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A randomized, placebo-controlled trial of oxycodone and of gabapentin for acute pain in herpes zoster

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ABSTRACT

Although acute pain in patients with herpes zoster can be severe and has a substantial impact on health-related quality of life, there have been no randomized clinical trials of oral medications specifically for its ongoing treatment. A randomized clinical trial was conducted in which 87 subjects $\geqslant$50 years of age with herpes zoster within 6 calendar days of rash onset and with worst pain in the past 24 h $\geqslant$ 3 on a 0–10 rating scale initiated 7 days of treatment with famciclovir in combination with 28 days of treatment with either controlled-release (CR) oxycodone, gabapentin, or placebo. Subjects were evaluated for adverse effects of treatment, acute pain, and health-related quality of life. The results showed that CR-oxycodone and gabapentin were generally safe and were associated with adverse events that reflect well-known effects of these medications. Discontinuing participation in the trial, primarily associated with constipation, occurred more frequently in subjects randomized to CR-oxycodone (27.6%) compared with placebo (6.9%). Treatment with CR-oxycodone reduced the mean worst pain over days 1–8 ($p = 0.01$) and days 1–14 ($p = 0.02$) relative to placebo but not throughout the entire 28-day treatment period as pain resolved in most subjects. Gabapentin did not provide significantly greater pain relief than placebo, although the data for the first week were consistent with a modest benefit. By demonstrating that CR-oxycodone is safe, generally adequately tolerated, and appears to have efficacy for relieving acute pain, the results of this clinical trial provide a foundation for evidence-based treatment for acute pain in herpes zoster.

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1. Introduction

Herpes zoster has the highest incidence of all neurological diseases [34], occurring during the lifetimes of up to 30% of the population [7], in as many as 50% of those living until 85 years of age [27], and in approximately one million people each year in the United States [29]. Herpes zoster is caused by reactivation of varicella-zoster virus and its spread from a single sensory ganglion to the neural tissue and dermatome of the affected segment [12,23]. The characteristic rash usually heals within two to four weeks, and acute pain is typically the most distressing symptom. In a substantial percentage of patients, the pain associated with herpes zoster does not resolve when the rash heals but persists for months or years, a chronic neuropathic pain condition termed postherpetic neuralgia (PHN).

A substantial number of randomized clinical trials have investigated the efficacy of various treatments for PHN [10,25], but there have been no randomized clinical trials of oral medications specifically for the ongoing treatment of acute pain in patients with herpes zoster. This is unfortunate because the results of recent studies

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have demonstrated that acute pain in herpes zoster has a substantial impact on health-related quality of life, including multiple aspects of physical and emotional functioning [32,43]. In addition, it has been hypothesized that aggressive treatment of acute pain in herpes zoster—a major risk factor for PHN [31,46]—has the potential to prevent the development of PHN [3,5,12] by attenuating central functional and structural mechanisms of chronic pain, for example, central sensitization and damage to GABAergic inhibitory pathways from excitotoxicity [36,40,47].

Although there have been recent major advances in the treatment of PHN and other chronic neuropathic pain syndromes [13,19], it is unknown whether these treatments—which not only reduce pain but also improve quality of life—would be beneficial in herpes zoster. A randomized, double-blind, placebo-controlled clinical trial of controlled-release (CR) oxycodone and gabapentin was conducted in herpes zoster patients treated with the antiviral agent famciclovir. The primary objective was to determine the safety and tolerability of relatively aggressive titration schedules for CR-oxycodone and gabapentin in patients with herpes zoster to prepare for a clinical trial of these medications for the prevention of PHN. The secondary objective was to examine the efficacy of each of these two medications for reducing acute pain in herpes zoster when used in combination with an antiviral agent.

2. Methods

2.1. Participants

Patients with herpes zoster were recruited from clinics associated with two study sites (Houston, TX; Rochester, NY) and from referrals from physicians in their communities. The inclusion criteria for the trial were: men or women $\geqslant$50 years of age with herpes zoster within 6 calendar days of rash onset; worst pain in the past 24 h $\geqslant$ 3 on a 0–10 numerical rating scale (NRS; 0 = no pain; 10 = worst possible pain); and ability to provide written informed consent. The major exclusion criteria were prodrome of unilateral dermatomal pain in the area of the rash beginning >7 days prior to rash onset; cutaneous or visceral dissemination; immunosuppression that in the investigator's opinion would significantly increase the risk of dissemination; any clinically significant medical condition, laboratory abnormality, or cognitive impairment; use of systemic antiviral therapy within 8 weeks prior to baseline, except for treatment with acyclovir, famciclovir, or valaciclovir for herpes zoster if the subject agreed to take study famciclovir instead; alcohol or drug abuse history within the previous 5 years; use of tricyclic antidepressants, antiepileptic medications, mexiletine, any topical analgesics, or nerve block of the affected or adjacent dermatomes within 2 weeks prior to the baseline visit and for 1 month after randomization; use of opioid analgesics or tramadol on a regular basis within 2 weeks prior to the baseline visit and for 1 month after randomization (use of these medications for prodromal or herpes zoster acute pain before the baseline visit was allowed if the patient was willing to discontinue the medication to enroll); unwillingness or inability to limit use of acetaminophen to a maximum of 2500 mg/day while receiving third-tier rescue medication (see below); and a history of herpes zoster prior to the current episode. Women could not be lactating and had to be surgically sterile or postmenopausal for 2 years, or with a negative urine pregnancy test and using a medically acceptable contraceptive regimen for at least 60 days prior to the baseline visit and agreeing to continue such use until 30 days after the final dose of study medication.

