

# Morphine versus Mexiletine for Treatment of Postamputation Pain

## A Randomized, Placebo-controlled, Crossover Trial

Christopher L. Wu, M.D.,\* Shefali Agarwal, M.B.B.S., M.P.H.,† Prabhav K. Tella, M.B.B.S., M.P.H.,† Brendan Klick, M.S.,‡ Michael R. Clark, M.D., M.P.H.,§ Jennifer A. Haythornthwaite, Ph.D.,|| Mitchell B. Max, M.D.,# Srinivasa N. Raja, M.D.\*\*

**Background:** Stump and phantom pains are debilitating sequelae of amputations that are often resistant to treatment. The efficacy of pharmacologic therapies, including opioids and sodium channel blockers, for postamputation pain is uncertain.

**Methods:** The authors conducted a double-blind, randomized, placebo-controlled, crossover study in adult patients with postamputation pain of 6 months or longer and greater than 3 on a 0-10 numeric pain rating scale. Each of the three treatment periods (morphine, mexiletine, or placebo) included a 1-week drug-free interval followed by 4-week titration, 2-week maintenance, and 2-week drug-taper phases. The primary outcome measure was change in average pain intensity from the drug-free baseline to the last week of maintenance.

**Results:** Sixty amputees were enrolled; data were analyzed from 56 subjects for one drug period, 45 subjects for two drug periods, and 35 subjects who completed all three drug periods. The mean morphine and mexiletine dosages were 112 and 933 mg, respectively. Morphine treatment provided lower pain scores compared with placebo and mexiletine ( $P = 0.0003$ ). The mean percent pain relief during treatment with placebo, mexiletine, and morphine was 19, 30, and 53%, respectively ( $P < 0.0001$ , morphine vs. placebo and mexiletine). The numbers needed to treat to obtain 50% and 33% decreases in pain intensity with morphine were 5.6 and 4.5, respectively. Treatment with morphine was associated with a higher rate of side effects.

**Conclusions:** Therapy with morphine, but not mexiletine, resulted in a decrease in intensity of postamputation pain but was associated with a higher rate of side effects and no improvement in self-reported levels of overall functional activity and pain-related interference in daily activities.

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 Klass M, Csete M: One from column A and one from column B: May I take your order? ANESTHESIOLOGY 2008; 109:165-6.

\* Associate Professor, † Research Assistant, \*\* Professor, Department of Anesthesiology and Critical Care Medicine, ‡ Research Statistician, § Associate Professor, || Professor, Department of Psychiatry and Behavioral Sciences, The Johns Hopkins University School of Medicine, Baltimore, Maryland. # Visiting Professor, Departments of Anesthesiology and Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania.

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Address correspondence to Dr. Raja: The Johns Hopkins Hospital, Osler 292, 600 North Wolfe Street, Baltimore, Maryland 21287. srja2@jhmi.edu. Information on purchasing reprints may be found at [www.anesthesiology.org](http://www.anesthesiology.org) or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

MORE than 1 million Americans have lost limbs, and another 185,000 have amputations annually. Postamputation (including stump and phantom) pains are distressing and debilitating sequelae of limb amputations that are often resistant to conventional analgesic treatment. Nearly all amputees report at least one type of amputation-related pain, with approximately 30-39% reporting "severe" pain (7-10 on a 1-10 scale) in a large national survey.<sup>1</sup> The etiology of phantom and stump pains may be interrelated, and a relatively high prevalence (approximately 50-80%) of both phantom limb and stump pains are reported, which may be a barrier to rehabilitation and cause a significant reduction in patients' quality of life.<sup>2-7</sup> Both peripheral (e.g., ectopic neural activity, neuromas, expression of tetrodotoxin-resistant sodium channel subtypes in injured neurons) and central (e.g., cortical reorganization, spinal cord sensitization) mechanisms may contribute to postamputation pain.<sup>6-10</sup>

