ORIGINAL ARTICLE

Morphine, Gabapentin, or Their Combination for Neuropathic Pain

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ABSTRACT

BACKGROUND

The available drugs to treat neuropathic pain have incomplete efficacy and dose-limiting adverse effects. We compared the efficacy of a combination of gabapentin and morphine with that of each as a single agent in patients with painful diabetic neuropathy or postherpetic neuralgia.

METHODS

In this randomized, double-blind, active placebo–controlled, four-period crossover trial, patients received daily active placebo (lorazepam), sustained-release morphine, gabapentin, and a combination of gabapentin and morphine — each given orally for five weeks. The primary outcome measure was mean daily pain intensity in patients receiving a maximal tolerated dose; secondary outcomes included pain (rated according to the Short-Form McGill Pain Questionnaire), adverse effects, maximal tolerated doses, mood, and quality of life.

RESULTS

Of 57 patients who underwent randomization (35 with diabetic neuropathy and 22 with postherpetic neuralgia), 41 completed the trial. Mean daily pain (on a scale from 0 to 10, with higher numbers indicating more severe pain) at a maximal tolerated dose of the study drug was as follows: 5.72 at baseline, 4.49 with placebo, 4.15 with gabapentin, 3.70 with morphine, and 3.06 with the gabapentin–morphine combination ($P<0.05$ for the combination vs. placebo, gabapentin, and morphine). Total scores on the Short-Form McGill Pain Questionnaire (on a scale from 0 to 45, with higher numbers indicating more severe pain) at a maximal tolerated dose were 14.4 with placebo, 10.7 with gabapentin, 10.7 with morphine, and 7.5 with the gabapentin–morphine combination ($P<0.05$ for the combination vs. placebo, gabapentin, and morphine). The maximal tolerated doses of morphine and gabapentin were lower ($P<0.05$) with the combination than for each drug as single agent. At the maximal tolerated dose, the gabapentin–morphine combination resulted in a higher frequency of constipation than gabapentin alone ($P<0.05$) and a higher frequency of dry mouth than morphine alone ($P<0.05$).

CONCLUSIONS

Gabapentin and morphine combined achieved better analgesia at lower doses of each drug than either as a single agent, with constipation, sedation, and dry mouth as the most frequent adverse effects.

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Neuropathic pain is a common complication of cancer, diabetes mellitus, degenerative spine disease, infection with the human immunodeficiency virus, the acquired immunodeficiency syndrome, and other infectious diseases, and it has a profound effect on quality of life and expenditures for health care.[1] Gabapentin and opioids have been proposed as two of several first-line treatments for neuropathic pain.[2] However, the maximal tolerated doses of these drugs, administered as single agents, reduce pain by only 26 to 38 percent, owing to incomplete efficacy, dose-limiting adverse effects, or both.[3-6] The combination of mechanistically distinct analgesic agents may result in additivity or synergism and may improve efficacy at lower doses, with fewer side effects than with the use of one agent alone. This strategy has been advocated in cases of partial treatment response, though, admittedly, in the absence of rigorous supportive evidence.[2] Gabapentin is a 3-alkylated analogue of γ-amino butyric acid, which modulates $\alpha_2\delta$ calcium-channel subunits, a mechanism thought to be important in neuropathic pain.[7] Gabapentin analgesia is unaffected by opioid antagonism, and repeated administration of gabapentin does not lead to analgesic tolerance.[8] Furthermore, preclinical studies suggest that additive interactions may occur between gabapentin and morphine[9-11] and that opioid tolerance can be prevented by the use of gabapentin.[12]

Common adverse effects associated with morphine include respiratory depression, sedation, nausea and vomiting, constipation, and pruritus.[13] Common adverse effects associated with gabapentin include sedation, ataxia, and dizziness.[14] Except for sedation, most opioid-related adverse effects rarely occur with gabapentin, suggesting that most adverse effects would not "overlap" if the drug were used in combination with morphine. Although sedation is an effect of both drugs, it is mediated only supraspinally, whereas both these drugs have been shown to have analgesic effects at supraspinal, spinal, and even peripheral sites of action.[15-17] Thus, a combination of gabapentin and morphine may provide more additivity for analgesia than for sedation.

Painful diabetic neuropathy and postherpetic neuralgia are two neuropathic pain syndromes that have been investigated in mechanism-based studies[18,19] as well as in many clinical trials of analgesic agents. Both conditions have been shown to respond to opioids[3,4] and to gabapentin.[5,6] We compared the combination of gabapentin and morphine with each drug used as a single agent in patients with diabetic neuropathy or postherpetic neuralgia.

METHODS

PARTICIPANTS

Our trial was approved by an institutional ethics review board. Patients were recruited between February 2001 and November 2003 by means of advertisements and physician referrals and were enrolled after giving written informed consent for participation. Patients with diabetic neuropathy had distal, symmetric, sensory diabetic polyneuropathy as determined on the basis of their medical history and either an unequivocal decrease in response to pinprick, temperature, or vibration in both feet or bilaterally decreased or absent ankle-jerk reflexes. Patients with postherpetic neuralgia had had an eruption of herpes zoster rash not more recently than six months before enrollment. General criteria for inclusion were daily moderate pain for three months or more, an age of 18 to 89 years, a serum alanine aminotransferase or aspartate aminotransferase level less than 1.2 times the normal level, a creatinine level less than 1.5 times the upper limit of the normal range, and sufficient language skills to communicate with research staff. Exclusion criteria were hypersensitivity to study medications, another painful condition as severe as the diabetic neuropathy or postherpetic neuralgia, a recent myocardial infarction, unstable angina or congestive heart failure, any central neurologic disorder (including seizures), a serious mood disorder, a history of serious drug or alcohol abuse, pregnancy, lactation, and lack of a primary care physician.