2.2. Procedures

The United States Food and Drug Administration granted the trial's off-label uses of famciclovir (beyond 72 h of rash onset; in patients with ophthalmic zoster) and gabapentin (in patients with herpes zoster) Investigational New Drug application exemptions. The study was approved by the Institutional Review Boards (IRBs) of the sites, and all patients provided written informed consent. At the randomization visit, all patients began treatment with open-label famciclovir 500 mg 3 times daily for a total of 21 doses, and were randomized using a "double-dummy" design to one of the three groups for 28 days of double-blind treatment with (1) CR-oxycodone plus placebo gabapentin; (2) gabapentin plus placebo CR-oxycodone; or (3) placebo CR-oxycodone plus placebo gabapentin.

There were six scheduled study visits: baseline and days 4, 8, 14, 28, and 35. Subjects were not compensated for participation, but were reimbursed for travel expenses for study visits. A Data and Safety Monitoring Board (DSMB) consisting of three physicians and one biostatistician periodically reviewed enrollment and all adverse events (AEs) to ensure subject safety throughout the trial. The DSMB was instructed to consider recommending modification or halting of the trial if unblinded interim analyses of the accumulating data indicated that >80% of the subjects in both the active treatment groups with pain >2/10 could not be titrated on day 14 to the day 3 dosages of the blinded study medications (see below) because of adverse events. All personnel involved in the study except for the biostatistical programmer who generated the randomization plan and interim reports for the DSMB, the pharmacist responsible for medication distribution, and the DSMB were blinded to subject assignment.

2.3. Study treatments

Blinded medication and placebo were titrated in tandem to reduce the average pain in the past 24 h to $\leqslant$2 on a 0–10 NRS according to the schedule in Appendix A. Subjects were treated according to a three-tier rescue medication protocol for unacceptable pain. First-tier rescue medication was provided at the baseline visit and consisted of acetaminophen 500 mg titrated to a maximum of 8 tablets daily. If necessary, second-tier rescue medication was provided on day 4 or at an unscheduled study visit and consisted of ibuprofen 200 mg titrated to a maximum of 8 tablets daily. This tier was skipped to limit gastrointestinal toxicity if subjects were taking any NSAID medication other than a cardioprotective dosage of aspirin on a regular basis or had a history of a gastrointestinal disorder that in the investigator's opinion was a contraindication for the treatment with an NSAID.

If necessary, third-tier rescue medication was provided on day 8 or at an unscheduled study visit. Because provision of rescue opioid medication could interfere with titration to the maximum dosages of the active blinded study medications (which could be continued until day 14), subjects in the CR-oxycodone or gabapentin groups received placebo third-tier rescue medication prior to day 14 or the completion of titration, whereas subjects in the placebo group received oxycodone 5 mg/acetaminophen 325 mg prior to day 14 or the completion of titration, titrated as needed to a maximum of 1 tablet every 6 h. Following day 14 or the completion of titration, all subjects who required third-tier rescue medication received open-label oxycodone 5 mg/acetaminophen 325 mg titrated as needed to a maximum of 1 tablet every 6 h. Subjects who could not tolerate severe pain that remained intractable to the blinded study medications and rescue medications were reminded of their right to exit the trial and be referred to a physician with expertise in pain treatment.

Once subjects reported average pain ⩽2 for one day, use of rescue medication was halted but titration of blinded medications continued. If subjects reported the next day that pain remained ⩽2, titration of blinded medications was halted. When titration of blinded medications was halted because pain was ⩽2 for two days, titration could be re-initiated before day 14 if pain became >2. Titration of blinded medications and escalation of rescue medication to the next tier were halted for unacceptable side effects. If the subject tolerated the dosage at which titration had been halted for unacceptable side effects, this was maintained for 2 days, followed by re-challenge of titration at the investigator's discretion if necessary to reduce pain to ⩽2. If unacceptable side effects continued, blinded study medications were reduced in tandem one step according to the reverse of the titration schedule.

All subjects were provided with docusate sodium-senna concentrate tablets at the baseline visit, and were given instructions for their use if constipation developed. Subjects began tapering off of study medication on day 29 using the reverse of the titration schedules and could use the tiered rescue medications to control pain. To prevent withdrawal symptoms, the taper protocol was followed whenever subjects discontinued participation. At the end of the medication taper, subjects exited the trial except for ongoing documentation of the resolution of any serious adverse events (SAEs).

