Effect of Minocycline on Lumbar Radicular Neuropathic Pain

A Randomized, Placebo-controlled, Double-blind Clinical Trial with Amitriptyline as a Comparator

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ABSTRACT

Background: Less than 50% of patients experience sufficient pain relief with current drug therapy for neuropathic pain. Minocycline shows promising results in rodent models of neuropathic pain but was not studied in humans with regard to the treatment of neuropathic pain.

Methods: In this randomized, double-blind, placebo-controlled clinical trial, patients with subacute lumbar radicular pain received placebo, amitriptyline 25 mg, or minocycline 100 mg once a day (n = 20 per group) for 14 days. Primary outcome measure was the pain intensity in the leg as measured by a numeric rating scale ranging from 0 to 10 on days 7 and 14. Secondary outcome measures were the reduction of neuropathic pain symptoms in the leg as determined with a neuropathic pain questionnaire, consumption of rescue medication, and adverse events on days 7 and 14.

Results: Sixty patients were randomized and included in an intention-to-treat analysis. After 14 days, patients in the minocycline and amitriptyline groups reported a reduction of 1.47 (95% confidence interval, 0.16–2.83; $P = 0.035$) and 1.41 (95% confidence interval, 0.05–2.78; $P = 0.043$), respectively, in the numeric rating scale compared to the placebo group. No differences were seen in the neuropathic pain questionnaire values at any time point during treatment between the three groups. The rate of adverse events in the amitriptyline group was 10% *versus* none in the minocycline and placebo groups. No differences were noted in the consumption of rescue medication.

Conclusions: Although both groups differed from placebo, their effect size was small and therefore not likely to be clinically meaningful. **(ANESTHESIOLOGY 2015; 122:399-406)**

CHRONIC pain imposes a heavy burden on patients and society. With an annual cost of U.S. $560 billion, the expenditure of pain in the United States exceeds those of cancer, heart disease, and diabetes combined.[1] Neuropathic pain, defined as pain arising from a lesion within the somatosensory nervous system,[2] is one of the most debilitating forms of chronic pain. Although neuropathic back and leg pain are the most common forms of neuropathic pain,[3] they are the least researched with regard to drug efficacy. Amitriptyline, for instance, is a tricyclic antidepressant and first-line drug in the treatment algorithm of neuropathic pain[4] but was never studied in patients with lumbar radicular pain. Furthermore, efficacy of a drug for a particular type of neuropathic pain cannot be extrapolated to another type of neuropathic pain,[5–7] and, moreover, first-line therapies for neuropathic pain are often accompanied by considerable

What We Already Know about This Topic

- Minocycline reduces hypersensitivity in rodent models of neuropathic pain by a mechanism involving reduced neuroinflammation but the clinical relevance of this is unclear

What This Article Tells Us That Is New

- In a controlled trial of 60 patients with subacute lumbar radicular pain, a 2-week treatment with minocycline or amitriptyline reduced pain compared to placebo
- Reductions in pain over this short time period were small and unlikely to be clinically significant

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side effects, limiting their usability.[8–10] Consequently, there is a strong need for studies with accepted first-line drugs therapies in patients with lumbar radicular pain, as well as for novel drugs to treat neuropathic pain.

Minocycline is a semisynthetic tetracycline with antibiotic action against a wide range of Gram-positive, Gram-negative, and atypical microorganisms. It attenuates mechanical allodynia and thermal hyperalgesia in rodent models of neuropathic pain when administered preemptively[11,12] and postinjury,[13] mainly through microglial inhibition and decreased expression of brain-derived neurotrophic factor.[11,13] Beneficial effects of minocycline have been observed in the neurological and functional recovery of patients with stroke,[14] spinal cord injury,[15] and multiple sclerosis.[16] A first indication that minocycline can improve neuropathic pain was recently obtained by Syngle *et al.*[17] in patients experiencing polyneuropathy associated with type 2 diabetes. With the present study, we aim to confirm and extend their observation by testing the effect of minocycline on lumbar radicular neuropathic pain. Because in humans, minocycline is readily absorbed by the gastrointestinal tract[18] and easily crosses the blood–brain barrier with cerebrospinal fluid levels ranging between 25% and 30% of serum concentrations,[19] oral administration of this drug is suitable to treat central nervous system diseases.

