were randomized to receive continuous intrathecal gabapentin (0 [placebo], 1, 6, or 30 mg/day) during 22 days of blinded treatment after implantation of a permanent drug delivery system. The highest dose, 30 mg/day, was selected to maintain a safety margin below the 100-mg/day dose that was explored in a phase 1 study. The authors found no statistically significant difference in the primary outcome measure, which was the numerical pain rating scale and response rate after 3 weeks, for any dose *versus* placebo. Physical functioning, quality of life, and emotional functioning also revealed no differences. Small, nonsignificant changes occurred in opioid medication use. The most frequent device-related adverse events were transient postimplant (lumbar puncture) headache, pain, and nausea. The most frequent gabapentin-related adverse events were nausea, somnolence, headache, dizziness, fatigue, and peripheral edema.
Conclusion: Twenty-two days of intrathecal gabapentin did not demonstrate statistically significant or clinically meaningful analgesic effects. The study sponsor has no current plans for further studies. Drug-related adverse events were similar to those for oral gabapentin. Most device-related adverse events resulted from the implant surgery or anesthesia.

What We Already Know about This Topic

- Oral gabapentin is widely used to treat neuropathic and sometimes other forms of chronic pain
- Gabapentin has a presumed spinal site of action when used for chronic pain

What This Article Tells Us That Is New

- In a prospective, blinded, placebo-controlled trial conducted on a heterogeneous group of patients with chronic pain, no analgesic effects were identified during 22 days of intrathecal gabapentin infusion

PAIN, an unpleasant experience associated with actual or potential tissue damage, or described in terms of such damage, is always subjective.[1] When pain lasts longer than 3 months and is no longer associated with tissue damage, it may be defined as chronic. Chronic pain treatment regimens involve drugs of different classes and escalating potency, including systemic opioids.[2,3] None is effective indefinitely, and all are associated with adverse effects that can be dose-limiting or life-threatening. Pain physicians sometimes use implantable spinal cord stimulation or intrathecal drug delivery systems once oral or systemic medications and less invasive interventions prove inadequate. Preservative-free morphine sulfate and the cone snail peptide, ziconotide, are

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the only analgesic agents presently approved in the United States for long-term intrathecal administration (Infumorph; West-Ward Pharmaceutical Corp., Eatontown, NJ and Prialt; Jazz Pharmaceuticals plc, Dublin, Ireland). When the putative site of action of an analgesic drug is the dorsal horn of the spinal cord, continuous intrathecal delivery can achieve therapeutic spinal drug concentrations at daily dosages that are orders of magnitude lower than the estimated equianalgesic oral or systemic dose, providing analgesia with fewer cerebral or systemic side effects than systemic administration.[4]

Anticonvulsants, such as phenytoin and carbamazepine, that are effective for trigeminal or glossopharyngeal neuralgia act on membrane receptors that maintain or influence neuronal hyperexcitability.[5] Gabapentin, first approved as an adjunctive anticonvulsant, subsequently was approved for the treatment of postherpetic neuralgia. Although gabapentin, 1-(aminomethyl) cyclohexane acetic acid, was synthesized as an analog of the inhibitory amino acid neurotransmitter γ-aminobutyric acid, it has no known activity at γ-aminobutyric acid-A or γ-aminobutyric acid-B receptors or at γ-aminobutyric acid uptake sites in the brain.[6] Hypothesized mechanisms and sites of analgesic action—based on animal models, clinical trials, and case series—include the neuronal α-2-δ subunit of voltage-gated calcium channels, increased γ-aminobutyric acid and/or glutamate synthesis, or interaction with *N*-methyl-D-aspartic acid receptors.[7–18] Other studies suggest a cerebral site of potential analgesic action.[19] Off-label usage at higher than recommended doses and incomplete reporting in the medical literature have complicated investigators' efforts to sort out the efficacy and safety profile of oral gabapentin to treat other chronic pain states. Some of those controversies have unfolded in the pages of medical journals and in the popular press.[20–23] Gabapentin's hypothesized spinal site of analgesic action, its short plasma half-life, and variable absorption and bioavailability provided the pharmacological rationale to explore continuous intrathecal administration.[24–26]

Materials and Methods

Study Oversight

This phase 2 dose-finding study was designed and executed in compliance with U.S. regulatory requirements under U.S. Food and Drug Administration's Investigational New Drug Application. Medtronic, Inc. (Minneapolis, MN) prepared the clinical investigational plan, including the protocol and informed consent form. Each investigator obtained written institutional review board approval before patient enrollment. An Adverse Event Advisory Committee met at least quarterly to review the patients' medical history, concomitant medications, study assessment results, laboratory findings, and the pattern, frequency, and severity of all adverse events (AEs). The committee was composed of voting members external to the sponsor: a clinical trials expert (chair), neurologist, psychiatrist, medical oncologist, clinical pharmacologist, and a biostatistician—and had authority to recommend study termination at any time.

Study Patients

Patients were men and women between 18 and 70 yr of age who provided written informed consent. The 17 study sites included academic medical centers and private practice pain clinics throughout the United States. Patients were recruited by referral or during routine care assessments and were willing and able to attend scheduled visits and comply with the protocol. The first patient was enrolled on December 22, 2006; the final patient was enrolled on October 2, 2009, and completed the blinded phase on December 16, 2009. All women patients were nonlactating, nonpregnant, and agreed to take precautions to prevent pregnancy. Patients also satisfied the criteria listed in table 1—which allowed for a heterogeneous group of diagnoses representative of the painful conditions and syndromes commonly evaluated by pain physicians or neurosurgeons for intrathecal drug therapies. Implicit in the trial design was the notion that intrathecal gabapentin might be effective for patients with a range of pain indications that would not be expected to respond to oral gabapentin. Previous oral gabapentin exposure was permitted but not required. Patients taking oral gabapentin or pregabalin at the time of enrollment were weaned from those medications before receiving intrathecal gabapentin or placebo in this trial. A related hypothesis was that patients whose pain had not responded to oral gabapentin or pregabalin might respond to intrathecal therapy. Although selection of oral drug-responsive patients was considered, we did not seek to enroll such patients. Doing so would have exposed individuals who responded satisfactorily to oral therapy to unnecessary risks and follow-up care associated with device implantation.