2.4. Evaluations and assessments

The diagnosis of herpes zoster was made by physicians with expertise in diagnosing and conducting herpes zoster clinical trials on the basis of history, symptoms, the presence of characteristic lesions, and a unilateral dermatomal distribution. The subject's medical history was also assessed, and a physical examination was conducted with particular attention to neurological symptoms and signs and assessments of rash severity, including number of lesions, proportion of the dermatome affected, and rash healing [22,45].

Prodromal pain was assessed at the baseline visit with questions about whether dermatomal pain preceded the appearance of the rash, and if so, by how many days. Subjects rated their average and worst "pain since rash onset" at the baseline visit and their worst pain "during the past day" at bedtime each day using a 0–10 NRS (0 = no pain; 10 = pain as bad as you can imagine); such ratings of daily worst pain intensity provided the basis for the primary efficacy analyses in the pivotal herpes zoster vaccine trial [9,37]. At the baseline visit and on days 8, 14, and 28, all subjects were administered the Short-form McGill Pain Questionnaire (SF-MPQ) [35] to assess the sensory and affective dimensions of pain and the Brief Pain Inventory (BPI) [1] Interference Scale to assess the impact of pain on health-related quality of life [15]. To evaluate the integrity of the double-blind, all subjects were asked at the day 28 visit whether they believed they were assigned to active medication or placebo.

2.5. Statistical analysis

The primary measure used to assess the tolerability and safety of CR-oxycodone and gabapentin was non-completion of the trial. The sample size was selected to provide adequate power to determine whether greater percentages of subjects receiving CR-oxycodone or gabapentin than those receiving placebo failed to complete the 28-day treatment period. Specifically, 25 subjects per group were required to provide 80% power to detect a 20% group difference (25% non-completion in an active treatment group vs. 5% non-completion in the placebo group) using a one-tailed 10% significance level and the Wald test, which was used to analyze group differences in the proportions of subjects who did not complete the study.

The principal secondary outcome variables were the averages of the worst pain intensity ratings calculated from the daily diaries over days 1–8, days 1–14, and days 1–28. Although the double-blind treatment lasted 28 days, group differences over these first two time periods were examined because the goal of the titration schedule was to achieve analgesia as promptly as possible by completing titration on day 8, with titration allowed to continue until day 14 if necessary because of adverse events. In addition, because herpes zoster acute pain resolves in most patients within two to three weeks of rash onset, the effects of analgesic treatment might not be expected to be as pronounced during the second two weeks of follow up.

Analysis of covariance was used to estimate treatment effects for each of these three outcomes, adjusting for age, sex, number of days since rash onset, and worst pain in the previous 24 h at the baseline visit. Analyses were performed on an intention-to-treat basis with the missing data imputed by carrying forward the last available observed value; two-tailed p values are reported. The SF-MPQ total and subscale scores and the BPI Interference Scale scores were analyzed similarly.

Pain reductions of ⩾30% and ⩾50% from baseline have been demonstrated to be clinically important changes in acute and chronic pain clinical trials [8,16,17,30]. Treatment group comparisons for the proportions of subjects who achieved these magnitudes of pain reduction from the baseline in their average worst pain scores for days 1–8, days 1–14, and days 1–28 were performed using logistic regression models that adjusted for age, sex, number of days since rash onset, and worst pain in the previous 24 h at the baseline visit.

3. Results

3.1. Subject characteristics

The planned sample size was 75 subjects, but an adequate supply of blinded medication was available for 87 subjects, and enrollment was continued until this number was reached following IRB and DSMB approval. Subject disposition is presented in Fig. 1, and baseline characteristics of the subjects are presented in Table 1. Subjects were enrolled an average of 3.0 (SD = 1.8) days following the onset of their herpes zoster rash, and none had fully crusted lesions or had lost all crusts at the time of enrollment. On average, subjects had moderate-to-severe acute pain since rash onset and this intensity of pain was still present at the time of enrollment. Although subjects in the CR-oxycodone group had greater worst pain in the previous 24 h than those in the gabapentin and placebo groups at the baseline visit, the statistical analyses of the worst pain intensity ratings adjusted for these differences.

3.2. Safety and tolerability

Significantly more subjects in the CR-oxycodone group (27.6%) than the placebo group (6.9%) did not complete the trial ($p = 0.02$), whereas the percentages of subjects who did not complete the trial in the gabapentin (17.2%) and placebo groups did not differ significantly ($p = 0.11$). Of the eight subjects in the CR-oxycodone group who did not complete the trial, six dropped out because of AEs or SAEs (four with constipation, two of whom also had dizziness, one with disorientation and dizziness, and one with disorientation and dehydration that was an SAE), one withdrew consent on the second day of the study after taking several doses of CR-oxycodone because of concerns that side effects might develop, and one was discontinued from the trial by the investigator for noncompliance after taking only study famciclovir. Four of the subjects in the gabapentin group did not complete the trial because of