In the present randomized, double-blind, placebo-controlled clinical trial with amitriptyline as a comparator, we are the first to test the hypothesis that minocycline reduces neuropathic pain in patients experiencing lumbar radicular pain. Because we performed this trial as a proof of concept study, we choose the smallest number of participants needed based on our power analysis together with a relatively short follow-up period of 2 weeks in order not to withhold patients from other treatments. The primary objective of this study was to analyze the effect of minocycline on pain intensity compared to placebo and amitriptyline. Secondary outcome measures included assessment of neuropathic pain symptoms, consumption of rescue medication, and possible adverse events. This study was part of a larger clinical trial that included determination of plasma and serum concentrations of brain-derived neurotrophic factor in patients with lumbar radicular pain (clinicaltrials.gov number NCT01869907).

Materials and Methods

Study Design and Settings

In this single-center, randomized, double-blind, placebo-controlled, clinical trial with amitriptyline as an active comparator, we investigated the effect of minocycline on neuropathic lumbar radicular pain. The trial was conducted at the Ziekenhuis Oost-Limburg, Genk, Belgium, and was approved by the local ethics committee (Commissie voor Medische Ethiek) and registered at clinicaltrials.gov (trial number: NCT01869907). The study started in September 2011 and ended in August 2013 when the objective of 60 enrolled patients had been reached.

Participants

Patients were recruited by means of physician referrals to our tertiary multidisciplinary pain clinic at the Ziekenhuis Oost-Limburg, Genk, Belgium. Eligible patients presented with lumbosacral radicular pain radiating into the leg below the knee caused by disc herniation, spinal canal stenosis, or failed back surgery syndrome. Patients were included only if the level of the pathology on computer tomography or magnetic resonance imaging correlated with the dermatome in which they indicated their leg pain and if the leg pain was predominant over the back pain (11-point numeric rating scale [NRS] score for leg pain > NRS score for back pain). The dermatomal distribution of the leg pain was determined with the adapted dermatomal map from Wolff *et al.*[20] The neuropathic nature of the leg pain was determined by a validated Dutch translation of the douleur neuropathique 4 (DN4) questionnaire (cutoff ≥ 4).[21] The inclusion and exclusion criteria are presented in table 1. All patients gave written informed consent before inclusion in the study.

Interventions

Sixty patients were randomized in a 1:1:1 ratio to receive once daily, during 2 weeks, placebo (starch; Fagron, Waregem, Belgium), amitriptyline 25 mg (Aca Pharma, Waregem, Belgium), or minocycline 100 mg (ABC Chemicals, Wouters-Brakel, Belgium). Patients were instructed to take the study medication in the morning with a glass of water 1 h before or 1 h after breakfast, to prevent interference of food with gastrointestinal absorption with the study drug.[18] Continuation of paracetamol or nonsteroidal antiinflammatory drugs was permitted during the trial period on the condition that patients were on a stable dose for at least 1 week before enrollment. Otherwise, the only pain medications permitted during the trial period were the study drug and rescue medication. Rescue medication consisted of 50 mg tramadol (Tradonal Odis; Meda Pharma, Brussels, Belgium) with a maximum of three intakes daily and 6 h between consecutive ingestions. During the trial period, patients completed three study visits: a baseline visit and visits after 7 and 14 days during which the pain intensity in the leg measured by an NRS and DN4 score was obtained, and a supply for 1 week of trial (7 capsules) and rescue medication (21 tablets) was provided. During visits two and three, patients were asked if they experienced any adverse events. Drug logs were kept to record the amount of rescue medication the patients had consumed during the past week and to record if the patients had taken the entire amount of investigational drugs.