STUDY DESIGN

In our single-center, four-period, crossover, randomized trial, we compared four treatments (with each treatment given for five weeks) — morphine (M-Eslon, Aventis-Pharma), gabapentin (Neurontin, Pfizer), these drugs in combination, and active placebo (low-dose lorazepam). Benzodiazepines have no efficacy in neuropathic pain,[20] yet their sedative effects provide more effective blinding than those of inert placebo in trials of sedating analgesics.[21,22] With the use of a balanced Latin-square crossover design,[23] patients were allocated, in a double-blind, randomized fashion, to one of four treatment sequences: morphine, placebo, gabapentin, and the gabapentin–morphine combination;

placebo, the gabapentin–morphine combination, morphine, and gabapentin; gabapentin, morphine, the gabapentin–morphine combination, and placebo; and the gabapentin–morphine combination, gabapentin, placebo, and morphine. At the commencement of the trial, a pharmacist at the Kingston General Hospital in Kingston, Ontario, Canada, prepared a concealed allocation schedule randomly assigning the four sequences, in blocks of four, to a consecutive series of numbers. On enrollment, each patient was assigned to the next consecutive number, and the corresponding series of study medications was dispensed.

Medications were placed in blue and gray gelatin capsules by the investigational pharmacist in order to maintain double-blind conditions. Patients received identical-appearing blue and gray capsules during each treatment regimen in accord with a double-dummy design. Blue capsules were administered twice daily, and gray capsules three times daily. For the morphine treatment, blue capsules contained sustained-release morphine (30 mg) and gray capsules contained lactose placebo; for the treatment with the gabapentin–morphine combination, blue capsules contained sustained-release morphine (15 mg) and gray capsules contained gabapentin (300 mg); for the gabapentin treatment, blue capsules contained lactose placebo and gray capsules contained gabapentin (400 mg); and for the placebo treatment, blue capsules contained lorazepam (0.2 mg) and gray capsules contained lorazepam (0.1 mg).

The target daily-dose ceilings were morphine at a dose of 120 mg (morphine treatment), morphine at a dose of 60 mg and gabapentin at a dose of 2400 mg (gabapentin–morphine combination treatment), gabapentin at a dose of 3200 mg (gabapentin treatment), and lorazepam at a dose of 1.6 mg (placebo treatment). To facilitate the gradual titration, for some doses there was a slightly uneven distribution of the number of capsules within a day — for example, in the morning, one blue capsule and one gray capsule might be administered; at midday, two gray capsules; and at bedtime, one blue capsule and two gray capsules.

In the expectation that older patients and those with smaller body size might tolerate a less steep dose titration with smaller increments than patients no more than 60 years of age or with larger body size, adjustments were made for those more than 60 years of age and those weighing less than 60 kg: for the morphine treatment, blue capsules contained sustained-release morphine (15 mg) and gray capsules contained lactose placebo; for treatment with the gabapentin–morphine combination, blue capsules contained sustained-release morphine (15 mg) and gray capsules contained gabapentin (300 mg); for the gabapentin treatment, blue capsules contained lactose placebo and gray capsules contained gabapentin (300 mg); for the placebo treatment, blue capsules contained lorazepam (0.2 mg) and gray capsules contained lorazepam (0.1 mg). Among these older or smaller patients, the target daily-dose ceilings were morphine at a dose of 60 mg (morphine treatment); morphine at a dose of 60 mg and gabapentin at a dose of 2400 mg (treatment with the gabapentin–morphine combination); gabapentin at a dose of 2400 mg (gabapentin treatment); and lorazepam at a dose of 1.6 mg (placebo treatment).

PROTOCOL

Patients completed a baseline diary in which they rated the intensity of pain three times a day for seven consecutive days after discontinuing treatment with previously prescribed opioids or gabapentin. A similar daily pain diary was kept throughout the study. Nonopioid drugs other than gabapentin were permitted at a steady dose throughout the trial; procedural pain therapies (e.g., nerve blocks) were forbidden. The schedule of dose escalation for each set of capsules was identical in each treatment period. During the first three weeks of each five-week treatment period, the dose was escalated toward a maximal tolerated dose or the target ceiling dose, whichever was reached first. In the fourth week of each period, each patient received his or her maximal tolerated dose for the particular treatment. During the fifth week of each treatment period, patients underwent a four-day dose tapering and a three-day complete washout.

A research nurse telephoned patients twice weekly to evaluate adverse effects and guide drug titration. With each increase in the dose of study medications, adverse effects were rated (as mild, moderate, or severe), and patients were asked whether they could tolerate the increased dose for another two to three days. If they could, this dose was continued in the expectation that side effects would diminish. If, however, the side effects were intolerable or did not diminish, the study medications were decreased and an increase was attempted one more time, at the next telephone call. If this next increase again resulted in intolerable side effects, the

study drugs were decreased to the level of the previous dose, which was defined as the maximal tolerated dose. Patients were given docusate sodium (100 to 300 mg per day) as prophylaxis against constipation. Those in whom constipation developed during any treatment period were given sennosides (17 to 34 mg twice daily) in addition.