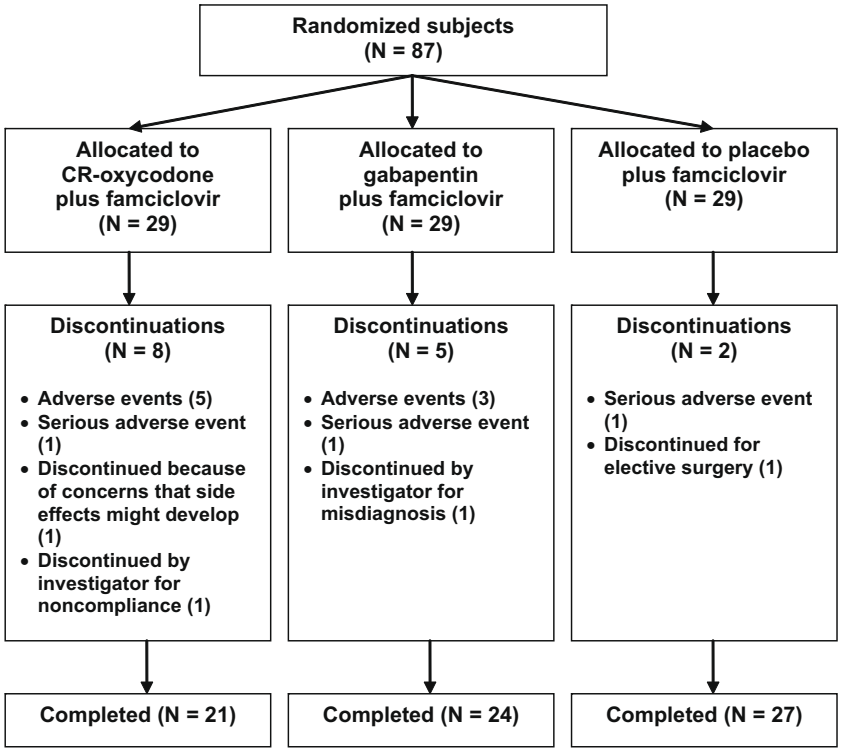

Fig. 1. Subject disposition.

Table 1
Subject characteristics at baseline.

Measure[a]	CR-oxycodone	Gabapentin	Placebo
Number enrolled	29	29	29
Age	65.3 (11.3)	66.2 (10.9)	66.0 (8.3)
Sex (% female)	65.5	65.5	55.2
Race (%)			
White	72.4	72.4	75.9
Black	3.5	6.9	6.9
Asian or other	24.1	20.7	17.2
Number of concomitant medications at enrollment	6.2 (5.2)	7.0 (6.6)	7.5 (6.3)
Days since rash onset	2.8 (1.6)	2.9 (1.7)	3.0 (1.4)
Presence of a painful prodrome (%)	93.1	89.7	96.6
Prodrome duration in days	3.0 (1.7)	3.2 (2.1)	2.8 (1.7)
Primary dermatome (%)			
Trigeminal: mandibular, maxillary	3.5	0.0	10.3
Trigeminal: ophthalmic	3.5	20.7	24.1
Cervical	13.8	10.3	13.8
Thoracic	69.0	55.2	44.8
Lumbar	3.5	10.3	3.5
Sacral	6.9	3.5	3.5
Number of lesions (%)			
1–24	27.6	37.9	27.6
25–49	44.8	20.7	44.8
50–74	25.0	50.0	25.0
75–99	3.5	10.3	6.9
⩾100	13.8	10.3	10.3
Percentage of primary dermatome with lesions (%)			
⩽25	32.1	34.5	37.9
25–49	39.3	31.0	34.5
50–74	10.7	20.7	17.2
⩾75	17.9	13.8	10.3
Average pain since rash began[b]	6.5 (2.3)	5.9 (2.7)	5.7 (1.7)
Worst pain since rash began[b]	7.8 (1.9)	7.4 (2.2)	7.4 (1.5)
Worst pain in past 24 h[b]	7.6 (1.8)	7.0 (2.5)	6.7 (1.5)

[a] Values are mean (standard deviation) unless otherwise indicated.
[b] Pain was rated by patients on 0–10 numerical rating scales.

AEs or SAEs (two with imbalance and dizziness, one with tremulousness and dizziness, and one with fever that was an SAE) and one was discontinued from the trial by the investigator because of misdiagnosis. One subject in the placebo group did not complete the study because of an SAE (congestive heart failure) and a second discontinued for elective surgery. Four subjects experienced an SAE: one subject with disorientation and dehydration and one with pre-syncope (who completed the trial) in the CR-oxycodone group, one with fever in the gabapentin group, and one with congestive heart failure in the placebo group. The numbers-needed-to-harm for discontinuing participation in the trial because of an AE or SAE were 5.8 for CR-oxycodone and 9.7 for gabapentin.

At least one AE was reported by 85.1% of subjects enrolled in the trial (75.9% in the CR-oxycodone group, 93.1% in the gabapentin group, and 86.2% in the placebo group). The proportions of subjects in each of the three treatment groups that experienced AEs reported by at least two subjects in either the CR-oxycodone or gabapentin groups are presented in Appendix B. Not surprisingly, the AEs with the greatest differences in incidence between CR-oxycodone or gabapentin and placebo were well-known side effects of these medications, including constipation, dizziness, drowsiness, emesis, nausea, and sedation.