The long-term efficacy of most pharmacologic therapies for the treatment of postamputation pain has not been carefully evaluated, with many pharmacologic therapies used in an uncontrolled fashion.<sup>11-13</sup> The available randomized controlled trials do not consistently demonstrate that drugs (e.g., gabapentin and tricyclic antidepressants) recommended by consensus panels<sup>14,15</sup> as first-line therapies for neuropathic pain are effective in treating postamputation pain.<sup>13,16</sup> Local anesthetics may diminish postamputation pain by binding to sodium channels and attenuating peripheral ectopic neural activity.<sup>17</sup> Studies suggest that opioids and systemically administered local anesthetics may be effective in providing pain relief for patients with postamputation and other neuropathic pains.<sup>17-19</sup> Lidocaine and morphine infusions may be efficacious in providing short-term pain relief in patients with postamputation pain<sup>20</sup>; however, the long-term analgesic efficacy of these agents in a more practical oral formulation has not been evaluated. We designed a placebo-controlled, double-blind, randomized, crossover trial to determine the analgesic efficacy of oral mexiletine (an oral congener of lidocaine) and sustained-release morphine for the treatment of postamputation pain.

## Materials and Methods

### Study Population

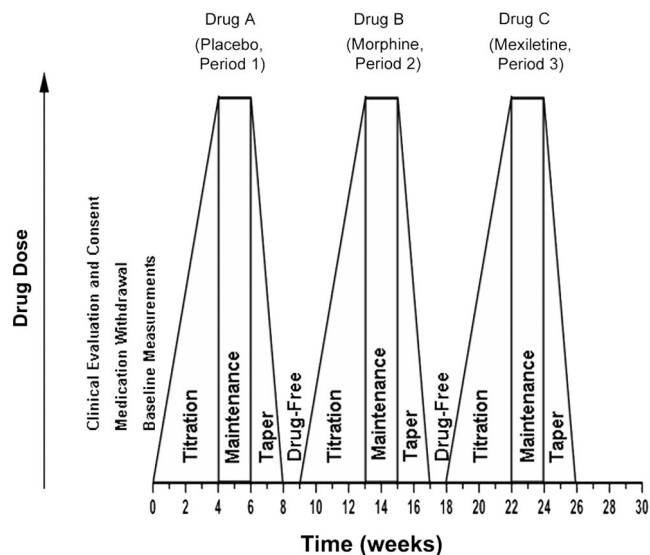
This protocol was approved by the institutional human subjects review board of Johns Hopkins Medical Institu-

tions, Baltimore, Maryland. Written informed consent was obtained for each subject before enrollment into the study. Recruitment and enrollment of all subjects occurred at the Johns Hopkins Medical Institutions. Inclusion criteria consisted of adults (aged  $\geq 18$  yr) and presence of persistent postamputation pain rated as greater than 3 on a 0–10 numerical rating scale for a period of 6 months or longer. Exclusion criteria included history of allergic reaction to any of the study drugs (*i.e.*, morphine and mexiletine), cardiac conduction defects (*e.g.*, second-degree or complete heart block), myocardial infarction within 3 months of evaluation, severe pulmonary disease, current history of alcohol or substance abuse, seizures, dementia, encephalopathy, current pregnancy or breast-feeding, chronic hepatic disease, hepatic or renal failure, any hematologic disease associated with leukopenia or thrombocytopenia, or the presence of any terminal disease with a life expectancy of less than 6 months. Baseline physical examination and electrocardiograms were obtained and evaluated before initiation of the study.

### Study Design

The study was designed as a randomized, placebo-controlled, double-blind, crossover study in which each subject would undergo three treatment periods (sustained-release morphine, mexiletine, or placebo). The duration of each treatment period was approximately 8 weeks and consisted of 4-week titration, 2-week maintenance, and 2-week taper phases, which were followed by a 1-week drug-free period (fig. 1). Once enrolled and randomized, subjects were gradually withdrawn from any opioids, benzodiazepines, antiepileptics, mexiletine, baclofen, or other neuroleptic drugs prescribed for their pain such that they took none of these medications for a 2-week period before their beginning the study (baseline). They were allowed to take acetaminophen (up to 4 g/day) or nonsteroidal antiinflammatory agents as needed during this period.