Outcome Measures

The primary outcome measure was the effect on pain intensity in the leg. Patients were asked to rate their average leg pain during the past 24 h on an 11-point NRS, with 0 indicating no pain and 10, the worst pain imaginable.[22] Secondary outcome measures were changes in neuropathic pain

Table 1. Inclusion and Exclusion Criteria of the Study

Inclusion Criteria	Exclusion Criteria
Age 18 to 80 yr	Diabetic, alcoholic, or drug-induced polyneuropathies
Neuropathic lumbar radicular pain caused by:	Depression or psychiatric comorbidity affecting pain sensation
Lumbar disc herniation, spinal canal stenosis, or failed back surgery syndrome (epidural fibrosis) confirmed by computer tomography or magnetic resonance imaging	Use of antidepressants
	Fibromyalgia and chronic fatigue syndrome
Level of pathology on imaging studies correlates with dermatomal distribution in the leg	Pregnancy
	Spinal cord damage
	Malignancy
	Allergy for minocycline or amitriptyline

symptoms in the leg (burning pain sensation, cold painful sensation, electric shocks, paresthesia, "pins and needles" sensation, numbness, itching pain sensation, hypoesthesia to touch, hypoesthesia to pinprick, and mechanical allodynia, with a score of 1 awarded for every symptom present) as measured with the DN4,[21] changes in consumption of rescue medication, and adverse events. The assessments were made at baseline (visit one) and after 7 (visit two) and 14 days (visit three) for the NRS and DN4 scores and during visits two and three for consumption of rescue medication and adverse events. To detect adverse events, patients were asked on days 7 and 14 of the trial if they had experienced side effects during the past week attributable to the study drugs.

Blinding and Randomization

A hospital pharmacist prepared study kits containing the study drug and rescue medication for each patient for the entire duration of the study and randomly assigned a number to each kit ranging from 1 to 60. Each kit contained two white vials labeled "study medication," each vial containing seven capsules and two white vials labeled "rescue medication," each vial containing 21 tablets of 50 mg tramadol. The encryption key linking the numbers of each kit to its content was safeguarded by the pharmacist until the end of the study and was unknown to all the outcome assessors. Placebo, amitriptyline, and minocycline were encapsulated in identical opaque white capsules so that patients and study staff were unable to visually distinguish their contents. Upon inclusion, patients were randomized by assigning them a study kit number by a computerized random number generator.

Statistical Methods

A decrease of 2 or more points on an 11-point NRS has been shown to be moderately clinically meaningful.[23] To detect this difference with a standard deviation of 1.7[24] and a power of 90% with a significance level set $\alpha = 0.05$, we calculated that a sample size of 16 patients per group would be needed.[25] To compensate for an estimated dropout rate of 20%, we included 20 patients per group. An intention-to-treat analysis was performed with none of the patients excluded because of missing data. To determine the effect of placebo, amitriptyline 25 mg, and minocycline 100 mg on NRS and DN4 scores, we used a linear regression model with time in weeks, the baseline value of the outcome, dummies for the active interventions, and an interaction between time and the intervention dummies as covariates. The two interaction terms were entered to estimate the change over time for the different interventions. A random intercept model was used to take into account the statistical dependence of the measurements. A mixed model analysis of variance with Bonferroni *post hoc* test was used to assess changes in consumption of rescue medication. Finally, a cumulative proportion of responder analysis,[26] which displays the level of response at all possible cutoff points, was performed for NRS and DN4 scores on day 14. The cutoff points are the percentage change in NRS pain intensity or DN4 score, respectively, on day 14 compared to day 1 (*e.g.*, 50% signifies that the NRS score or DN4 score has halved on day 14). Data are presented as means ± SEM. Statistical analyses were carried out using IBM SPSS version 20, release 20.0.0.1, Armonk, NY).

Results

Study Population

Sixty patients were randomized, 20 to each treatment group. Nine patients (three patients per study arm) discontinued the trial in the first week, two because of violation of the study protocol (one patient took the study medication for 2 days and then switched to nonsteroidal antiinflammatory drugs, the other patient stopped study medication after 2 days without giving a reason), two because of adverse effects (both in the amitriptyline group), and five patients withdrew their informed consent. In total, 51 patients (17 per treatment arm) completed the study (fig. 1). The baseline characteristics were similar across the three study arms (table 2).