Study Materials and Procedures

Gabapentin Source and Formulation. Gabapentin injection was manufactured by AAI Pharma, Inc. (Wilmington, NC) and supplied to investigative site pharmacies as a clear, colorless, preservative- and pyrogen-free, sterile aqueous solution in a single-use 10-ml vial at a concentration of 80 mg/ml and diluted with preservative-free normal saline. Preservative-free 0.9% Sodium Chloride Injection, USP, (placebo) was also supplied in single-use vials, and prepared by the investigational site pharmacies.

Implant Procedure. Study subjects were implanted with the SynchroMed® (Medtronic, Inc.) intrathecal drug delivery system during general anesthesia, or less commonly, local anesthesia with sedation. The pump was implanted into a subcutaneous pocket in the abdominal wall, and the intrathecal catheter was inserted percutaneously *via* lumbar puncture (through the supplied Tuohy needle) with the catheter tip placed into the intrathecal space at or below the T-10 vertebral level. The catheter was then tunneled

Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Chronic, intractable pain below the neck for a minimum of 1 yr and have at least one of the following conditions: Back pain with or without leg pain Postherpetic neuralgia CRPS 1 or 2 Diabetic neuropathy A general neuropathic condition	Currently enrolled or planning to enroll in another investigational drug or device trial Any previous intrathecal drug exposure, including a test or trial dose
Use of one or more systemic pain medications without achieving adequate pain control	Participated in an investigational drug or device study within 30 days
New candidate for chronic intrathecal drug therapy	Known allergy or sensitivity to gabapentin
Medically stable and able to undergo implantation of the infusion system	Any condition that impairs the circulation of cerebrospinal fluid
Average daily NPRS ≥5 at the screening visit	
Current NPRS of ≥6 averaged over the final 7 days of the 2-wk drug stabilization visit	
No new pain medications or dose changes during the 2-wk drug stabilization period	
Successfully complete daily electronic NPRS on at least 11 of the final 14 days before the 2-wk drug stabilization period	

CRPS = complex regional pain syndrome; NPRS = numerical pain rating score.

subcutaneously and connected to the pump. Pumps were filled intraoperatively with preservative-free normal saline, which was administered until the pumps were refilled with blinded study drug at the randomization visit.

Randomization and Blinding. Subjects were randomized (1:1:1:1) into one of four treatment groups: placebo (preservative-free 0.9% Sodium Chloride Injection, USP) or gabapentin injection (1, 6, or 30 mg/day). Treatment group assignment was balanced within each investigational site according to a randomization schedule prepared by a statistician employed by the sponsor, but who was not associated with the study. Aptuit, LLC (Greenwich, CT) prepared coded drug syringe labels, which were stored in sealed, sequentially numbered randomization envelopes at the investigational site pharmacies. Upon notification that a subject had completed device implantation and recovery from surgery, the pharmacist selected the next sequential randomization envelope, prepared the assigned study drug for that subject, and attached the coded label to the syringe before sending it to the clinic.

Investigators, site, and sponsor staff were blinded to treatment assignments. An unblinded contract monitor conducted pharmacy monitoring. Each investigational site pharmacy maintained randomization records securely and provided code-labeled drug syringes for pump refills. Breaking the blind was to occur only in the case of life- or health-threatening situations for study subjects.

Selection of Intrathecal Gabapentin Doses. The lowest active dose (1 mg/day) may have been effective based on cerebrospinal fluid (CSF) concentrations of gabapentin in the 1-mg/day cohort of the phase 1 study, which were comparable with CSF levels measured after oral administration.[26] CSF and plasma gabapentin levels showed linear, dose-dependent pharmacokinetics as the daily intrathecal dosage was escalated; however, systemic exposure to gabapentin was minimal. On the basis of previous laboratory and clinical toxicity studies, the 6- and 30-mg/day intrathecal doses administered during this study were anticipated to achieve CSF and spinal cord drug levels greater than what could be achieved with oral gabapentin administration. The maximum intrathecal dose, 30 mg/day, was below the scaled human-equivalent upper limit that was safely administered in unpublished animal toxicology studies and in the phase 1 inpatient human study—which used a temporary external catheter and portable pump in 20 patients with chronic pain. The rationale for limiting the daily dose to 30 mg/day was to maintain a margin of safety during the 22 days of therapy in outpatients who had to maintain their normal activities.

The placebo was preservative-free 0.9% Sodium Chloride Injection, USP, which seemed identical to gabapentin. Pump programming and flow rates were similar in all patients, regardless of randomization assignment. After recovery from surgery (fig. 1), patients were assigned to one of the four treatments described in the previous section for 22 days, followed by a 7-day drug weaning period during which the flow rate and dose were reduced by half to 0.2 ml/day.