After the initial 2-week drug-free phase, subjects received directly from the investigational pharmacy a bottle for the first medication (see Randomization and Blinding section for details of drug preparation), with the initial dose as 1 capsule taken orally every morning. Each capsule consisted of either 75 mg mexiletine, 15 mg sustained-release morphine, or placebo. This dose was then titrated up to 1 capsule taken orally twice per day. In the absence of significant side effects, subsequent increments in dosing occurred at 3- to 4-day intervals and consisted of increases of 2 capsules/day (1 each in the morning and evening) up to a maximum of 16 capsules/day (maximum of 1,200 mg mexiletine or 180 mg morphine). The extent of titration or increases in medication was guided by the pain relief score, with the goal being maximal pain relief with tolerable side effects. Patients were called twice weekly to assess pain levels



**Fig. 1.** Study design. This figure illustrates the study design (placebo-controlled, double-blind, randomized, crossover study) in which each subject would undergo a period of three treatment periods (sustained-release morphine, mexiletine, or placebo) with a 1-week washout period between treatment periods. The duration of each treatment period was approximately 8 weeks and consisted of 4-week titration, 2-week maintenance, and 2-week taper phases, which were followed by a 1-week drug-free period. A total of 93 patients were approached regarding enrollment in the study, and 60 patients were ultimately enrolled.

and the presence of side effects. Patients were not allowed to take supplemental analgesics, with the exception of nonsteroidal antiinflammatory agents, as previously described.

After the 4-week drug-titration phase, subjects entered a 2-week drug-maintenance phase during which they received a stable dosage of test drug based on results of the drug titration period (fig. 1). After the drug-maintenance phase, subjects underwent a 2-week drug-taper phase during which the treatment drug was gradually withdrawn. The maintenance dose was decreased approximately 25% every 3 days until the study drug was entirely withdrawn. A 1-week drug-free phase followed the drug-taper phase, and then the process was repeated with the second and third test drugs.

### Randomization and Blinding

The subjects were randomized in balanced blocks of 12 so that an equal number of subjects would receive mexiletine, sustained-release morphine, or placebo as the first drug treatment (*i.e.*, subjects were randomized to one of six possible combinations of morphine, mexiletine, and placebo: mexiletine-morphine-placebo, mexiletine-placebo-morphine, morphine-mexiletine-placebo, morphine-placebo-mexiletine, placebo-morphine-mexiletine, or placebo-mexiletine-morphine). The randomization sequence was computer generated by a biostatistician, and the sequence of drug and placebo treatment periods for each subject was provided in

sealed envelopes to the investigational pharmacy and the monitoring committee. Patients and investigators were unaware of the contents of the study drug and randomization scheme. The investigational pharmacy manufactured the study drug as gelatin capsules, which are readily dissolved in the upper gastrointestinal tract within 15 min. Sustained-release morphine tablets were placed in sealed capsules along with an inert powder (lactose) to prevent the subject from recognizing the medication. Mexiletine and placebo were similarly packaged in sealed capsules that were identical in appearance.

### Outcome Measures

The primary outcome measure was the average change in overall pain intensity from the baseline to the last week of maintenance therapy, using a numerical scale to rate pain (with 0 corresponding to no pain and 10 corresponding to the worst pain imaginable). Baseline pain measurements for the first period were taken as the average of the pain ratings during the last week of the baseline phase, and for the second and third treatments were obtained during the drug-free week after the tapering of the previous treatment. Patients were asked to rate their overall pain because patients with stump and phantom pains had difficulty rating their pains separately.

Secondary outcomes included other measures of pain, such as pain relief (0–100%) and the interference and general activity subscales from the Multidimensional Pain Inventory.<sup>21</sup> Pain relief and functional assessments were completed at the end of the drug-maintenance and drug-taper phases. Finally, the presence of common medication-related side effects (*i.e.*, dizziness, drowsiness, nausea, constipation) was assessed during the twice-weekly calls to the patient. If the patient indicated the presence of a side effect, the severity (*i.e.*, mild, moderate, or severe) was assessed on a 3-point Likert scale.

### Statistical Analysis

The primary outcome was the change in mean pain score during the last week of the assigned drug treatment from the respective pretreatment baseline. Sample size was calculated based on previous estimates of variance in pain scores in neuropathic pain patients<sup>22,23</sup> and included a correction for the three planned pairwise comparisons (*i.e.*, placebo *vs.* each treatment and comparison of morphine with mexiletine). We calculated that 38 patients would be required to provide the study with 90% power to detect (with a two-tailed  $\alpha$  of 0.05) a mean difference in pain intensity among two drug treatments that was equivalent to 1.5 points (SD = 2.0). On the basis of previous dropout rates in a clinical trial using a similar study design,<sup>23</sup> we calculated that if 60 patients were enrolled, 38 would complete all three treatment periods.