OUTCOME MEASURES

The primary outcome measure was the mean intensity of pain (on a scale from 0 to 10, with 0 indicating no pain and 10 indicating "the worst pain imaginable"), which patients rated three times daily. Ratings were averaged over seven days in which the patients were receiving the maximal tolerated dose of the study drug. Secondary outcomes were adverse effects, including major adverse events; pain assessed according to responses on the Short-Form McGill Pain Questionnaire (on a scale from 0 to 45, with higher numbers indicating more severe pain)[24]; pain-related interference assessed according to the Brief Pain Inventory (on a scale from 0 to 10, with 0 indicating no interference and 10 indicating complete interference)[25]; mood assessed according to the Beck Depression Inventory (on a scale from 0 to 63, with higher numbers indicating more severe depression)[26]; health status assessed according to the Medical Outcomes Study 36-Item Short-Form General Health Survey (SF-36 Health Survey) (on a scale from 0 to 100, with higher numbers indicating better health-related quality of life)[27]; mental status assessed according to the Mini–Mental State Examination (on a scale from 0 to 30, with lower numbers indicating impaired mental status)[28]; and global pain relief assessed in response to questions from the research nurse on the following scale: pain worse, no relief, slight relief, moderate relief, a lot of relief, or complete relief. The assessments were made at baseline and during each treatment period at the point when patients were receiving the maximal tolerated dose. A "blinding" questionnaire to assess which treatments the patients and the research nurse thought the patients were receiving was completed by both patients and the nurse when the patients were taking the maximal tolerated dose of the assigned study drug.

ANALYSIS

The preplanned primary analysis of the primary outcome was to compare patients' mean scores for pain while taking the maximal tolerated dose of the assigned drug during week 4 across all treatments. On the basis of previous estimates of variance,[3] and accounting for five pairwise comparisons (i.e., placebo vs. each treatment plus treatment with the gabapentin–morphine combination vs. each single agent), we calculated that 40 patients would be required to provide the study with 80 percent power to detect (with a two-sided alpha of 0.05) a mean difference in pain intensity at week 4 among the treatments that was equivalent to 1 point on a scale from 0 to 10.[29] On the basis of previous dropout rates[22] of approximately 10 percent during treatment periods of four to six weeks, we calculated that if 58 patients were enrolled, 40 would complete all four treatment periods. Patients who completed at least two treatment periods (allowing for one pairwise comparison) were included in the efficacy analysis. Patients who received at least one dose of any study medication were included in the analysis of adverse effects.

Before the analyses were performed, we defined the intensity of pain as an average of the scores for pain in the patient's diary for week 4 in each treatment period if no more than 50 percent of the scores were missing. If more than 50 percent of the scores were missing, the mean daily score for pain intensity was considered to be missing. A linear mixed model[30] in which the drug regimen, sequence, treatment period, and the first-order carryover term (the carrying over of treatment to the next treatment period — i.e., from period A to period B but not to period C or D)[30] were the fixed effects and the patient (nested in the sequence of treatment periods) was the random effect was fitted with the pain-intensity data. If the carryover effect was not significant, then a reduced model that excluded the carryover term was refitted. The least-square means and associated standard errors estimated from the initial model or the reduced model were calculated for each treatment. We used Fisher's least-significant-difference method to calculate multiple comparisons among treatments.[31] According to this method, the global difference among all treatments was first tested in the model. Only when this test was significant at the 0.05 level were pairwise comparisons made, also at the 0.05 level, with the use of the estimated contrast from the initial or the reduced model (i.e., the gabapentin–morphine combination vs. gabapentin as a single agent, the combination vs. morphine as a single agent, the combination vs. placebo, gabapentin vs. placebo, and morphine vs. placebo).

As a sensitivity analysis, the level of change in the intensity of pain during each treatment period

was calculated as the difference between the score for pain at baseline (the mean of the last three days of the pretrial baseline before treatment period A started or at washout for treatment periods B, C, and D) and the scores for pain during treatment (the mean of the last three days while the patient was taking the maximal tolerated dose). The percent change was calculated as the change in pain divided by the score for pain at baseline times 100 percent. These estimates were analyzed in the linear mixed model. Secondary continuous outcome measures were analyzed in a similar fashion. Data on proportions were analyzed with the use of Fisher's exact test, with the use of Fisher's least-significant-difference method for multiple comparisons.[32] A preplanned interim analysis without stopping rules was performed and reviewed approximately halfway through the trial.

All reported P values are two-sided. All statistical analyses were conducted with the use of SAS software (version 8.0, SAS Institute). All authors vouch for the veracity and completeness of the reported data, and all authors contributed to various aspects of the trial design, data gathering and analysis, and preparation of the manuscript.

RESULTS

SUBJECTS

Eighty-six patients underwent screening assessment in the research clinic. Of these, 29 were excluded, 57 underwent randomization, and a total of 16 withdrew during the treatment periods — 13 before completing the second treatment period (period B), and 3 because of adverse effects but after completing at least two treatment periods (these 3 were therefore included in the efficacy analysis). Forty-one patients completed the trial (Fig. 1). Table 1 lists the demographic and baseline characteristics of patients who underwent randomization; these characteristics were balanced among the four treatment sequences.