Outcome Measures and Statistical Analyses

Primary Efficacy Measure. The average daily numerical pain rating scale (NPRS)—where 0 represented no pain and 10 represented the worst possible pain—was used for the

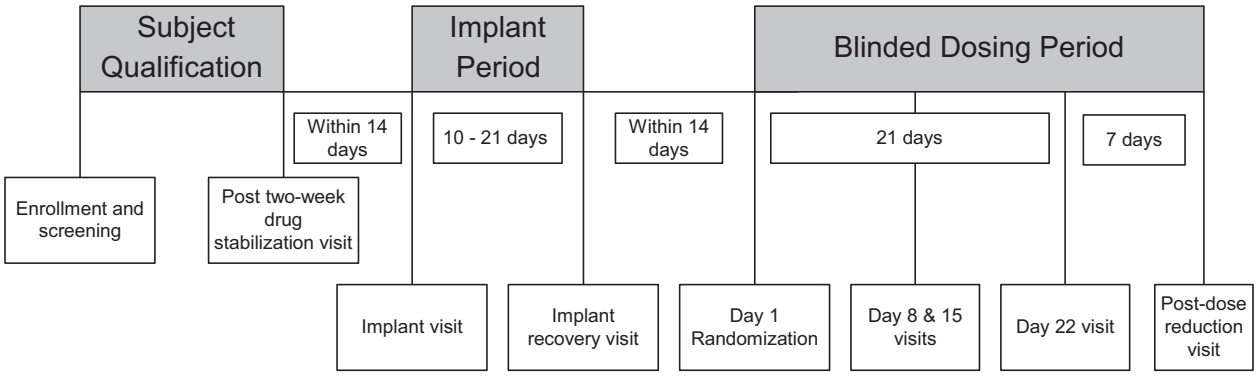


Fig. 1. Patients' oral pain medications had to remain stable for at least 2 weeks before being scheduled for implantation of the intrathecal pump and catheter systems. Their stable medication regimen was maintained through the postimplant recovery period, after which the pumps were filled with blinded study drug or placebo.

primary efficacy analysis.[27–31] NPRS scores collected during the final 7 days before the randomization visit were averaged for each patient and used as that individual's baseline score immediately before commencement of blinded placebo or intrathecal gabapentin. Each patient's NPRS scores during the final 7 days before the day-22 visit were averaged to obtain their final score. For patients who discontinued before day 22, the NPRS scores during the last 7 days before their dose reduction or discontinuation were averaged and carried forward to obtain their final score. The difference between each patient's baseline and day-22 average NPRS scores (change from baseline score) was calculated to determine improvement or worsening of his/her pain.[32,33] To assure that on-treatment pain scores and baseline pain scores were collected and assessed in as similar a manner as possible, only patients who completed at least 4 days of the electronic diary during the last 7 days before their day-22 visit were included in the primary analysis. Patients were not aware of this feature of the study plan. An intent-to-treat analysis also was performed for the primary efficacy objective, which included data from all randomized subjects, and assigned a value of zero change (no change) from baseline for the three subjects with missing data.

The study was powered to test the primary efficacy objective in the entire cohort—to identify the minimum effective dose of gabapentin using Williams test.[34,35] Williams test uses an averaging process over successive dose levels to create monotonically increasing estimates of the mean. A test statistic similar to Student *t* test is used to compare each of these estimates with the placebo mean, controlling type I error. Tables for Williams test were used to determine a sample size of 144 subjects (36 per group) that was required for three active dose levels, an SD for change from baseline NPRS equal to 2.5, a clinically meaningful difference equal to 2.0, α of 0.05 two-sided, and 90% power.

A secondary efficacy objective was to compare the proportion of responders in each of the gabapentin-treated groups with the placebo group.[34,35] The two responder levels were defined as at least a 30 or 50% reduction in NPRS between baseline and day 22. With 36 subjects per group, a true placebo responder rate of 15%, α of 0.05 two-sided, and no adjustment for multiple comparisons, a true responder rate for a treated group of 48% or greater could be detected with 80% power.

Secondary Efficacy Measures. Secondary efficacy measures included the Brief Pain Inventory, the SF-36 (a quality of life instrument), the Beck Depression Inventory of emotional functioning, and daily opioid use normalized to oral morphine-equivalent dosages.[36–38] Differences between the baseline and day-22 values for secondary efficacy measures and subscores in each dose group were assessed using ANOVA methods. The baseline value was included as a covariate in the analysis for Brief Pain Inventory, SF-36, and Beck Depression Inventory. Analyses compared changes from baseline among the dose groups.

Safety. The safety set consisted of all 170 patients who were implanted and randomized. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA® Version 8; MedDRA MSSO, Reston, VA). Infusion system–related AEs were categorized using methods accepted by the Food and Drug Administration for previous intrathecal drug and device trials. The number of AEs (occurrence) and the number of patients who experienced each event (incidence) were calculated by preferred term, severity, and relation to study drug and infusion system. Fisher exact test was used to compare the number of patients experiencing AEs between the placebo- and gabapentin-treated groups, although the final sample size (approximately 40 patients per group) was not large enough to definitively establish safety in this phase 2 trial. The Adverse Event Advisory Committee reviewed all AEs.

Results

Study Patients

Figure 2 and table 2 summarize the disposition of 254 patients enrolled at 17 sites. Eighty-three patients (32.7%) failed to meet eligibility criteria before device implantation and randomization. The remaining 171 patients were