Data from treatment periods were considered for analysis when patients took at least one dose of drug and provided subsequent ratings of pain. We also performed separate analyses on data from only those patients who had data from all three treatment periods because we were concerned that dropouts might be different from their nondropout colleagues in their response to treatment for some reason (*e.g.*, noncompliance). These analyses showed almost identical treatment effect in that the effect of the drugs in this subgroup was only minimally different (6% for morphine and 14.6% for mexiletine) than in the entire population. The number needed to treat (NNT) to achieve a reduction in pain intensity of 33% or greater (NNT<sub>33</sub>) and 50% or greater (NNT<sub>50</sub>) was also calculated. Because of the longitudinal nature of the data, general estimating equations were used to model the effects of drug treatment and the effects of time, which accounts for the correlation of repeated observations within subjects.<sup>24</sup> Data on the frequency of side effects were compared using chi-square statistics. We examined whether carryover effects associated with the first and second drug administrations influenced the subsequent baseline period pain ratings, using analysis of variance. Statistical analysis was performed using SAS 9.1 software (SAS Corporation, Cary, NC). A *P* value less than 0.05 was considered statistically significant.

## Results

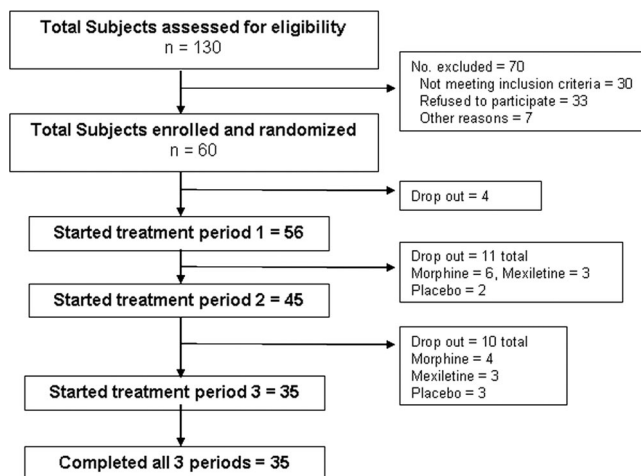
A total of 130 subjects were screened between 1999 and 2003. Of these, 30 subjects were not eligible for inclusion, primarily because of pain that was occasional or intermittent and of intensity that was lower than the inclusion criteria or because of the presence of concomitant end-stage hepatic or renal disease. Thirty-three subjects refused to participate, and the most common reason provided was difficulty in transportation for the multiple visits and seven were excluded for other reasons. Sixty subjects with postamputation pain of 6 months or longer were enrolled. Demographic data are shown in table 1. Of the 60 subjects randomized, 35 reported evaluable data from all three drug periods, 45 reported evaluable data from two drug periods (dropouts: 4 morphine, 3 mexiletine, 3 placebo), 56 reported evaluable data from one drug period (dropouts: 6 morphine, 3 mexiletine, 2 placebo), and 4 decided not to participate after randomization; therefore, data from 56 of 60 subjects were included in the statistical analysis (fig. 2). The mean ( $\pm$  SD) dosages used of morphine and mexiletine were  $112 \pm 62.7$  (range, 15–180) mg and  $933 \pm 257$  (range, 300–1200) mg, respectively.

Pain intensity scores are shown in figure 3 for all treatment periods, including data for patients who did not complete all treatments. The average change in pain intensity from baseline was  $-1.4$  (95% confidence inter-