Of subjects who completed the trial, 11 of 21 (52.3%) administered CR-oxycodone achieved the maximum allowed daily dosage of 120 mg and 18 of 24 (75.0%) administered gabapentin achieved the maximum allowed daily dosage of 1800 mg (Appendix C). The 27 subjects in the placebo group who completed the trial halted titration of blinded study medication on days 4 ($n = 1$), 7 ($n = 4$), 8 ($n = 20$), and 9 ($n = 2$).

The three treatment groups differed somewhat with respect to whether docusate sodium-senna concentrate tablets were used for constipation during the trial, with 69.0% of the subjects in the CR-oxycodone group, 31.0% of the subjects in the gabapentin group, and 44.8% of subjects in the placebo group having used this laxative during the trial. There was a trend ($p = 0.06$) suggesting greater

Table 2
Treatment effects on acute pain[a].

Days	CR-oxycodone	Gabapentin	Placebo	CR-oxycodone vs. placebo			Gabapentin vs. placebo		
	Adjusted mean (SE)	Adjusted mean (SE)	Adjusted mean (SE)	Difference	95% CI	*p* Value	Difference	95% CI	*p* Value
1–8	3.5 (1.6)	4.0 (1.6)	4.8 (1.6)	−1.26	−2.26, −0.26	0.01	−0.75	−1.73, 0.23	0.13
1–14	2.5 (1.6)	3.3 (1.6)	3.7 (1.6)	−1.22	−2.22, −0.23	0.02	−0.44	−1.41, 0.53	0.37
1–28	0.6 (1.7)	1.4 (1.7)	1.4 (1.7)	−0.78	−1.83, 0.27	0.14	0.00	−1.03, 1.03	1.00

[a] Based on daily diary ratings of worst pain in the past 24 h; group means and treatment effects are adjusted for age, sex, number of days since rash onset, and worst pain in the previous 24 h at the baseline visit using an analysis of covariance model. SE, standard error.

use of docusate sodium-senna concentrate in the CR-oxycodone group compared with the placebo group, whereas the difference between the gabapentin and placebo groups was not significant ($p = 0.28$).

3.3. Pain efficacy outcomes

Treatment with CR-oxycodone reduced the average worst pain over days 1–8 ($p = 0.01$) and days 1–14 ($p = 0.02$) relative to placebo (Table 2). The results for days 1–28 were consistent with a benefit of CR-oxycodone vs. placebo, but were not statistically significant ($p = 0.14$). Treatment with gabapentin did not yield a statistically significant reduction in pain relative to placebo for any of the three time periods, although there was a trend toward an effect for days 1–8 ($p = 0.13$). Fig. 2 presents the adjusted group mean worst pain ratings for each day of the 28-day treatment period by treatment group, computed using a repeated measures analysis of covariance model.

There were imbalances among the treatment groups in the distributions of the subject's primary affected dermatome. Because there are reports that the risk of severe acute pain and PHN may be greater in patients with ophthalmic zoster [14,26] and that PHN may be less common in patients with lumbar or sacral distributions [28,38], we conducted two sets of sensitivity analyses, one that also adjusted for ophthalmic vs. other primary affected dermatome and one that also adjusted for trigeminal vs. lumbar/sacral vs. cervical/thoracic dermatome. The results of these analyses generally paralleled the results when primary affected dermatome was not included as a covariate, with treatment effects for CR-oxycodone that were statistically significant when adjusting for ophthalmic vs. other primary affected dermatome or nearly so ($p = .07$) when adjusting for trigeminal vs. lumbar/sacral vs. cervical/thoracic dermatome.

As can be seen from Table 3, approximately twice as many subjects treated with CR-oxycodone compared with placebo achieved a $\geqslant$30% reduction from baseline in worst pain for days 1–8 ($p = 0.07$), and there was a significant benefit of CR-oxycodone for days 1–14 ($p = 0.02$). Significant treatment effects for this outcome, however, were not found for CR-oxycodone for days 1–28 or for gabapentin for any of the three time periods. Statistically significant treatment effects for pain reductions of $\geqslant$50% from baseline in worst pain were not found for either CR-oxycodone or gabapentin for any of the three time periods, although numerical differences between CR-oxycodone and placebo were consistent with a beneficial effect of treatment. The numbers-needed-to-treat (NNT) for the significant treatment effects of CR-oxycodone on $\geqslant$30% pain reduction from baseline were 3.6 for days 1–8 and 2.9 for days 1–14.

The only nominally significant group difference for the SF-MPQ was for the day 8 assessment, when treatment with gabapentin vs. placebo was associated with lower SF-MPQ sensory scores (mean difference = −0.29; 95% CI: −0.57 to −0.01; $p = 0.05$). No effects of either CR-oxycodone or gabapentin were apparent for the BPI Interference Scale scores for the day 8, 14, or 28 assessments.