PRIMARY OUTCOME

Among the patients included in the efficacy analysis, two assigned to the treatment sequence of gabapentin, morphine, the gabapentin–morphine combination, and placebo withdrew after completing two treatment periods and one assigned to the treatment sequence of morphine, placebo, gabapentin, and the combination withdrew after completing three treatment periods. No patients were excluded from the analysis because of missing data. Weekly averages of daily pain scores for each treatment sequence are shown in Figure 2A. The primary analysis showed no significant main effects of either sequence or treatment period, but the effects of drug treatment ($P<0.001$) and carryover ($P=0.04$) were statistically significant. An exploratory analysis of all differences in pairwise carryover effects showed a difference only between morphine and placebo ($P=0.005$); the effect of morphine is more likely to carry over to the next treatment period than that of placebo.

In the linear mixed model, all treatment contrasts were adjusted for all observed carryover effects. Mean pain intensity on a scale from 0 to 10 at baseline and at the maximal tolerated dose was calculated as follows: mean (±SE) at baseline, 5.72±0.23; with placebo, 4.49±0.34; gabapentin, 4.15±0.33; morphine, 3.70±0.34; and the gabapentin–morphine combination, 3.06±0.33 (Fig. 2B). Pain treated with the combination was rated lower than pain treated with morphine alone ($P=0.04$), gabapentin alone ($P<0.001$), or placebo ($P<0.001$). The analysis of the percent change in pain intensity indicated greater reduction of pain with the use of the gabapentin–morphine combination than with placebo (20.4 percent greater reduction, $P=0.03$). Other comparisons were not significant.

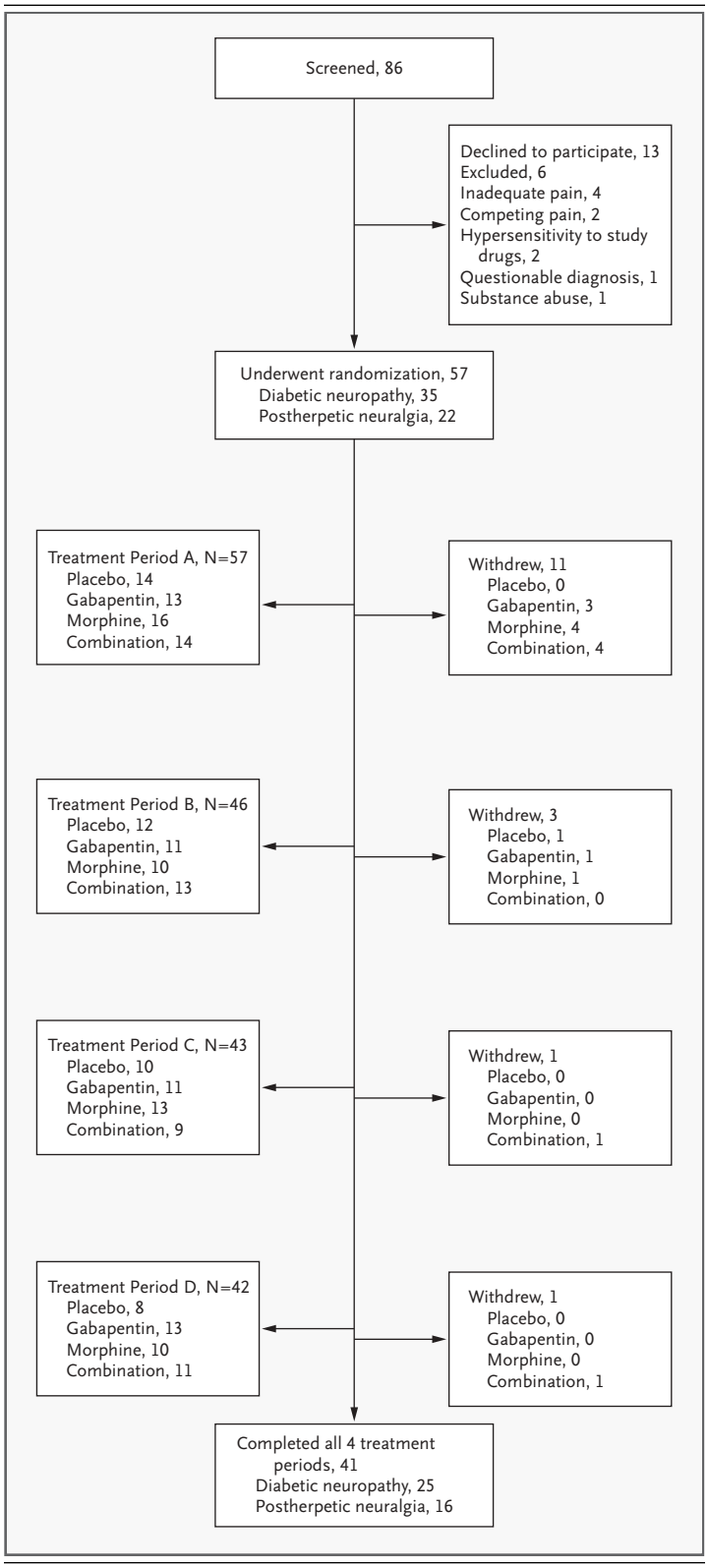
SECONDARY OUTCOMES

The mean maximal tolerated dose of morphine (Fig. 2C) was 45.3±3.9 mg as a single agent, as compared with 34.4±2.6 mg of morphine in the gabapentin–morphine combination ($P<0.05$). The mean maximal tolerated dose of gabapentin (Fig. 2C) was 2207±89 mg as a single agent, as compared with 1705±83 mg in the combination ($P<0.05$). The mean maximal tolerated dose of lorazepam (active placebo) was 1.38±0.05 mg.