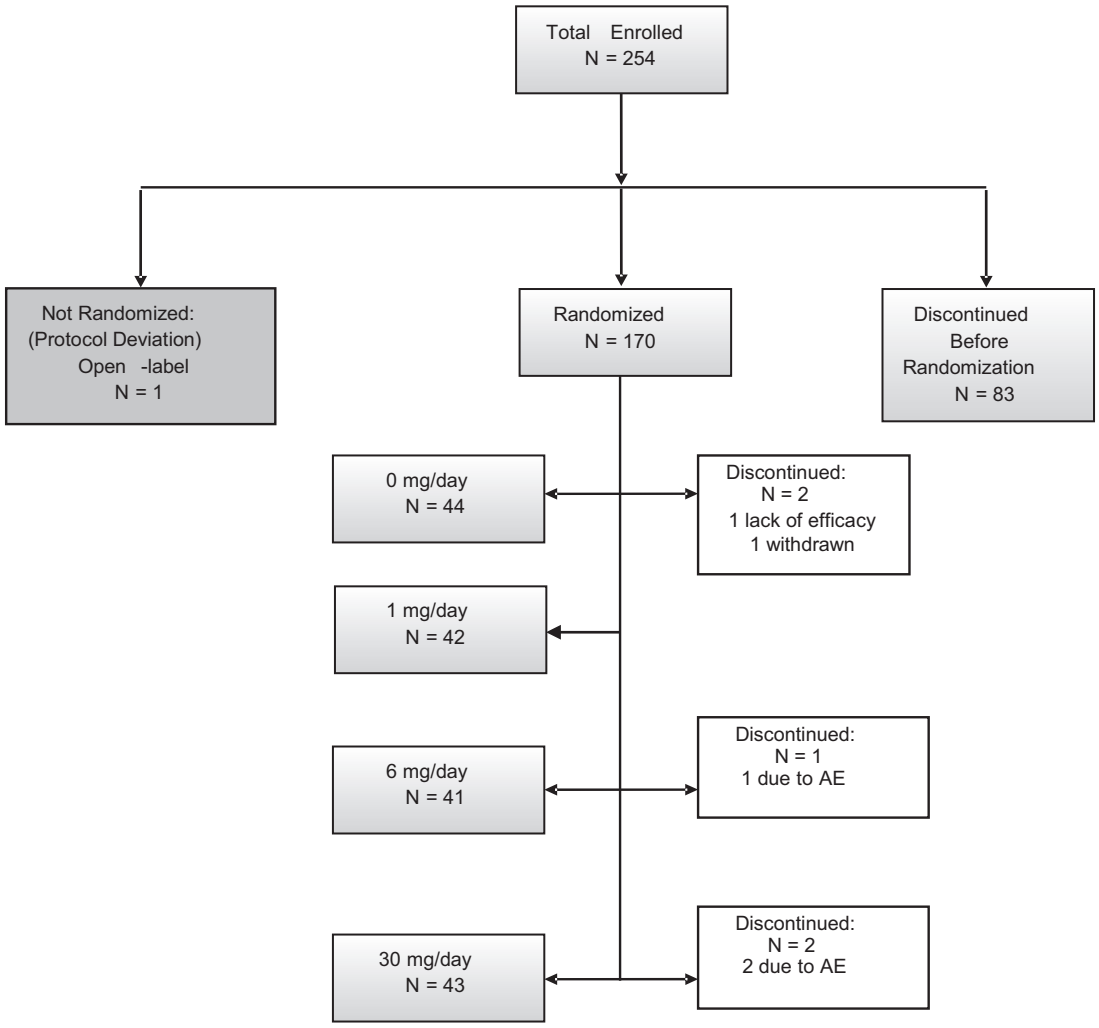


Fig. 2. Of the 254 patients enrolled and consented for study qualification, 83 discontinued before device implantation and randomization, and 1 mistakenly received open-label drug (intrathecal gabapentin). The remaining 170 patients underwent device implantation and study drug or placebo therapy.

implanted with the intrathecal pump and catheter system, and 170 were randomized to treatment groups. Owing to a randomization error, one patient received open-label study drug. Five patients (2.9%) exited the trial after commencing randomized study drug: two (1.2%, one each in the 6- and 30-mg/day groups) exited owing to device infection AEs (see Study Outcomes, Safety); one (0.6%) was explanted due to lack of efficacy and withdrawal of consent (placebo group); one (0.6%) was withdrawn by the sponsor and investigator because of multiple missed study visits after device explantation because of infection (placebo group); and one (0.6%, 30-mg/day group) due to an AE on the first day of dosing. One hundred sixty-five randomized patients (97.1%) completed blinded dosing, and two of the early drop outs—making a total of 167 subjects—provided at least 4 days of pain diary entries before discontinuation and were included in the primary analysis.

Pertinent demographic- and pain-related features of the 170 randomized patients and 167 patients included in the efficacy analyses were balanced across treatment groups as summarized in table 3 and Supplemental Digital Content 1, http://links.lww.com/ALN/A959, which is a table showing that concomitant medication intake also was balanced across treatment groups. Pain duration varied from 1.1 to 56.9 yr, and the most common symptoms were back pain with leg pain (n = 100; 59%) and general neuropathic condition (n = 33; 19%). Among the three pain categories assigned by investigators (nociceptive, neuropathic, and mixed), 23 of 170 (14%) had nociceptive pain, 68 of 170 (40%) had neuropathic pain, and 79 of 170 (46%) had mixed pain. Low back and leg pain constituted the majority of patients in the nociceptive (15 of 23, 65%) and mixed pain categories (64 of 79, 81%).

Study Outcomes

Efficacy. The primary efficacy analysis was performed on 167 of 170 randomized patients who completed at least 4 days of the electronic diary during the last 7 days before

Table 2. Patient Disposition

	Number of Subjects				
	Total	Gabapentin (mg/day)			
Disposition Category	N (%)*	0	1	6	30
Implanted and randomized to treatment	170 (100)	44	42	41	43
Completed through day 22	165 (97.1)	42	42	40	41
Discontinued before day 22	5 (2.9)	2	0	1	2
Adverse event	3 (1.8)	0	0	1	2
Lack of efficacy	1 (0.6)	1	0	0	0
Withdrawn by sponsor	1 (0.6)	1	0	0	0
Included in primary efficacy analysis*	167 (98.2)	43	42	41	41

Percent (%) = (n ÷ N) × 100, where n = number of patients per category and N = 170 implanted and randomized patients.