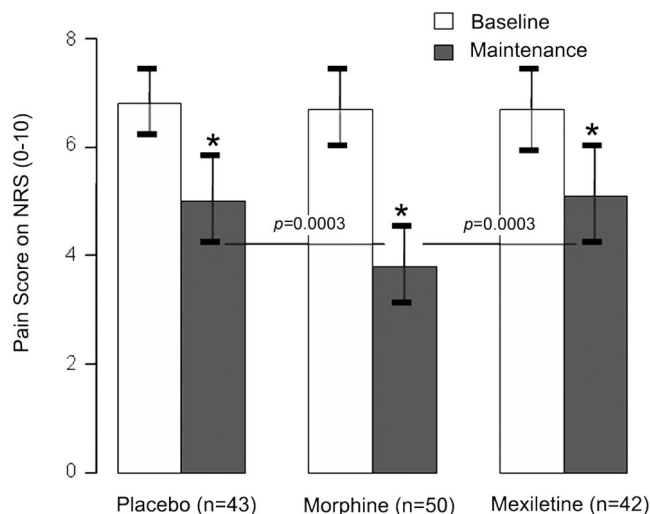
**Table 1. Demographic Data (n = 60)**

Age, mean ± SD, yr	63.4 ± 16.4
Education	
< 12 yr	21
> 12 yr	39
Sex	
Male	47
Female	13
Employment	
Employed	11
Disabled	27
Other	22
Ethnicity	
White	51
Nonwhite	9
Duration of pain, mean ± SD, months	51.3 ± 71.4
Type of pain	
Phantom pain	8
Stump pain	8
Both	44
Etiology	
Trauma	26
Vascular	22
Other	12
Side of amputation	
Right	25
Left	31
Both	4
Site of amputation	
Lower limb	48
Upper limb	12

val,  $-2.2$  to  $-0.6$ ) for placebo,  $-1.5$  (95% confidence interval,  $-2.2$  to  $-0.9$ ) for mexiletine, and  $-2.8$  (95% confidence interval,  $-3.4$  to  $-2.3$ ) for morphine ( $P < 0.0001$  vs. baseline for all three groups). *Post hoc* analysis showed that morphine treatment was significantly superior in providing analgesia compared with placebo ( $P = 0.0003$ ) and mexiletine ( $P = 0.0003$ ). Self-reported pain relief data are shown in figure 4. The mean self-reported percent pain relief during treatment was 53% for morphine, 30% for mexiletine, and 19% for placebo for all evaluable periods in which one or more doses of

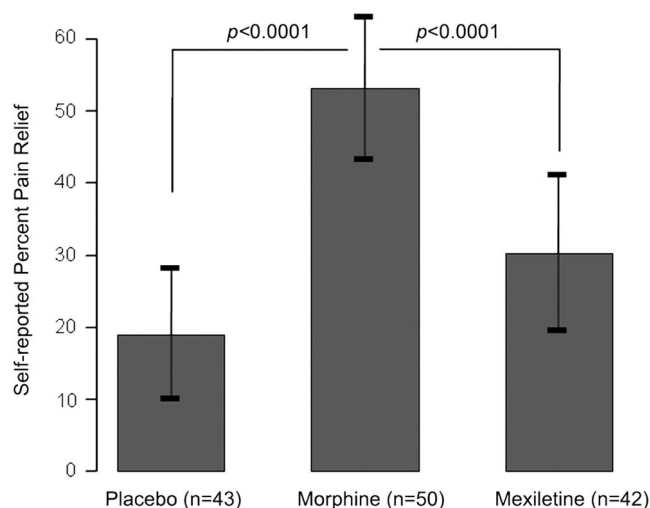


**Fig. 2.** Flow of study subjects. This figure shows the flow of subjects through the study once enrolled, the number excluded, and the number of dropouts at each stage.



**Fig. 3.** Average numerical pain ratings before and after treatment with morphine, mexiletine, and placebo. The figure compares self-reported baseline pain scores on a numeric rating pain scale (NRS; 0–10). All treatments resulted in significantly lower ( $* P < 0.0001$ , baseline vs. maintenance) pain scores compared with baseline; however, *post hoc* general estimating equation analysis showed that morphine resulted in significantly lower pain scores compared with mexiletine ( $P = 0.0003$ ) and placebo ( $P = 0.0003$ ).

a drug were taken by the subject. The administration of opioids resulted in significantly higher mean self-reported percent pain relief compared with placebo ( $P < 0.0001$ ) or mexiletine ( $P < 0.0001$ ). The proportion of responders with 33% and 50% change in pain intensity with the active drugs and placebo and the calculated NNT are shown in table 2. The proportions of subjects who experienced a 33% decrease in pain intensity for morphine, mexiletine, and placebo were 66, 38, and 44%, respectively. The proportions of subjects who experienced a 50% decrease in pain intensity for morphine,



**Fig. 4.** Percentage self-reported pain relief between placebo, morphine, and mexiletine. The use of morphine was associated (general estimating equation model) with significantly higher self-reported percentage pain relief error bars compared with mexiletine ( $P < 0.0001$ ) and placebo ( $P < 0.0001$ ).