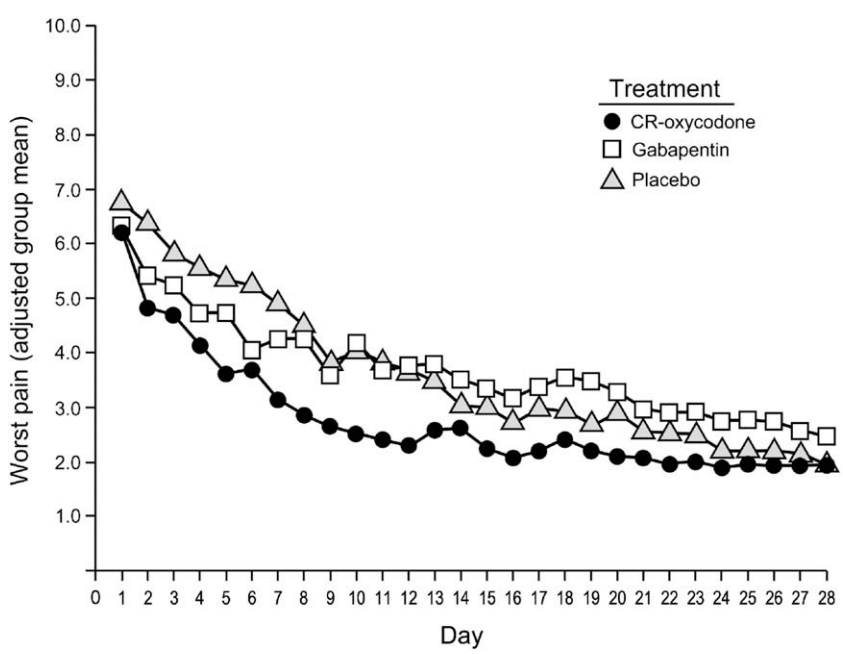

Fig. 2. Adjusted group mean daily diary ratings of worst pain in the past 24 h for the 28-day treatment period.

Table 3
Proportions of subjects with ⩾30% and ⩾50% pain reduction from baseline in mean daily diary ratings of worst pain in the past 24 h[a].

Days	CR-oxycodone	Gabapentin	Placebo	CR-oxycodone vs. placebo			Gabapentin vs. placebo		
	Unadjusted percentage	Unadjusted percentage	Unadjusted percentage	Odds ratio (NNT)	95% CI	*p* Value	Odds ratio (NNT)	95% CI	*p* Value
⩾30% Pain reduction from baseline									
1–8	55.2	34.5	27.6	2.88 (3.6)	0.92, 9.02	0.07	1.28 (14.5)	0.40, 4.08	0.68
1–14	79.3	55.2	44.8	4.30 (2.9)	1.27, 14.57	0.02	1.43 (9.6)	0.47, 4.32	0.53
1–28	86.2	62.1	75.9	1.90 (9.7)	0.47, 7.67	0.37	0.51[b]	0.16, 1.64	0.26
⩾50% Pain reduction from baseline									
1–8	24.1	17.2	13.8	1.88 (9.7)	0.45, 7.83	0.39	1.14 (29.4)	0.26, 4.98	0.86
1–14	44.8	27.6	24.1	2.43 (4.8)	0.74, 7.98	0.14	1.07 (28.6)	0.31, 3.71	0.92
1–28	72.4	48.3	51.7	2.46 (4.8)	0.78, 7.73	0.12	0.83[b]	0.29, 2.43	0.74

[a] Odds ratios are adjusted for age, sex, number of days since rash onset, and worst pain in the previous 24 h at the baseline visit using a logistic regression model.
[b] Number-needed-to-treat not calculated because the percentage of responders was greater in the placebo group than in the gabapentin group.

3.4. Rescue analgesia

Most subjects used acetaminophen, the first tier of rescue analgesia, during the trial (79.3% in the CR-oxycodone group, 82.8% in the gabapentin group, and 86.2% in the placebo group). Fewer subjects used ibuprofen, the second tier of rescue analgesia (17.2% in the CR-oxycodone group, 27.6% in the gabapentin group, and 24.1% in the placebo group), and oxycodone/acetaminophen, the third tier of rescue analgesia (3.5% in the CR-oxycodone group, 10.3% in the gabapentin group, and 24.1% in the placebo group). Although the group differences were generally not statistically significant, there was less use of all three tiers of rescue analgesia in the CR-oxycodone group compared with the placebo group, which is consistent with the beneficial treatment effect of CR-oxycodone on acute pain.

3.5. Blinding

Although more than half of the subjects in each treatment group guessed that they were receiving active medication (82.6% for CR-oxycodone, 70.3% for gabapentin, and 55.2% for placebo), the differences among the groups were not significant.