* Two of the early study drop outs (one each in the 0-mg/day [placebo] and 6-mg/day dose groups) provided at least 4 days of pain diary entries before discontinuation and were included in the primary efficacy analysis.

their day-22 visit (or before dose reduction for a drug-related AE). Mean baseline average daily NPRS and day-22 NPRS for each treatment group according to daily dosage are illustrated in figure 3 and by pain diagnosis groups in figure 4. Changes in pain scores were not statistically significant for any of the treatment groups when compared with placebo. The 95% CIs for each dose compared with placebo were −0.46 to 0.61, −0.17 to 0.92, and −0.05 to 1.04 for 1, 6, and 30 mg/day, respectively. The primary efficacy objective, to determine the minimum effective dose of gabapentin, could not be determined owing to absence of a significant treatment effect. To assess the effect of excluding the three subjects with no pain diary data during their final 7 days on treatment, an intention-to-treat sensitivity analysis was performed. These individuals were assigned a change from baseline pain score equal to zero (no change). Results from the intention-to-treat efficacy data set were consistent with those from the primary data set (*P* values were 0.799, 0.871, and 0.899 for comparisons between placebo and 1-, 6-, and 30-mg/day dose levels, respectively).

Secondary Efficacy Measures. A secondary efficacy analysis to determine the responder rate based on a 30 or 50% reduction in average daily NPRS also revealed no statistically significant differences for the gabapentin-treated groups compared with placebo-treated groups. The responder rates based on a 30% reduction in pain were 9.1, 9.5, 2.4, and 4.7% for placebo, 1, 6, and 30 mg/day, respectively—showing no trend toward a positive dose–response. We also examined pain category subgroups (mixed, neuropathic, and nociceptive) and found no meaningful differences between gabapentin and placebo, although there was reduced statistical power with the smaller subgroup sample sizes.

The overall test for treatment effect was not statistically significant for the other secondary measures, and no additional pair-wise comparisons of treatment groups were performed (table 4). The *P* value for the nonparametric Kruskal–Wallis test for change in opioid use was 0.139, and average changes were small, consistent with the request to keep other pain medications stable during the trial.

Safety. Device safety analyses included 171 implanted patients, whereas drug safety analyses included the 170 patients who received randomized study drug (excluding the one unintentional open-label gabapentin exposure; table 5 and Supplemental Digital Content 2, http://links.lww.com/ALN/A960, which is a summary table of AEs from study enrollment to the blinded phase). One hundred twenty-five of 171 patients (73.1%) experienced a total of 314 AEs from enrollment to implantation of the intrathecal drug administration system—before randomization and exposure to blinded study drug. Fifty-seven of the 171 implanted patients (33.3%) experienced 89 device-related AEs during the same prerandomization interval. The most common prerandomization device-related AEs were transient lumbar puncture headache and pain as a consequence of device implant surgery. Two patients (1.2%) experienced device-related AEs that resulted in early discontinuation from the study after randomization and commencement of study drug: one (6-mg/day group) discontinued due to pump-site infection and complete device removal 3 weeks after implantation, and another patient (30-mg/day group) discontinued due to catheter-site infection and complete device removal 1 month after implantation.

One hundred forty-five of 170 patients (85.3%) reported a total of 407 AEs while receiving blinded intrathecal gabapentin or placebo (table 6 and Supplemental Digital Content 1, http://links.lww.com/ALN/A959). No unanticipated drug- or device-related AEs occurred during any phase of the trial. The most common drug-related AEs, similar to those for oral gabapentin, were nausea, somnolence, headache, dizziness, fatigue, and peripheral edema. We observed a trend toward an increased number of drug-related AEs with higher doses of intrathecal gabapentin, but the percent of subjects who experienced AEs was not statistically significant. Ten patients (5.9%) reported at least one serious AE during blinded dosing. No patient died or had laboratory,

Table 3. Demographic and Baseline Characteristics of Subjects (Blinded Phase) Gabapentin (mg/day)

		Number of Patients n (%)				
		Gabapentin Dose (mg/day)				
Variable		0 (Placebo) (n = 44)	1 (n = 42)	6 (n = 41)	30 (n = 43)	Total (N = 170)
Race	American Indian or Alaska Native	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	1 (0.6)
	Asian	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Black or African American	3 (6.8)	1 (2.4)	0 (0.0)	3 (7.0)	7 (4.1)
	White	41 (93.2)	40 (95.2)	39 (95.1)	39 (90.7)	159 (93.5)
	Other	0 (0.0)	1 (2.4)	1 (2.4)	1 (2.3)	3 (1.8)
	Not specified	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity	Hispanic or Latino	0 (0.0)	2 (4.8)	1 (2.4)	1 (2.3)	4 (2.4)
	Not Hispanic or Latino	42 (95.5)	39 (92.9)	37 (90.2)	41 (95.3)	159 (93.5)
	Subject refused	2 (4.5)	1 (2.4)	3 (7.3)	1 (2.3)	7 (4.1)
	Not specified	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sex	Women	27 (61.4)	28 (66.7)	20 (48.8)	23 (53.5)	98 (57.6)
Age	Mean	51.8	50.1	48.1	48.3	49.6
	Range	(22.0–69.9)	(22.0–65.8)	(24.2–66.2)	(28.5–72.3)	(22.0–72.3)
Pain type	Mixed	23 (52)	20 (48)	14 (34)	22 (51)	79 (46)
	Neuropathic	18 (41)	16 (38)	18 (44)	16(37)	68 (40)
	Nociceptive	3 (7)	6 (14)	9 (22)	5(12)	23 (14)
Primary pain diagnosis	Back and leg pain	29 (66)	25 (60)	22 (54)	24 (56)	100 (59)
	Back pain	3 (7)	3 (7)	5 (12)	5 (12)	16 (9)
	CRPS 1	3 (7)	6 (14)	4 (10)	2 (5)	15 (9)
	CRPS 2	1 (2)	0 (0)	2 (5)	2 (5)	5 (3)
	General neuropathic condition	7 (16)	8 (19)	8 (20)	10 (23)	33 (19)
	Diabetic neuropathy	1 (2)	0 (0)	0 (0)	0 (0)	1
	Traumatic injury	23 (52)	26 (62)	24 (59)	19 (44)	92 (54)
Years since primary pain diagnosis	N	44	42	41	42*	169
	Mean	11.1	9.8	13.5	9.8	11.0
	Range	(1.1–50.4)	(1.2–56.9)	(1.1–47.7)	(1.2–33.4)	(1.1–56.9)