Patients' total scores in response to the Short-Form McGill Pain Questionnaire (Table 2) when receiving the gabapentin–morphine combination were lower than when receiving placebo ($P<0.05$), gabapentin as a single agent ($P<0.05$), or morphine as a single agent ($P<0.05$). Patients' scores for pain-related interference with mood when receiving the gabapentin–morphine combination were lower than when receiving placebo ($P<0.001$) or morphine ($P=0.03$), and scores for pain-related interference with general activity, normal work,

Figure 1. Enrollment, Randomization, Withdrawals, and Completion of the Four Treatment Periods.

Two of the three patients included as having withdrawn after treatment period B withdrew before week 4. Combination denotes the gabapentin–morphine combination.



sleep, and enjoyment of life were significantly lower when patients were receiving any of the active treatments than when receiving placebo (Table 2).

According to responses to the SF-36 Health Survey, the gabapentin–morphine combination was associated with higher scores for vitality (P=0.007) and social functioning (P=0.004) than was placebo and higher scores than morphine for vitality (P=0.03) and social functioning (P=0.04). All active treatments were associated with significantly higher scores for the domains of "role-physical" (problems with work or other daily activities as a result of physical health) and bodily pain and for mental health than was placebo (Table 2). All treatments were associated with significantly lower scores on the Beck Depression Inventory (Table 2) than was placebo.

Table 3 lists adverse effects reported by patients during dose titration (weeks 1 through 3) and at the maximal tolerated dose. At the maximal tolerated dose, the gabapentin–morphine combination was associated with a higher frequency of constipation than gabapentin (P=0.006) but not morphine, and with a higher frequency of dry mouth than morphine (P=0.03) but not gabapentin (Table 3).

The numbers of patients who completed a given treatment and reported at least moderate pain relief at the maximal tolerated dose were as follows: placebo, 13 (31 percent, P<0.05 for the comparison with all treatments); gabapentin as a single agent, 27 (61 percent); morphine as a single agent, 35 (80 percent); and the gabapentin–morphine combination, 32 (78 percent). The mean scores on the Mini–Mental State Examination were 28.9±0.3 when receiving placebo, 28.8±0.3 when receiving gabapentin as a single agent, 29.0±0.2 when receiving morphine as a single agent, and 29.0±0.3 when receiving the combination.

According to responses to the blinding questionnaire, the numbers of correct guesses by patients with regard to their treatment assignment were 25 (66 percent) among those receiving placebo, 16 (42 percent) among those receiving gabapentin, 16

Table 1. Demographic and Baseline Characteristics of the Patients.*

Characteristic	Patients with Diabetic Neuropathy (N=35)	Patients with Postherpetic Neuralgia (N=22)
Age — yr		
Median	60	68
Range	40–75	47–81
Sex — no. (%)		
Male	18 (51)	14 (64)
Female	17 (49)	8 (36)
Race or ethnic group — no. (%)†		
White	34 (97)	22 (100)
Other	1 (3)	
Duration of pain or time since onset of herpes zoster — yr	4.5±3.8	4.6±5.2
Duration of diabetes — yr	10.8±8.5	—
Glycosylated hemoglobin — %	8.0±2.0	—
Affected site — no. (%)		
Trigeminal	—	4 (18)
Thoracic	—	13 (59)
Lumbar	—	3 (14)
Sacral	—	2 (9)
Score for intensity of pain‡	5.8±1.8	5.6±1.6
Allodynia — no. (%)	17 (49)	14 (64)
Concomitant medications — no. (%)		
None	22 (63)	17 (77)
TCA	4 (11)	2 (9)
SSRI	2 (6)	1 (5)
Anticonvulsant drug	1 (3)	0
Acetaminophen or NSAIDs	8 (23)	2 (9)
Previous drugs for pain — no. (%)		
None	14 (40)	4 (18)
Codeine as needed	9 (26)	17 (77)
Regular doses of morphine or oxycodone	3 (9)	1 (5)
Gabapentin	6 (17)	8 (36)
TCA	10 (29)	9 (41)
Other anticonvulsant drugs	4 (11)	5 (23)

* Plus–minus values are means ±SD. TCA denotes tricyclic antidepressant, SSRI selective serotonin-reuptake inhibitor, and NSAID nonsteroidal antiinflammatory drug.
† Race was determined on the basis of hospital registration data.
‡ Pain was measured on a scale from 0 to 10, with 0 indicating no pain and 10 "the worst pain imaginable."

(44 percent) among those receiving morphine, and 8 (25 percent) among those receiving the combination. The numbers of correct guesses by the research nurse with regard to patients' treatment assignments were 29 (71 percent) for placebo, 18 (43 percent) for gabapentin, 14 (33 percent) for morphine, and 21 (53 percent) for the combination.