**Table 2. Number Needed to Treat**

	Morphine	Mexiletine	Placebo
Subjects with 33% decrease in pain intensity	33/50 (66%)	16/42 (38%)	19/43 (44%)
NNT <sub>33</sub>	4.5	NA	NA
Subjects with 50% decrease in pain intensity	23/50 (46%)	11/42 (26%)	13/43 (30%)
NNT <sub>50</sub>	5.6	NA	NA

NA = not applicable; NNT<sub>33</sub> = number needed to treat for 33% reduction in pain intensity; NNT<sub>50</sub> = number needed to treat for 50% reduction in pain intensity.

mexiletine, and placebo were 46, 26, and 30%, respectively. The cumulative proportions of subjects with varying degrees of reduction in pain intensity (0–100%) during the three treatment periods are shown in figure 5.

Side effect data are shown in table 3. Forty-one patients reported side effects: 27 for the morphine group, 7 for the mexiletine group, and 7 for the placebo group. When the side effects were analyzed individually, the incidence of only constipation (but not nausea, drowsiness, or dizziness) was higher for morphine compared with either mexiletine or placebo ( $P < 0.001$ , morphine compared with placebo or mexiletine). The side effects were rated as moderate or severe in 20 of 27 patients who received morphine, in 2 of 7 who received mexiletine, and in 1 of 7 who received placebo.

There were no differences between groups with regard to the effects of study drug on self-reported levels of overall functional activity and pain-related interference in daily activities as assessed by the Multidimensional Pain Inventory. Finally, we investigated the possibility of

**Table 3. Side Effects**

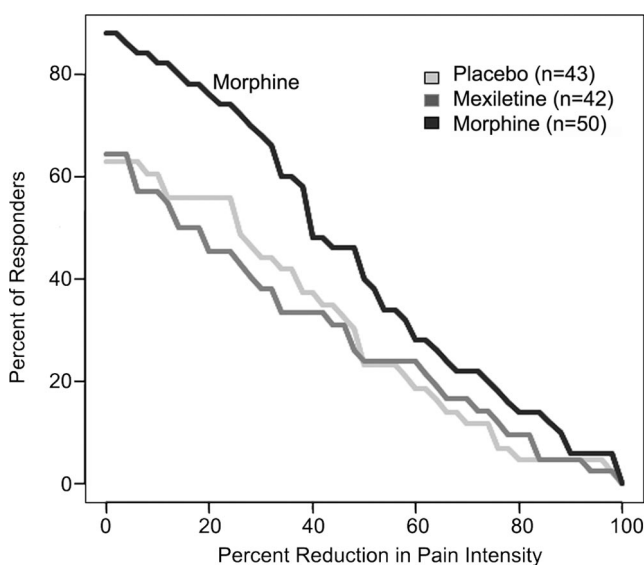
Type of Side Effect	Morphine (n = 50)	Mexiletine (n = 42)	Placebo (n = 43)	P Value
Constipation	17	2	2	<0.001
Nausea	4	0	1	0.11
Drowsiness	9	4	3	0.41
Dizziness	2	2	2	0.98
Total subjects with side effects	27	7	7	<0.001

a carryover effect because it could be a potential weakness of our analysis. Although it was found that the first baseline period differed significantly from both the second and third baseline periods ( $P < 0.001$  in both cases), indicating a time effect, there was no evidence that the second period differed from the third ( $P > 0.10$ ). Analyses of variance performed to determine whether the first drug administered was associated with changes in subsequent baseline period pain ratings and the second drug administered was associated with changes in subsequent baseline period pain ratings revealed no evidence that the first drug caused a differing pain rating from the second baseline ( $P = 0.25$ ) or the second drug caused a differing pain rating from the third baseline ( $P = 0.58$ ). The baseline visual analog scale (SD) pain scores were 8.0 (1.9), 6.0 (2.0), and 5.5 (2.4) for baselines 1, 2, and 3, respectively. Therefore, we concluded that no significant drug carryover effects, independent of a time effect, occurred.