* One subject did not disclose the number of years since primary pain diagnosis.

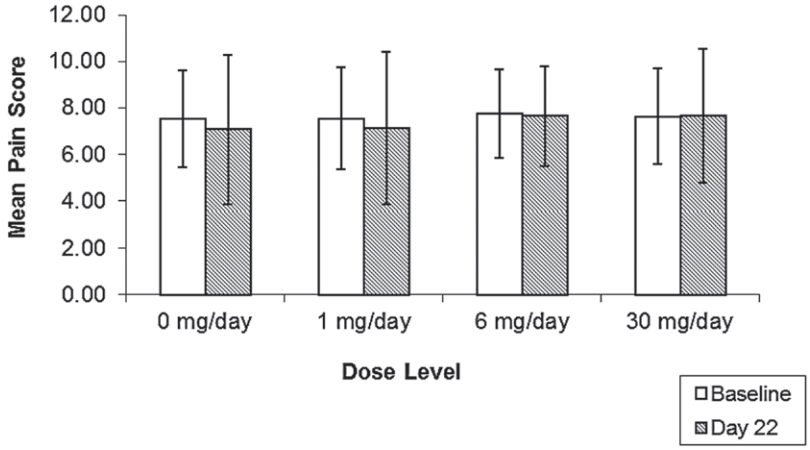
CRPS = complex regional pain syndrome; n = number of subjects per category; N = total number of subjects per treatment group.

electrocardiogram, or vital sign abnormalities considered clinically significant by investigators or the Adverse Event Advisory Committee.

Discussion

This study investigated the safety and efficacy of intrathecal gabapentin in patients with chronic, intractable pain. Based on a limited 3-week exposure, the safety profile of intrathecal gabapentin at daily doses of 30 mg/day or less compared favorably with morphine and ziconotide, the two approved intrathecal drugs. Although one cannot draw definitive conclusions, the data suggest that dose-limiting side effects, such as those associated with initiation of intrathecal morphine (respiratory depression, urinary retention, vomiting) or ziconotide (mental status changes), were not observed in greater numbers with gabapentin compared with those drugs, placebo, or compared with the prerandomization period in this study. However, this study did not reveal analgesic efficacy or placebo effects in the chronic noncancer pain population that we studied. These results seem to conflict with previous interpretations of animal studies.[7–18] A previously completed (unpublished) short-term phase 1 open-label intrathecal safety trial in a similar noncancer chronic pain population was designed to determine safe and tolerable dosage levels, and not designed to detect analgesic efficacy (Gabapentin for Intrathecal Injection, Investigator's Brochure, Version 3.0, September 3, 2009). Although daily pain scores decreased over the 4-day dosing period, those observations should not be misconstrued to predict long-term analgesic efficacy.

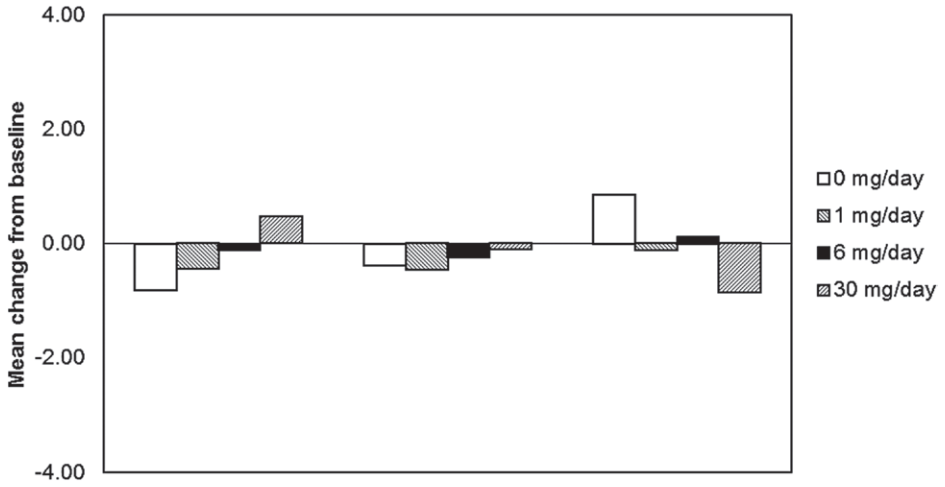
Limitations of the current study might have contributed to the lack of observed efficacy, but most likely did not cause a false-negative result. Study limitations included a patient population that was intentionally heterogeneous, with a