DISCUSSION

Our results suggest that treatment of neuropathic pain with the combination of gabapentin and morphine results in less pain than treatment with either gabapentin or morphine as a single agent, as indicated by patients' pain intensity (the primary outcome) and responses on the Short-Form McGill Pain Questionnaire (a secondary outcome). The absence of statistically significant differences in the percent change in pain level between baseline and treatment with the combination and between baseline and treatment with the single agents may have been due to the study's insufficient statistical power with respect to this sensitivity analysis. Among patients receiving the maximal tolerated dose of a study drug, the frequency of adverse effects was similar among all treatments, except that patients receiving the gabapentin–morphine combination had a higher frequency of constipation than those receiving gabapentin alone and a higher frequency of dry mouth than those receiving morphine alone. As compared with morphine, the combination was associated with less pain-related interference with mood and with higher scores for vitality and social functioning.

The maximal tolerated doses of morphine and gabapentin were significantly lower with the combination than in treatment with each as a single agent, which suggests an additive interaction. A previous study in healthy subjects suggested that the addition of morphine to gabapentin resulted in higher serum concentrations of gabapentin than are seen with gabapentin alone.[10] Although our trial did not involve pharmacokinetic characterizations, this previously observed pharmacokinetic interaction may, in part, explain the differences between treatment with the combination and treatment with gabapentin as a single agent.

Unlike laboratory studies of analgesic agents in combination in which such techniques as isobolographic analysis are used, our trial was not designed to distinguish between additivity and synergism. Although a drug combination may demonstrate synergism, it is crucial also to characterize adverse drug interactions (i.e., whether there is also additivity or synergism for adverse effects). Specifically, the gabapentin–morphine combination should produce fewer adverse effects than either drug as a sin-

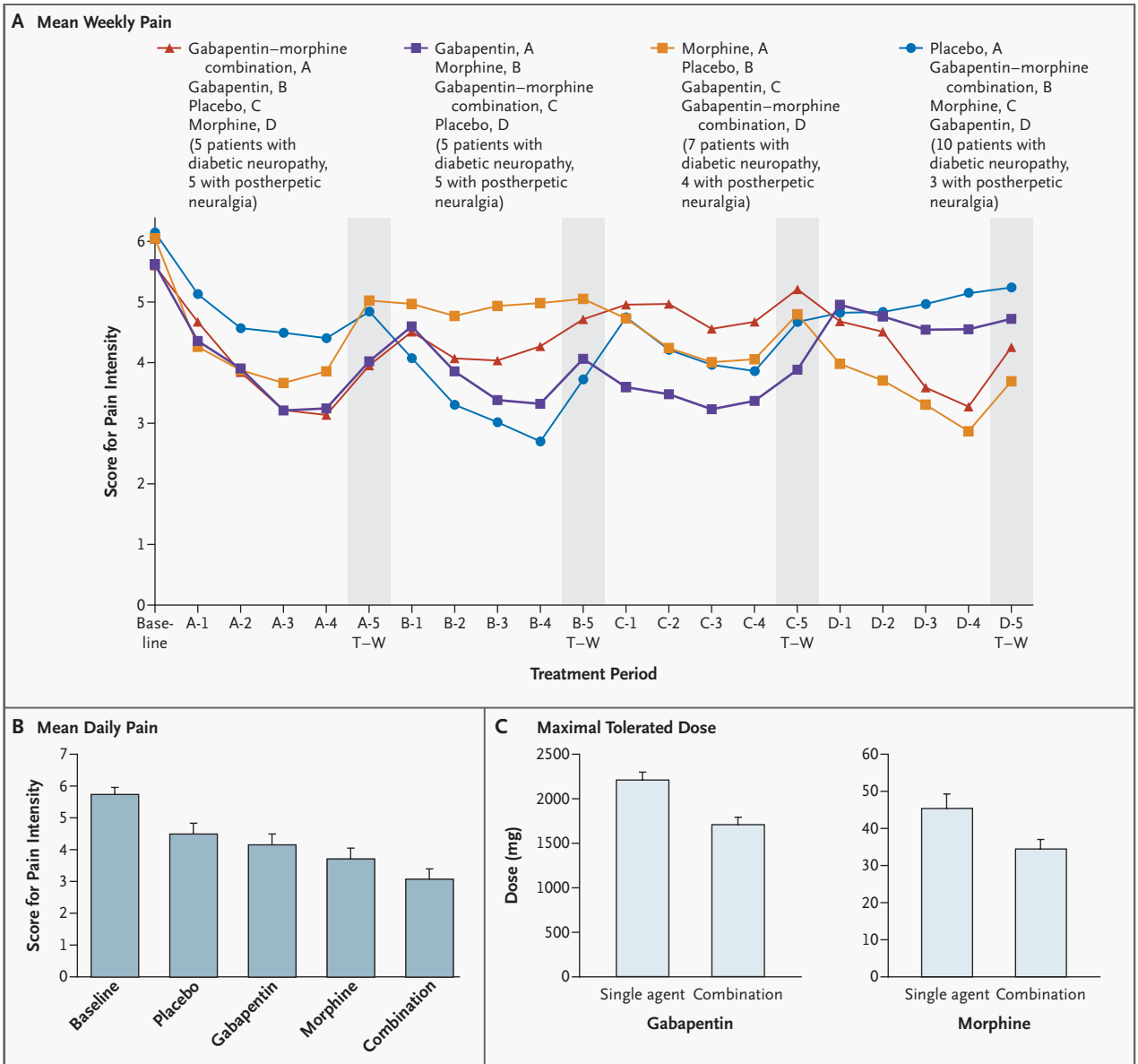


Figure 2. Mean Daily Pain and Maximal Tolerated Doses of the Study Drugs.