4. Discussion

The objectives of this study were to determine the safety and tolerability of relatively aggressive titration schedules for CR-oxycodone and gabapentin in patients with herpes zoster and to examine the efficacy of these medications in reducing herpes zoster acute pain. CR-oxycodone and gabapentin were generally safe in these older individuals with herpes zoster, with AEs that reflect well-known effects of these medications. There was, however, a high rate of subjects who did not complete the trial because of constipation associated with the treatment with CR-oxycodone, which could be addressed by initiating routine laxative therapy at the beginning of the treatment rather than using laxatives on an as needed basis. Because of the side effects and relatively high rate of discontinuations, using more rapid titration schedules for CR-oxycodone and gabapentin would likely be problematic in patients with herpes zoster. However, given the severity of the pain in these patients and the hypothesis that aggressive treatment of acute pain in herpes zoster can prevent the development of PHN by attenuating central functional and structural mechanisms of chronic pain [3,5,12], using a less aggressive titration schedule might not relieve acute pain rapidly and effectively enough. It is also possible that a less aggressive titration schedule would limit the number of patients who discontinue treatment because of intolerable side effects, and ultimately prevent more cases of PHN because a larger number of patients obtain treatment of their acute pain.

The data demonstrated a significant reduction in acute pain in herpes zoster patients treated with CR-oxycodone during the first two weeks of the trial, during which titration occurred, but not throughout the entire 28-day treatment period. It is likely that the lack of a significant benefit over the entire treatment period reflects the natural history of herpes zoster, in which pain resolves within approximately two to three weeks following rash onset in most patients (as can be seen from the placebo group data in Fig. 2). The clinical importance of the pain relief that occurred with CR-oxycodone during the first two weeks of treatment is supported by the percentages of subjects that experienced pain reductions of ⩾30% from baseline (Table 3), which has been demonstrated to be a clinically meaningful improvement for patients in acute and chronic pain clinical trials [8,16,17,30]; as would be expected, however, fewer patients obtained pain reductions of ⩾50% from baseline, and the treatment effects using this more stringent criterion of improvement were not significant.

Gabapentin did not provide greater pain relief than placebo, although the daily pain diary and SF-MPQ data for the first week are consistent with a modest benefit. We expected that gabapentin would be efficacious in relieving acute pain in herpes zoster on the basis of multiple randomized clinical trials that have demonstrated its efficacy in patients with PHN and other types of neuropathic pain [13,19], a recent study that reported analgesic effects of a single 900 mg dose of gabapentin vs. placebo in herpes zoster [4], and open-label reports of its effectiveness in patients with herpes zoster [2,5,18]. Moreover, gabapentin has been shown to be analgesic in animal models of pain due to chronic herpes simplex infection [33] and chronic latent herpes zoster infection [21,24].

Although it is possible that the sample size was too small to detect a potentially important effect of gabapentin, it is more likely that a beneficial effect was not found (assuming that it exists) because the maximum dose we administered was 600 mg (given three times daily), which could have less of an analgesic effect than a single dose of 900 mg, which was shown to reduce herpes zoster pain for 6 h [4], and the generally higher daily dosages used for PHN [39,41]. However, titration to higher dosages (e.g., 3600 mg/day) would take at least three weeks, too long a period of time in patients for whom relief of acute pain should occur rapidly. Pregabalin appears to provide more rapid pain relief than gabapentin [11], and it would be valuable to study its efficacy in patients with herpes zoster for both acute pain and prevention of PHN [12].

There were several limitations of our study that should be noted. We studied a non-generic opioid analgesic rather than a less expensive generic medication. Although it can be expected that a generic extended-release oxycodone would also be efficacious, it is impossible to know whether our results can be extrapolated to other opioid analgesics, for example, hydrocodone or morphine. In addition, the study did not include many individuals over 75 years of age, who are at higher risk for medication adverse effects

than younger individuals, especially with higher dosages and more rapid titration schedules. Moreover, subjects with mild pain were excluded from the trial, but it is not uncommon for acute pain in herpes zoster to worsen over the first week or two following rash onset. The generalizability of our results to individuals whose acute pain will worsen later in the course of herpes zoster and then require treatment is therefore unknown. Because we excluded patients with mild acute pain, it is also impossible to determine from our study whether such individuals should be treated with an opioid analgesic or whether non-opioid analgesics might be efficacious for mild acute pain in herpes zoster.

We included patients whose prodrome had lasted seven days or less and who were within six days of rash onset. Compared to antiviral trials that have typically enrolled patients within 72 h of rash onset [12], our subjects could have been treated relatively late after the initiation of viral reactivation. It is possible that this reduced the efficacy of acute pain treatment, but it is more likely that such a delay in pain relief would attenuate any beneficial effect of treatment on the development of chronic pain, which our study was not designed to examine. Although we excluded patients whose worst pain in the past 24 h was <3 on a 0–10 NRS, subjects whose worst pain was 3 or 4 on the 0–10 NRS were included, and it is possible that including subjects with such relatively mild levels of pain decreased the assay sensitivity of the trial to detect treatment effects.