Gabapentin Treatment	N	Baseline Score Mean ± SD	Day 22 Score Mean ± SD	Change Mean ± SD	Williams' Test p-value
0 mg/day	43	7.55 ± 1.04	7.07 ± 1.61	-0.48 ± 1.52	—
1 mg/day	42	7.54 ± 1.10	7.14 ± 1.64	-0.40 ± 1.33	0.802
6 mg/day	41	7.76 ± 0.95	7.66 ± 1.08	-0.10 ± 0.99	0.874
30 mg/day	41	7.65 ± 1.03	7.66 ± 1.44	0.02 ± 1.11	0.899

Fig. 3. Lower scores indicate less pain. Total N = 167 patients. The mean ± 2SDs are shown.

variety of painful conditions observed in office-based pain medicine practices. Another potential limitation was that investigator assignment of pain categories (table 3) was not always consistent—a factor which might have been more important if an efficacy signal had emerged. However, mitigating factors included the fact that 79 of 170 (46.5%) randomized patients were assigned by investigators to the mixed pain category—and 64 of 79 (81% with mixed pain) had low back and leg pain. Moreover, among the 23 patients assigned by investigators to the nociceptive pain category, 15 of 23 (65%) also had low back and leg pain. Despite inconsistencies in pain category assignment, a sufficient number of patients with the most common painful condition—low back and leg pain—were assessed within the same categories across all dose groups to have observed an analgesic effect, if one was present.



Gabapentin Treatment	Neuropathic (n=67) Mean ± SD	Mixed Pain (n=77) Mean ± SD	Nociceptive (n=23) Mean ± SD
0 mg/day	-0.82 ± 1.63	-0.38 ± 1.41	0.86 ± 1.13
1 mg/day	-0.44 ± 1.44	-0.46 ± 1.41	-0.12 ± 0.76
6 mg/day	-0.12 ± 0.88	-0.23 ± 1.34	0.12 ± 0.55
30 mg/dy	0.48 ± 0.85	-0.11 ± 1.21	-0.86 ± 0.72

Fig. 4. Negative numbers indicate pain reduction. Total N = 167 patients. Pertinent demographic- and pain-related features were balanced across treatment groups as described in table 3.

Table 4. Results of Secondary Efficacy Measures

Measure	Dose Group, mg/day	Baseline	Day 22 (Final)	Change (Day 22 Minus Baseline) Mean ± SD	*F* Test for Treatment *P* Value
BPI*	0	7.24 ± 1.96	7.05 ± 1.88	−0.19 ± 1.59	0.375
	1	7.45 ± 1.29	7.00 ± 2.10	−0.45 ± 1.98	
	6	7.50 ± 1.69	7.62 ± 1.65	0.13 ± 1.52	
	30	7.59 ± 1.44	7.22 ± 1.97	−0.37 ± 1.71	
SF-36: overall physical component†	0	27.8 ± 7.4	29.3 ± 6.7	1.5 ± 6.2	0.257
	1	28.6 ± 6.0	29.8 ± 6.2	1.2 ± 5.0	
	6	27.7 ± 5.7	27.3 ± 5.8	−0.4 ± 5.6	
	30	27.1 ± 7.5	28.3 ± 6.1	1.2 ± 6.6	
SF-36: overall mental component†	0	37.4 ± 11.6	37.6 ± 11.9	0.2 ± 8.5	0.392
	1	35.4 ± 11.8	39.1 ± 11.6	3.7 ± 10.8	
	6	38.2 ± 11.5	38.0 ± 10.8	−0.2 ± 10.5	
	30	36.6 ± 13.0	39.3 ± 13.6	2.7 ± 11.5	
Beck Depression Inventory*	0	18.1 ± 10.9	17.7 ± 12.4	−0.4 ± 8.5	0.565
	1	20.1 ± 9.4	17.2 ± 10.7	−3.0 ± 8.0	
	6	19.4 ± 11.7	18.8 ± 11.0	−0.6 ± 9.4	
	30	18.2 ± 11.1	17.1 ± 12.4	−1.1 ± 7.0	
Daily opioid use (normalized to oral morphine, mg/day)*	0	142.1 ± 144.4	139.1 ± 138.4	−3.0 ± 21.7	0.139‡
	1	195.5 ± 263.4	173.8 ± 249.0	−21.7 ± 97.8	
	6	226.8 ± 263.7	230.9 ± 269.3	4.1 ± 26.6	
	30	213.8 ± 193.7	221.9 ± 223.2	8.1 ± 51.4	

The overall test for treatment effects was not statistically significant; no pair-wise comparisons were performed.

* Negative change values indicate improvement for these measures compared with baseline. † Positive change values indicate improvement for these measures compared with baseline. ‡ Kruskal–Wallis test *P* value.

BPI = Brief Pain Inventory; SF-36 = a generic 36-question quality of life test instrument, scored 0–100 for each sub-scale, and with a normative value of 50 (±10 = SD); the sub-scales are combined into two components, physical and mental, which are measures of patients' self-perceived health and well-being.

Another feature of this study is that patients did not have to respond to oral gabapentin, electrophysiological studies were not required to document neural injuries in patients with neuropathic pain or complex regional pain syndrome, and gabapentin was studied alone as an intrathecal monotherapy. Safety considerations also limited the maximum daily dose of intrathecal gabapentin to 30 mg/day during this 3-week trial in outpatients, lower than the 100 mg/day maximum dose that was explored for side effects in the 4-day inpatient phase 1 study where the patients were under near constant observation.