Primary Outcome

All patients were included in the regression analysis. After 2 weeks of therapy, patients in the minocycline and amitriptyline groups reported a reduction of 1.47 (95% confidence interval, 0.16–2.83; $P = 0.035$) and 1.41 (95% confidence interval, 0.05–2.78; $P = 0.043$) in NRS score, respectively,

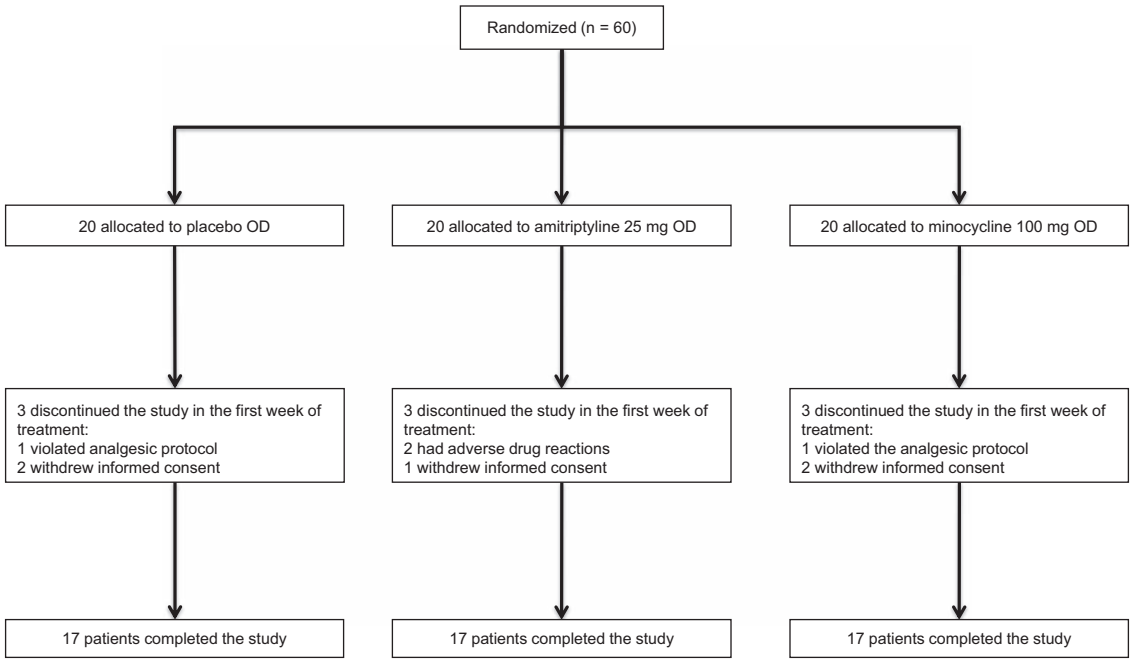

Fig. 1. CONSORT flowchart. Patients were required to complete at least 1 week of the study (allowing for repeated analysis) to be included in the modified intention-to-treat analysis. Seventeen patients per treatment arm were included in the modified intention-to-treat analysis. OD = once daily.

Table 2. Demographic Data and Baseline Characteristics of the Patients

Characteristic	Placebo (n = 20)	Amitriptyline (n = 20)	Minocycline (n = 20)
Age, yr	51 ± 3	50 ± 3	47 ± 3
Sex, no. (%)			
Male	9 (45)	13 (65)	11 (55)
Female	11 (55)	7 (35)	9 (45)
Culprit nerve root, no. (%)			
L3	0 (0)	2 (10)	1 (5)
L4	3 (15)	1 (5)	7 (35)
L5	8 (40)	6 (30)	8 (40)
S1	9 (45)	11 (55)	4 (20)
Cause of neuropathic pain, no. (%)			
Disc herniation	16 (80)	16 (80)	17 (85)
Spinal canal stenosis	4 (20)	2 (10)	1 (5)
Failed back surgery syndrome	0 (0)	2 (10)	2 (10)
Duration of pain, mo	2.8 ± 0.4	3.2 ± 0.6	2.5 ± 0.3
NRS score	7.4 ± 0.3	6.9 ± 0.4	7.1 ± 0.4
DN4 score	4.2 ± 0.4	4.3 ± 0.4	4.9 ± 0.3

Plus-minus values are mean ± SEM. Higher scores indicate more neuropathic pain symptoms are present. Cutoff for the presence of neuropathic pain is a score ≥4.