Panel A shows weekly mean scores for daily pain intensity throughout the trial for each of the four treatment sequences. The numbers of patients include 41 who completed the trial and 3 who completed at least two treatment periods. Scores for pain intensity were rated on a scale from 0 to 10, with higher numbers indicating more severe pain. A, B, C, and D denote the four treatment periods, and numbers 1 through 4 the weeks within each period; in week 5, patients underwent a four-day dose tapering (T) and a three-day complete washout (W). Secondary outcomes were assessed with the use of the Short-Form McGill Pain Questionnaire, Beck Depression Inventory, Brief Pain Inventory, Medical Outcomes Study 36-Item Short-Form General Health Survey, global pain relief, and Mini–Mental State Examination, which were administered at baseline and again in week 4 of each treatment period. Panel B shows the mean (±SE) daily pain scores during week 4 at the maximal tolerated dose of each regimen. Baseline pain intensity is included for comparison only and was not used in the efficacy analysis. $P<0.001$ for the comparison of gabapentin as a single agent with the gabapentin–morphine combination; $P=0.01$ for the comparison of morphine as a single agent with placebo; $P=0.04$ for the comparison of morphine as a single agent with the combination; and $P<0.001$ for the comparison of the combination with placebo. Panel C shows the mean (±SE) maximal tolerated doses of gabapentin and morphine administered as single agents as compared with them in combination. $P<0.05$ for the comparison of the gabapentin–morphine combination with gabapentin as a single agent, and $P<0.05$ for the comparison of the combination with morphine as a single agent.

Table 2. Mean (±SE) Scores on the Short-Form McGill Pain Questionnaire, Brief Pain Inventory, Medical Outcomes Study 36-Item Short-Form General Health Survey (SF-36 Health Survey), and Beck Depression Inventory.*

Measure	Mean Score				
	Baseline	Placebo	Gabapentin	Morphine	Gabapentine and Morphine
Score on Short-Form McGill Pain Questionnaire					
Sensory	14.7±1.0	11.1±1.0	8.7±1.0†‡	8.1±1.0†‡	6.0±1.0†
Affective	4.2±0.4	3.3±0.4	2.0±0.4†	2.6±0.4‡	1.5±0.4†
Total	18.9±1.3	14.4±1.3	10.7±1.3†‡	10.7±1.3†‡	7.5±1.3†
10-cm visual-analogue scale	5.0±0.4	3.9±0.4	3.5±0.4‡	3.3±0.4	2.6±0.4†
Present pain intensity	2.40±0.16	2.07±0.16	1.64±0.16†‡	1.57±0.16†	1.22±0.16†
Score on Brief Pain Inventory					
General activity	4.7±0.4	4.5±0.4	3.0±0.4†	3.1±0.4†	2.9±0.4†
Mood	3.9±0.4	3.3±0.4	1.8±0.4†	2.5±0.4†‡	1.7±0.4†
Walking	4.4±0.5	4.3±0.5	2.9±0.5†	3.2±0.5	2.8±0.5†
Normal work	3.9±0.4	3.6±0.4	2.3±0.4†	2.3±0.4†	2.1±0.4‡
Social relations	2.7±0.3	2.2±0.3	1.5±0.3	1.6±0.3	1.4±0.3†
Sleep	4.2±0.4	3.4±0.4	1.5±0.4†	1.6±0.4†	1.1±0.4†
Enjoyment of life	5.4±0.5	4.1±0.5	2.6±0.5†	2.5±0.5†	2.2±0.5†
Score on the SF-36 Health Survey					
Physical functioning	51.7±3.5	56.0±4.0	61.1±4.0†	57.8±4.0	62.4±4.0†
Role-physical	48.2±6.7	42.1±6.3	63.1±6.2†	58.7±6.3†	63.1±6.4†
Bodily pain	52.1±2.7	56.0±3.0	65.6±2.9†	64.4±2.9†	70.4±3.0†
General health	61.5±3.3	64.4±3.4	66.5±3.4	63.1±3.4	64.1±3.4
Vitality	49.5±2.9	47.7±3.2	56.1±3.2†	51.5±3.2‡	58.1±3.2†
Social functioning	70.3±3.6	72.3±3.7	80.5±3.7†	75.9±3.7‡	84.2±3.8†
Role-emotional	69.8±6.4	58.0±5.9	75.1±5.8†	66.9±5.8	75.8±6.0†
Mental health	76.7±2.5	73.4±2.6	80.9±2.6†	78.0±2.6†	81.0±2.6†
Score on Beck Depression Inventory	10.3±1.1	8.5±1.0	6.4±1.0†	6.7±1.0†	6.0±1.0†