Older age and immune compromise are potent risk factors for herpes zoster, and increases in the incidence of both herpes zoster and PHN can be expected as the population ages and the prevalence of diseases and medical treatments associated with immunosuppression increases [12]. In addition, there is evidence that the incidence of herpes zoster has increased in the past two decades [42], and other recent data [48] are consistent with the prediction that herpes zoster in the United States will increase as a consequence of reduced opportunities for subclinical immune boosting resulting from varicella vaccination of children [6,20,44]. Although an increase in the incidence of herpes zoster could be offset by herpes zoster vaccination [37], the extent to which vaccination will become widespread is unknown. Because no randomized clinical trials of ongoing treatments for acute pain in patients with herpes zoster have been conducted, current guidelines emphasize antiviral therapy but have been unable to provide evidence-based recommendations for the treatment of acute pain or for additional methods to prevent PHN [12]. By demonstrating that CR-oxycodone is safe, generally adequately tolerated, and efficacious in relieving acute pain in patients with herpes zoster, the results of this clinical trial provide a foundation for evidence-based treatment for herpes zoster pain.

5. Financial disclosure

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Dedication

The authors would like to dedicate this article to the memory of Mitchell B. Max, MD, whose landmark randomized clinical trials in patients with painful diabetic peripheral neuropathy and postherpetic neuralgia provided an essential foundation and pivotal impetus for all subsequent clinical trials of treatments for neuropathic pain and other chronic pain conditions.

Appendix A

Blinded medication titration schedules.

Day	CR-oxycodone	Gabapentin
1	10 mg or 10 mg every 12 h[a]	300 mg at bedtime
2	10 mg every 12 h	300 mg in the morning, 300 mg at bedtime
3	10 mg in the morning, 20 mg 12 h later	300 mg every 8 h
4	20 mg every 12 h	300 mg in the morning, 300 mg 8 h later, 600 mg 8 h later
5	30 mg every 12 h	300 mg in the morning, 300 mg 8 h later, 600 mg 8 h later
6	40 mg every 12 h	600 mg in the morning, 300 mg 8 h later, 600 mg 8 h later
7	50 mg every 12 h	600 mg in the morning, 300 mg 8 h later, 600 mg 8 h later
8–28	60 mg every 12 h	600 mg every 8 h

[a] Depending on time of day of enrollment and investigator's discretion.

Appendix B

Adverse events reported by at least two subjects in either the CR-oxycodone or gabapentin groups.

Adverse events	CR-oxycodone	Gabapentin	Placebo
	Percentage (*n*)	Percentage (*n*)	Percentage (*n*)
Anxiety	0.0 (0)	6.9 (2)	10.3 (3)
Appetite change	20.7 (6)	6.9 (2)	3.5 (1)
Chills	10.3 (3)	0.0 (0)	3.5 (1)
Concentration change	3.5 (1)	6.9 (2)	0.0 (0)
Constipation	51.7 (15)	20.7 (6)	24.1 (7)

(*continued on next page*)

Appendix B (*continued*)

Adverse events	CR-oxycodone	Gabapentin	Placebo
	Percentage (*n*)	Percentage (*n*)	Percentage (*n*)
Cough	0.0 (0)	6.9 (2)	3.5 (1)
Diarrhea	6.9 (2)	3.5 (1)	3.5 (1)
Dizziness	27.6 (8)	34.5 (10)	20.7 (6)
Drowsiness	17.2 (5)	10.3 (3)	0.0 (0)
Dry mouth	3.5 (1)	6.9 (2)	0.0 (0)
Dyspepsia	10.3 (3)	6.9 (2)	3.5 (1)
Emesis	31.0 (9)	0.0 (0)	13.8 (4)
Extremity pain	6.9 (2)	3.5 (1)	6.9 (2)
Fatigue	6.9 (2)	20.7 (6)	17.2 (5)
Fecal impaction	6.9 (2)	0.0 (0)	0.0 (0)
Hallucinations	6.9 (2)	0.0 (0)	0.0 (0)
Headache	17.2 (5)	24.1 (7)	20.7 (6)
Imbalance	13.8 (4)	17.2 (5)	6.9 (2)
Insomnia	6.9 (2)	3.5 (1)	6.9 (2)
Light-headed	13.8 (4)	6.9 (2)	3.5 (1)
Nausea	37.9 (11)	20.7 (6)	20.7 (6)
Pruritis	20.7 (6)	13.8 (4)	20.7 (6)
Sedation	17.2 (5)	6.9 (2)	0.0 (0)
Shortness of breath	0.0 (0)	6.9 (2)	0.0 (0)
Vision change	0.0 (0)	10.3 (3)	3.5 (1)

Appendix C

Maximum tolerated daily dosages in subjects who completed the trial with the day at which this dosage was achieved.

CR-oxycodone ($n = 21$)

20 mg: 1 subject (day 3)
30 mg: 1 subject (day 4)
40 mg: 2 subjects (1 on day 4, 1 on day 10)
60 mg: 2 subjects (day 10)
100 mg: 4 subjects (2 on day 9; 1 on day 12; 1 on day 14)
120 mg: 11 subjects (10 on day 8; 1 on day 14)

Gabapentin ($n = 24$)

600 mg: 1 subject (day 2)
1200 mg: 1 subject (day 4)
1500 mg: 4 subjects (day 6)
1800 mg: 18 subjects (day 8)

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