DN4 = douleur neuropathic questionnaire, scores ranging from 0 to 10. NRS = numeric rating scale ranging from 0 to 10 for leg pain (higher scores indicate more pain).

compared to the placebo group. There was no statistically significant difference in NRS score between the minocycline and amitriptyline group after 2 weeks of therapy (fig. 2A). The cumulative proportion of responder analysis at day 14 showed more responders in the minocycline and amitriptyline group than in the placebo group for all cutoff points (fig. 2B). The number needed to treat for moderate (≥30%) and substantial (≥50%) clinically important improvements in NRS score[27] are 3 and 6 for minocycline and 3 and 4 for amitriptyline, respectively.

Secondary Outcomes

With respect to DN4 scores, 2-week therapy resulted in decrease of 1.26 points (95% confidence interval, −0.01 to 2.25; $P = 0.053$) and 0.35 points (95% confidence interval, −0.8 to 1.48; $P = 0.54$) in the amitriptyline and minocycline

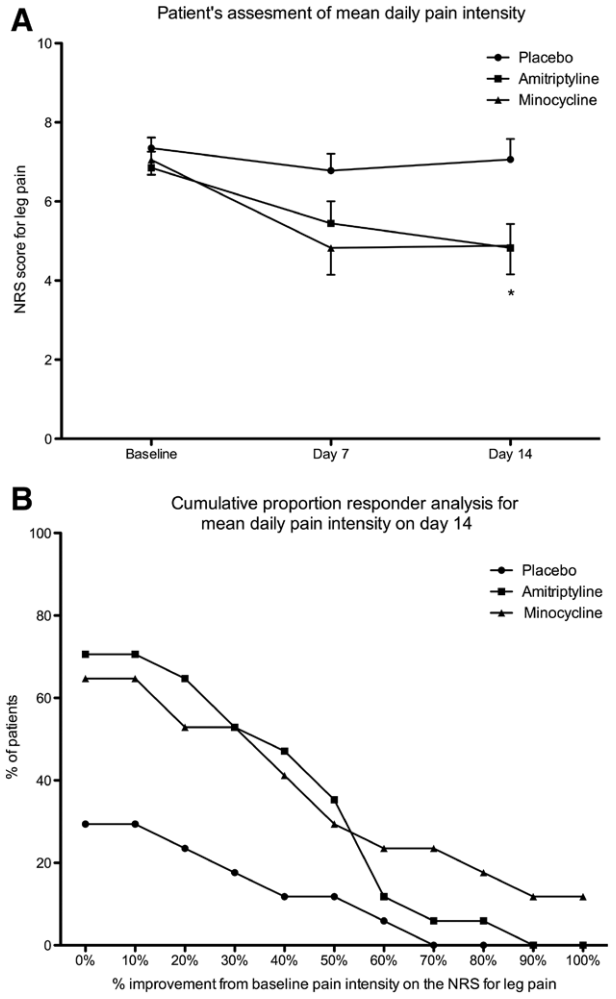

Fig. 2. Primary outcome measures. (*A*) Patient's assessment of pain intensity numeric rating scale (NRS): 11-point NRS ranging from 0 to 10 for leg pain. Higher scores indicate more pain. *P < 0.05 for NRS score in the minocycline and amitriptyline group compared to placebo on day 14. (*B*) Cumulative proportion of responder analysis for mean daily pain intensity in the leg on day 14 as measured by the NRS. X-axis: level of response (% improvement) in mean daily pain intensity from baseline NRS score on day 14. Y-axis: proportion of patients (%) that equal or exceed the level of response. 11-point NRS ranging from 0 to 10 for leg pain. Higher scores indicate more pain.

group, respectively, compared to placebo. Cumulative proportion of responder analysis of neuropathic symptoms also showed closely matched responder curves for amitriptyline, minocycline, and placebo, indicating no obvious differences between the three treatment groups (fig. 3). There were no statistically significant differences in the consumption of rescue medication between the three groups at any time point (table 3).