Table 5. Summary of Drug- and Device-related AEs

	Enrollment through Device Implant (171 Patients)	Randomization through Blinded Period (170 Patients)	Totals (171 Patients)
	Number (%) of patients with AEs from randomization to the blinded period		
Drug-related AEs*	Not applicable†	71/170 (41.8) 130 AEs	71/171 (41.5) 130 AEs
Device-related AEs	57/171 (33.3) 89 AEs	30/170 (17.6) 34 AEs	77/171 (45.0) 123 AEs
All AEs (including nonstudy drug-related events)	125/171 (73.1) 314 AEs	145/170 (85.3) 407 AEs	162/171 (94.7) 721 AEs
All serious AEs (including nonstudy drug-related events)	14/171 (8.2) 19 SAEs	10/170 (5.9) 12 SAEs	22/171 (12.9) 31 SAEs

One hundred seventy of 171 patients were counted in both time periods (before and after randomization). The 83 nonrandomized and nonimplanted patients are excluded from this analysis. Drug-related AEs are summarized in table 6. Additional information appears in Supplemental Digital Content 2, http://links.lww.com/ALN/A960, which is an AE table that covers the interval from study enrollment to the blinded period.

* Numbers and percents (%) are drug-related AEs that were categorized as Definite, Probable, or Possible, as defined in table 5. † Not applicable because intrathecal gabapentin was administered only after randomization.

AE = adverse event; SAE = serious adverse event.

Table 6. Summary of Drug-related Adverse Events by Daily Dose

Relation to Gabapentin	Gabapentin Daily Dose				
	0 (Placebo)	1 mg/day	6 mg/day	30 mg/day	Total
	Number (%)				
Possible	22 (88.0)	25 (92.6)	30 (96.8)	44 (93.6)	121 (93.1)
Probable	3 (12.0)	2 (7.4)	1 (3.2)	3 (6.4)	9 (6.9)
Definite	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Total	25	27	31	47	130

All adverse events were counted even if the same kind of event happened more than once in the same patient. Numbers and totals refer to the number of Possible, Probable, and/or Definite drug adverse events in each dose group. Additional information appears in Supplemental Digital Content 2, http://links.lww.com/ALN/A960, which is an adverse event table that covers the interval from study enrollment to the blinded period. Definitions of drug relationship assignments by investigators: Definite: the adverse event is associated with study drug administration, abates upon discontinuation of the study drug (dechallenge), and is confirmed by reappearance of the reaction upon repeat exposure (rechallenge). Probable: the adverse event is associated with study drug administration, abates upon discontinuation of the study drug (dechallenge), and cannot be reasonably explained by the known characteristics of the subject's clinical state. Possible: the adverse event is associated with study drug administration, and could have been produced by the study subject's clinical state or by other modes of therapy administered to the study subject.

With respect to preclinical models, apparent analgesia in animals has not reliably predicted clinically meaningful analgesic efficacy and safety in human patients in other drug development programs.[39] Despite promising results of laboratory investigations, only one analgesic drug besides morphine (ziconotide) has achieved U.S. Food and Drug Administration approval for chronic intrathecal administration in humans. Several factors also make it unlikely that the trial design, study conduct, and clinical features of the enrolled population explain the lack of observed efficacy. The investigative centers represented a balanced sample of academic and private practice settings across the United States, and the enrolled patient population corresponds to that reported in other interventional pain-device studies and case series.[40] Subset analyses by center, pain type, intrathecal dose, and by demographic features showed no clinically meaningful or statistical trends on any of the efficacy measures.[40] The absence of a placebo effect was not unique to this study or patient population and has been observed in other randomized trials and clinical practices.[40]

Among the 170 implanted and randomized patients, 44 (25.9%) were taking oral gabapentin or pregabalin at the time of their initial assessment. Given the heterogeneity of diagnoses and pain types in this study, and in light of the narrowly labeled indications for the oral drug formulations, it is not surprising that patients had not responded satisfactorily to those drugs in oral form. It is also likely that many of the patients in this trial who had no previous exposure to oral gabapentin would not have responded either.

One plausible consequence of these results is to reevaluate assumptions and hypotheses regarding the analgesic effects of gabapentin. The first is that the site of analgesic action for oral gabapentin is the spinal cord. Corollaries are that oral administration is dose-limiting owing to cerebral and systemic side effects and ineffective owing to minimal spinal cord exposure. Those hypotheses and corollaries are at least partly based on analogies to intrathecal opioids for pain and intrathecal baclofen for spasticity. Those drugs can be more effective and better tolerated in properly selected patients when administered *via* the intrathecal route, which brings the drugs more directly to their site of action in the dorsal horn of the spinal cord. Intrathecal delivery eliminates barriers related to absorption, hepatic metabolism, blood flow to the spinal cord, and the blood–central nervous system barrier. In contrast, oral gabapentin is effective for some patients with postherpetic neuralgia, a small subset of patients with neuropathic pain. Therefore, it is possible that oral gabapentin exerts analgesic effects at supraspinal sites and at similar oral dosages as when used as an antiepileptic medication. A recent animal study suggests that gabapentin may act at the locus coeruleus rather than at the dorsal horn of the spinal cord.[19] The finding that intrathecal gabapentin achieves high CSF and spinal cord drug levels in animals and humans is to no avail if the brain, instead of the spinal cord, is the primary site of analgesic activity. Another assumption not borne out by this trial was that intrathecal gabapentin would be an effective intrathecal monotherapy for a broader range of painful conditions than the oral drug. That notion influenced the trial design and inclusion criteria toward the development of safe and broadly effective nonopioid intrathecal drugs. In contrast, the current results support the findings of recent publications that noted a lack of reliable efficacy (in previously unpublished industry-sponsored studies) for off-label analgesic use of oral gabapentin.[20–22] That information only came to light after all of the patients in this trial had completed the blinded phase. In summary, this adequately powered and blinded placebo-controlled trial revealed that intrathecal gabapentin, in the doses tested, was not effective in treating the chronic painful conditions that are commonly treated with approved intrathecal medications. Accordingly, the study sponsor has no immediate plans to conduct further studies on intrathecal gabapentin toward approval for chronic administration in noncancer pain patients.

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