* Scores for present pain intensity are on a scale from 0 to 3, with higher numbers indicating more severe pain. Total scores on the Short-Form McGill Pain Questionnaire are on a scale from 0 to 45, with higher numbers indicating more severe pain. Scores on the Brief Pain Inventory are on a scale from 0 to 10, with 0 indicating pain that does not interfere with the activity specified and 10 indicating pain that completely interferes. Scores on the SF-36 Health Survey are on a scale from 0 to 100, with higher numbers indicating better health status; in this survey, "role-physical" denotes problems with work or other daily activities as a result of physical health and "role-emotional" problems with work or other daily activities as a result of emotional problems. Scores on the Beck Depression Inventory are on a scale from 0 to 63, with higher numbers indicating more severe depression.
† $P<0.05$ for the comparison with placebo.
‡ $P<0.05$ for the comparison with gabapentin and morphine in combination.

gle agent. Thus, a clinically useful combination may have an additive or even less than additive analgesic interaction, provided that the adverse effects show even less additivity in the combination.[33] Data from the present trial that indicate superior efficacy without greatly increased adverse effects suggest that a combination of gabapentin and morphine has a therapeutic profile superior to that of either drug as a single agent.

In addition to evaluating combination therapy, this trial replicates evidence from previous studies of the efficacy of opioids in neuropathic pain. Analgesia with morphine was associated with mood improvement and reduced pain-related in-

Table 3. Adverse Effects.*

Adverse Effect	Dose Titration, Wk 1–3				At Maximal Tolerated Dose, Wk 4			
	Placebo	Gabapentin	Morphine	Gabapentin–Morphine	Placebo	Gabapentin	Morphine	Gabapentin–Morphine
	percent of patients							
Constipation	4.7	4.2†	43.2‡	44.2‡	4.7	2.1†	38.6‡	20.9‡
Sedation	18.6	10.4†	36.4	39.5	14.0	8.3	15.9	20.9
Dry mouth	2.3	8.3†	11.4	32.6‡	0.0	6.3	4.6†	20.9‡
Insomnia	25.6	4.2‡	13.6	2.3‡	7.0	8.3	2.3	2.3
Vomiting	0.0	0.0‡	9.1	16.3	0.0	0.0	0.0	0.0
Pruritus	7.0	0.0	15.9	9.3	0.0	2.1	6.8	2.3
Cognitive dysfunction	2.3	4.2	4.6	11.6	2.3	2.1	2.3	7.0
Dizziness	4.7	6.3	2.3	11.6	0.0	2.1	0.0	0.0
Nausea	2.3	2.1	11.4	9.3	0.0	0.0	4.6	7.0
Ataxia	0.0	2.2	4.6	9.3	0.0	0.0	4.6	7.0
Edema	2.3	2.1	6.8	9.3	2.3	0.0†	4.6	9.3
Anxiety	2.3	4.2	0.0	2.3	0.0	8.3	2.3	0.0
Blurry vision	2.3	2.1	4.6	7.0	2.3	0.0	4.6	7.0
Diarrhea	7.0	0.0	6.8	4.7	2.3	2.1	0.0	0.0
Restless legs	7.0	2.1	0.0	0.0	0.0	0.0	0.0	0.0
Headache	2.3	2.1	4.6	7.0	2.3	0.0	2.3	0.0
Decreased appetite	2.3	0.0	6.8	0.0	0.0	0.0	4.6	2.3

* Data are reported only for moderate-to-severe adverse effects with an incidence greater than 5 percent for any treatment.
† P<0.05 for the comparison with the gabapentin–morphine combination.
‡ P<0.05 for the comparison with placebo.

terference with patients' activity, work, sleep, and enjoyment of life, as well as improvement in mental health and in the domains of "role-physical" and bodily pain assessed with the use of the SF-36 Health Survey. In light of previous trials that showed efficacy of gabapentin as a single agent, it is surprising that gabapentin did not produce significantly better results than placebo with regard to the primary outcome of this trial.

Despite this result, patients' total scores for the intensity of pain in response to the Short-Form McGill Pain Questionnaire were significantly lower while they were receiving gabapentin than while receiving placebo, as was also the case for pain-related interference with activity, mood, walking, work, sleep, and enjoyment of life. Furthermore, gabapentin was associated with improvements in mood and in almost all domains of the SF-36 Health Survey. These discrepancies leave us with an equivocal result with regard to the analgesic efficacy of gabapentin.

Unlike previous studies, the present trial used an active placebo (low-dose lorazepam) that mimics the adverse effects of the active treatments without producing pharmacologic analgesia. Data from the blinding questionnaire indicate that approximately one third of the patients guessed that they were receiving an active drug while they were receiving placebo. Such guesses may have led to higher expectations during treatment with the active placebo [34] and may have resulted in lower self-assessments of pain intensity than might have been reported with the use of an inert placebo and consequently decreased the difference between treatment with gabapentin or placebo. Another possible explanation is that maximal tolerated doses were slightly lower than those reached in previous trials of gabapentin.[5,6] Nevertheless, the results of this trial unequivocally show that gabapentin significantly enhances the efficacy of morphine.

This trial suggests superior efficacy of a combination of gabapentin and morphine in the treat-

ment of neuropathic pain. Given the potential benefits (e.g., improved efficacy and fewer adverse effects) and drawbacks (e.g., adverse drug interactions) of any drug combination, trials are needed to compare other analgesic combinations with their respective single agents.

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