Adverse Events

In the amitriptyline group, 2 of 20 patients (10%) reported adverse events within the first week of treatment. One patient complained of nausea, vomiting, and a general

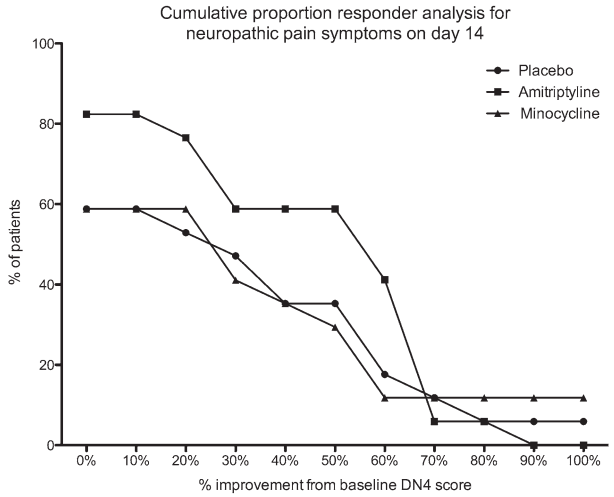

Fig. 3. Cumulative proportion of responder analysis for neuropathic pain symptoms in the leg on day 14 as measured by the douleur neuropathique 4 questionnaire (DN4). X-axis: level of response (% improvement) in neuropathic pain symptoms from baseline on day 14. Y-axis: proportion of patients (%) that equal or exceed the level of response.

unwell feeling, and a second patient developed a rash. All symptoms disappeared after discontinuation of the study medication. No adverse events were reported in the placebo and minocycline groups.

Discussion

The results from this study suggest that minocycline and amitriptyline improve lumbosacral radicular pain for at least 2 weeks and, furthermore, that treatment with minocycline is associated with less adverse events compared to amitriptyline. After 2 weeks of treatment, minocycline and amitriptyline reduced pain intensity by 1.47 and 1.41 points on the NRS, respectively. Although the NRS score of both groups differed from placebo, their effect size was small. Therefore, it remains to be seen if the effects of minocycline and amitriptyline are clinically meaningful. The result we observed was not caused by differences in the amount of rescue medication taken in the different groups. The placebo response for moderate improvement in NRS score was 18% in our study, approximating the placebo response of other neuropathic pain trials in a Cochrane review.[9] With this result, we not only support the conclusion made by Syngle *et al.*[17] that minocycline reduces neuropathy but also extend it to lumbar radicular pain.

To date, no other studies are available on the use of minocycline for the primary treatment of lumbar radicular neuropathic pain in humans. In one study, researchers investigated the preventive effect of minocycline on persistent pain after lumbar discectomy.[28] Minocycline was administered perioperatively for 8 days but failed to reduce the incidence of low back and leg pain 3 months after surgery. However, a subgroup analysis in the latter study suggested that patients with similar symptoms as the patients in our study (predominant

Table 3. Secondary Outcome Measures

	DN4 Score			Rescue Medication	
	Baseline	Day 7	Day 14	Week 1	Week 2
Placebo	4.2 ± 1.9	3.7 ± 2.3	3.6 ± 2.4	12 ± 7	12 ± 8
Minocycline	4.9 ± 1.4	4.2 ± 2.0	3.9 ± 2.2	11 ± 8	14 ± 8
Amitriptyline	4.3 ± 1.9	2.9 ± 1.6	2.2 ± 1.2	9 ± 7	9 ± 8

Plus-minus values are mean ± SD. DN4 = douleur neuropathique 4 questionnaire, scores ranging from 0 to 10. Higher scores indicate more neuropathic pain symptoms are present. Cutoff for the presence of neuropathic pain is a score ≥4. Rescue medication is the number of 50 mg tramadol tablets taken over the course of the past week. No statistically significant differences in DN4 score or amount of rescue medication were noted between the three treatment groups at any time point.

deep spontaneous neuropathic leg pain) might benefit from minocycline treatment. Another study concerned the effect of a single dose of minocycline on neuropathic pain induced by an intradermal capsaicin injection in patients with unilateral sciatica, which showed no significant effect on NRS score.[29] The negative results in both these studies could be related to the timing and duration of minocycline administration because in our study the antinociceptive effect of minocycline only became apparent after 2 weeks of treatment.