**Discussion**

Our results suggest that sustained-release morphine was significantly superior to both mexiletine and placebo in the treatment of postamputation pains. Treatment with morphine resulted in significantly lower pain intensity scores and greater mean percentage pain relief. Although the NNT<sub>50</sub> of 5.6 and NNT<sub>33</sub> of 4.5 for morphine suggest an analgesic efficacy less than opioids for other neuropathic pain (e.g., NNT<sub>50</sub> of 2.7 for postherpetic neuralgia), it is comparable to other agents, such as tricyclic antidepressants and gabapentinoids (mean NNT<sub>50</sub> ranging from 2.7 to 4.9), for the treatment of postherpetic neuralgia.<sup>23</sup> Although treatment with morphine resulted in an overall higher incidence of patients reporting moderate to severe side effects, particularly constipation, and several more dropouts, this did not seem to affect the patients' overall functional status.

A number of pharmacologic agents have been used for the treatment of postamputation pain; however, many of these analgesic agents have been administered in an uncontrolled fashion, with the long-term effectiveness of these approaches uncertain. Recent randomized controlled trials and meta-analyses of randomized controlled trials indicate a beneficial effect of opioids on certain



**Fig. 5. Percent of subjects with varying degrees of reduction in pain with morphine, mexiletine, and placebo. The graph presents the proportion of responders over the entire range of possible cutoff points to allow comparison of treatment groups at any responder level.**

neuropathic states, such as postherpetic neuralgia and diabetic neuropathy.<sup>25,26</sup> Studies of the efficacy of drugs in other neuropathic pain states are often used as the rationale for the treatment of postamputation pain with tricyclic antidepressants, anticonvulsant drugs, and opioids.<sup>14,15,27</sup> However, the mechanisms of postamputation pain may differ from those of other neuropathic pain states; hence, efficacy of a drug in commonly used models of neuropathic pain, such as diabetic neuropathy or postherpetic neuralgia, may not predict its usefulness in postamputation pain states. For example, in a recent randomized controlled trial, gabapentin (a recommended first-line drug for neuropathic pain) failed to demonstrate a reduction in the intensity or incidence of postamputation pain when administered during the first month after amputation.<sup>13</sup> Our findings extend previous trials that demonstrated the efficacy of morphine in phantom pain in a small number of patients<sup>28</sup> and of the weak opioid tramadol on postamputation pain.<sup>29</sup>

Morphine and other opioids may be efficacious for the treatment of postamputation pain for several possible reasons. At the spinal level, opioids are widely recognized in producing analgesia *via* presynaptic and postsynaptic effects on pain-signaling neurons. In addition, opioids are important in the descending modulation of nociception. Finally, through their central actions, opioids may diminish cortical reorganization (*i.e.*, topographic representation of the lost extremity may be taken over by sensory input from other areas of the body, resulting in perceptual remapping after amputation)<sup>10,30-32</sup>—a reflection of the plasticity of the somatosensory cortex. Previous studies indicate a correlation between the intensity of phantom limb pain and the extent of cortical reorganization.<sup>32</sup> In a placebo-controlled, double-blind, randomized controlled trial that evaluated the efficacy of oral sustained-release morphine *versus* placebo in 12 patients with phantom limb pain, a significant reduction in phantom pain was noted in patients who received morphine but not placebo.<sup>28</sup> In this small sample, pain reduction of 50% or greater was noted in 42% of patient who received morphine, with the dose of sustained-release morphine titrated to at least 70 mg/day up to a maximum of 300 mg/day. Neuromagnetic source imaging suggested evidence for reduced cortical reorganization with morphine treatment but not with placebo.<sup>28</sup> Indirect support for diminished cortical reorganization after opioid therapy comes from our previous observations that indicated that intravenous morphine effectively diminished both stump and phantom pain.<sup>20</sup> Nevertheless, it should be noted that the analgesic efficacy of morphine noted in our relatively short-term study is less than that seen for other neuropathic conditions,<sup>23</sup> and the overall efficacy of morphine in our study may be limited by the significantly higher incidence of side effects with morphine.

In comparison, other data indicate that mexiletine may not be efficacious for the treatment of neuropathic pain. In a randomized, placebo-controlled, crossover study in 20 subjects with varying neuropathic pain states associated with prominent allodynia, no differences in pain scores, area of allodynia, or quality-of-life assessments were noted between those who received mexiletine (maximum dose of 900 mg/day) or placebo.<sup>33</sup> In another randomized, placebo-controlled, crossover study that examined the analgesic efficacy of mexiletine (maximum dose of 600 mg/day) *versus* placebo for the treatment of human immunodeficiency virus-related painful peripheral neuropathy, no differences were found between the groups in mean daily pain scores, with multivariate analyses showing no apparent differences in the analgesic response to mexiletine *versus* placebo.<sup>34</sup> Another study of mexiletine for the treatment of human immunodeficiency virus-related painful peripheral neuropathy did not result in significant pain relief.<sup>35</sup> Compared with placebo, mexiletine was found to have no significant effect on most neurosensory thresholds and pain assessments after application of intradermal capsaicin, suggesting that mexiletine has minimal effect on human experimental pain.<sup>36</sup>

The following limitations to our study are worthy of discussion. Although mexiletine was a pharmacologic option for the treatment of postamputation pain when this trial was designed, mexiletine is currently recommended only as a third-line medication for the treatment of neuropathic pain.<sup>14</sup> However, whether newer selective sodium channel-blocking agents demonstrate more analgesic efficacy than mexiletine needs further investigation. Another limitation is the relatively short-term duration (26 weeks total, with 6-week exposure to the drugs) and scope of pain assessments. As such, our results may not correlate with the clinical effectiveness of the drugs over a longer time frame (*i.e.*, months to years). In addition, we did not assess and analyze stump and phantom pains separately because patients who had both stump and phantom pains had difficulty rating their pains separately. Therefore, a differential analgesic response of stump and phantom pains to morphine or mexiletine might not have been detected by the study. A carryover effect of study medications from one treatment group to the next is a potential confounding factor in this type of study. However, the carryover effects were probably minimal, because the baseline pain scores before each treatment were not significantly different between groups. In addition, our analysis (see last paragraph in Results section) to specifically assess the presence of significant carryover effects revealed none. The number of dropouts has the potential for introducing bias, as subjects may not have completed the trial because of excessive pain or intolerable side effects. However, data from dropouts were included in the analyses, thereby protecting against this type of bias. In addition,

it is possible that subjects might have unknowingly (to us) taken some other analgesic agents that may have affected the pain scores. If a considerable number of subjects did so, there may have been smaller or even no differences in pain scores between the groups; however, there were significant differences in pain scores between the groups. In addition, it is possible that patients may have been unblinded with use of an inactive placebo, because use of an active placebo (such as diphenhydramine) has been recommended to prevent unmasking of the double-blind design.<sup>37</sup> However, this study had more protection against this potential bias because it was not just a comparison to inert placebo. Morphine was superior to mexiletine, a drug that presumably produced mild side effects in many patients. Finally, we were unable to analyze any differences between phantom and stump pains because our patients often had difficulty separating phantom and stump pains, which is consistent with similar reports in the literature.<sup>38</sup>

In summary, we performed a placebo-controlled, double-blind, randomized crossover trial to determine the analgesic efficacy of oral mexiletine and sustained-release morphine for the treatment of postamputation pain. Our data provide additional evidence for the analgesic efficacy of opioids for the treatment of neuropathic pain such as postamputation pain. Despite the analgesic efficacy of opioids, there was no improvement in self-reported levels of overall functional activity and pain-related interference in daily activities (as assessed by the Multidimensional Pain Inventory). In addition, clinicians should be aware of the incidence of side effects with use of opioids, and careful screening of patients may be prudent to minimize the risk for iatrogenic addiction.<sup>39</sup> Although mexiletine did not provide significant relief compared with opioids in the treatment of postamputation pain and currently has limited use for the treatment of neuropathic pain, other pharmacologic therapies such as tramadol<sup>29,40</sup> or newer sodium channel blockers may also be efficacious in the treatment of postamputation pain. Future studies are needed to examine the long-term efficacy of opioids and other newer agents in the treatment of postamputation pain and to directly compare the most efficacious therapies in an effort to facilitate a definitive algorithm for treatment.

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