In our study, minocycline shows a reduction in pain intensity with similar numbers needed to treat compared to amitriptyline, a first-line drug for the treatment of neuropathic pain. We found no randomized studies concerning amitriptyline and radicular neuropathic pain, but our number needed to treat values for amitriptyline match those found in a systematic review by Moore *et al.*,[9] where the effects of amitriptyline on painful diabetic neuropathy, postherpetic neuralgia, poststroke pain, and fibromyalgia were pooled. Our data are in contrast with a study by Khoromi *et al.*,[5] where nortriptyline, an active metabolite of amitriptyline and also a first-line drug for the treatment of neuropathic pain, failed to improve chronic lumbar radicular pain. Two important differences between our study and the study by Khoromi *et al.*[5] can provide an explanation for these opposing outcomes of two almost identical drugs. First, there is a different time interval to treatment: in our study, patients had a mean duration of pain of approximately 3 months while in the study by Khoromi *et al.*[5] the median duration of pain was 5 yr. It is known that pain becomes less responsive to treatment the longer it persists.[30] Whether this effect is due to consolidation of pathophysiologic processes, rendering neuropathic pain less responsive to drug treatment over time or due to acquired overlying psychosocial issues and psychopathology in patients with chronic pain, resulting in lower response rates for treatments remains to be elucidated. Second, there is a different timing in administration of the tested drugs: in our study, amitriptyline was administered in the morning, whereas nortriptyline in the study by Khoromi *et al.*[5] was administered in the evening. Chronopharmacology studies showed significant higher serum concentrations of amitriptyline when administered in the morning than in the evening due to a higher absorption rate constant and a shorter time to peak concentration.[31] This can also account for the fact that we found a significant clinical effect with relative low doses of amitriptyline.

In a randomized controlled trial[32] and in a systematic review,[33] combination therapy for neuropathic pain (tricyclic antidepressants or antiepileptics combined with opioids and nortriptyline or gabapentin alone or combined, respectively) was found beneficial over monotherapy. However, the usability of combination therapy is often limited due to overlapping side effects of the drugs. The absence of adverse events associated with minocycline treatment (*vs.* 10% in the amitriptyline group) in our study suggests that minocycline could be useful in combination therapy. The adverse event rate of 10% we noticed in the amitriptyline group was lower than the 64% previously reported in a systematic review[9] probably because of the short duration of our trial and the relatively low dose of amitriptyline we used.

The limitations of our study are related to the short follow-up period and a relative small number of participants. However, the optimal timing of, and duration for the treatment of, neuropathic pain in humans with minocycline is unknown and our power calculation was effective in predicting the amount of patients needed to detect a significant drop in pain intensity. The dosages of minocycline (100 mg daily) and amitriptyline (25 mg daily) we used were lower than those reported in other studies,[9,28] but in view of the fact that neuropathic pain often requires long-term treatment, the lowest dose of a drug with a clinically ample effect should be used, especially because 25 mg amitriptyline already impairs daily functions such as car driving.[34] Because potentially serious side effects have been reported with the use of minocycline,[35] larger studies with more detailed safety assessments are needed to determine the definite risk-benefit profile of this drug for the treatment of neuropathic pain. Finally, future studies may benefit from keeping a pain diary of NRS scores over a 24-h period.

In conclusion, our short-term results suggest that minocycline and amitriptyline reduce lumbar radicular neuropathic pain and, moreover, that treatment with minocycline is associated with fewer side effects. However, the observed effect size was small and therefore not likely to be clinically meaningful. This study warrants additional clinical trials

with larger patient populations, longer follow-up, and more intricate designs (*e.g.*, crossover) to evaluate long-term outcome and safety and to study the effects of minocycline on other neuropathic pain conditions.

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Competing Interests

The authors declare no competing interests.

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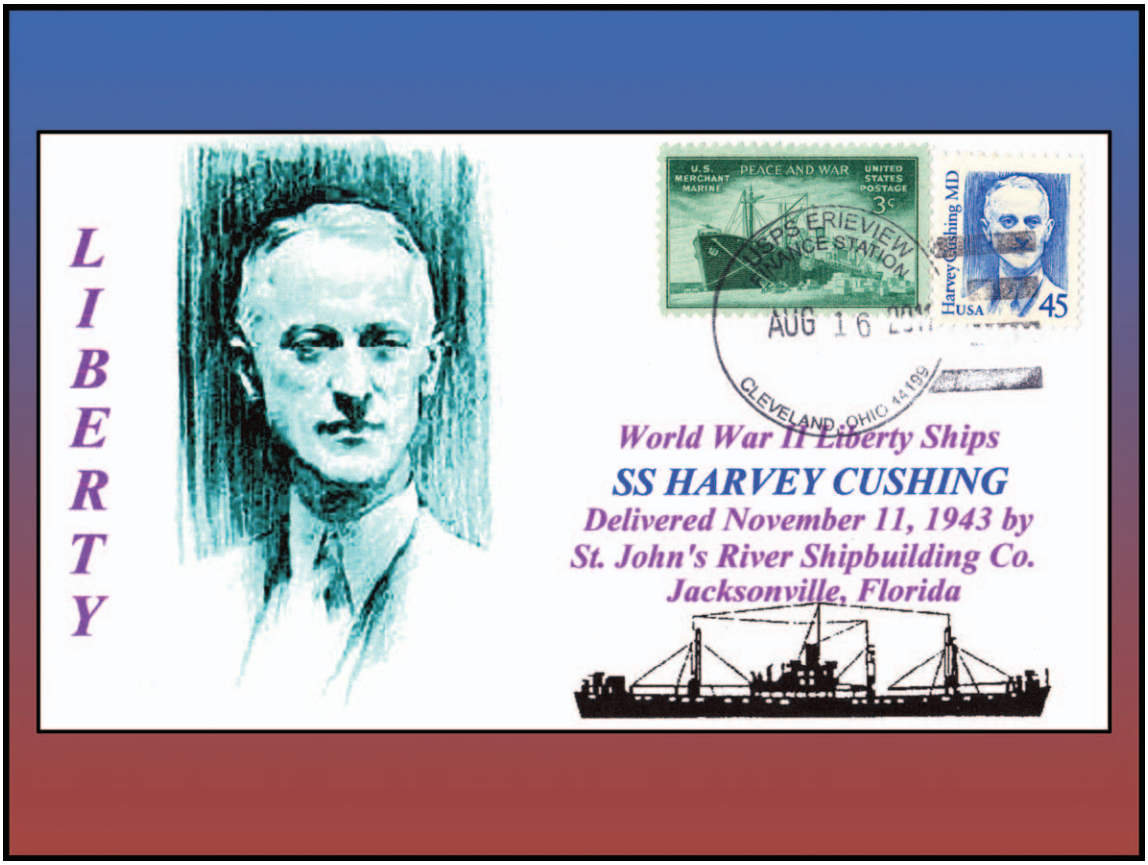
A Floridian Salute to a Clevelander: Liberty Ship SS *Harvey Cushing*



This postal cover (*above*) commemorates the 1943 delivery of the "Liberty Ship" SS *Harvey Cushing* and the celebrity of its namesake surgeon and anesthesia pioneer (Harvey Williams Cushing, M.D., "Father of Modern Neurosurgery"; Johns Hopkins, Harvard, and Yale Universities, USA) (1869–1939). Anesthesiologists salute Dr. Cushing for popularizing the use of anesthetic records and of intraoperative monitoring of patients' blood pressures and vital sounds (breathing and heart beat). This cover was postally cancelled in the city where Dr. Cushing was born and where he was buried—Cleveland, Ohio. (Copyright © the American Society of Anesthesiologists, Inc.)

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