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## Mexiletine Therapy for Chronic Pain: Survival Analysis Identifies Factors Predicting Clinical Success

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### Abstract

Mexiletine, a sodium channel blocker, treats neuropathic pain but its clinical value has been questioned due to its significant side effects and limited efficacy. We hypothesized that ongoing therapy with mexiletine would have limited patient acceptance, but that an analgesic response to intravenous (IV) lidocaine (a pharmacologically similar drug) would identify patients most likely to choose ongoing therapy with mexiletine. We identified a cohort of 37 patients with neuropathic pain who underwent IV lidocaine infusions at our institution and were subsequently prescribed mexiletine. Time until discontinuation of mexiletine was used as the primary endpoint. Time until discontinuation is a clinically relevant, discrete, objective endpoint gaining acceptance as a metric for assessing clinical performance of drugs with significant side effects and limited efficacy. We used the techniques of survival analysis to determine factors that predicted continued therapy with mexiletine. Median time to discontinuation of mexiletine was only 43 days. A stronger analgesic response to IV lidocaine significantly predicted continued acceptance of mexiletine therapy. Decreasing age and male gender also predicted continued acceptance of mexiletine therapy. Analyzing time to mexiletine discontinuation uncovers important limitations in mexiletine's clinical performance missed by studies with conventional endpoints, such as change in pain score. Despite claims of efficacy, acceptance of mexiletine therapy is poor overall. Test infusions with lidocaine identify patients most likely to continue mexiletine therapy. Further work is needed to confirm these results and evaluate the relative acceptance of mexiletine vs. other treatments of neuropathic pain.

### Keywords

Pain; neuropathic pain; mexiletine; intravenous lidocaine; lidocaine; survival analysis; chronic pain

### Introduction

Mexiletine is a class IB sodium channel blocker used to treat chronic neuropathic pain, a disorder afflicting 5.5 million Americans.<sup>1</sup> Tremont-Lukats et al. recently confirmed mexiletine's analgesic efficacy for neuropathic pain in a meta-analysis.<sup>2</sup> However, mexiletine induces nausea in up to 40% of patients and dizziness in up to 26% of patients.

Previous studies of oral mexiletine treatment have focused on conventional analgesic endpoints without integrating factors promoting treatment failure, such as side effects. These studies have focused on narrowly defined measures of efficacy (e.g., relief of spontaneous pain or mechanical allodynia) but have not captured an overall measure of mexiletine's clinical performance. In the absence of a more global measure indicating that mexiletine's limited efficacy offsets its prominent side effects, experts have recently questioned its clinical value.<sup>3</sup> One clear clinically relevant indication of overall treatment failure with mexiletine is the choice to discontinue it. Therefore, time until mexiletine discontinuation can be used as a discrete measure of overall mexiletine performance, integrating factors both promoting and discouraging continued treatment.

No studies have measured the proportion of patients who accept chronic therapy with mexiletine or what factors predict acceptance vs. discontinuation. Previous pilot studies of mexiletine used response to intravenous (IV) lidocaine, another class IB sodium channel blocker, to predict subsequent mexiletine response, as defined by relief of spontaneous pain<sup>4</sup> or mechanical allodynia.<sup>5</sup>

On the basis of mexiletine's limited efficacy and prominent side effects, we hypothesized that most patients with neuropathic pain would not accept chronic therapy with mexiletine. We further hypothesized that patient discontinuation of chronic mexiletine therapy could be predicted by poor results from a previous analgesic IV lidocaine test infusion.

To test our hypotheses, we conducted a retrospective cohort study of neuropathic pain patients who were treated with mexiletine following a lidocaine infusion at the Stanford Pain Management Center. Patient acceptance of mexiletine therapy was evaluated by measuring time to discontinuation. Time to discontinuation is a direct indicator of patient acceptance of chronic therapy and has been espoused as a clinically relevant, discrete composite endpoint of efficacy and side effects.<sup>1,6-8</sup> We analyzed time to discontinuation of mexiletine therapy using the tools of survival analysis (Kaplan-Meier and Cox proportional hazards) to determine factors responsible for failure of chronic mexiletine therapy.

## Methods

### Design and Setting

We conducted a retrospective cohort study of patients who had undergone IV lidocaine infusions for treatment of neuropathic pain at the Stanford Pain Management Center, a tertiary referral-based pain management center. The study was approved by our institutional review board.

### Study Participants

Patients were identified retrospectively by screening sequential charts of patients currently under treatment at the Stanford Pain Management Clinic. We randomly selected three separate starting points in the alphabet—charts that began with the letters A, K, and R. Three starting points were used to reduce the possibility of bias being introduced by selecting only names that began with a particular letter (which might enrich for specific ethnic groups). All patients who were prescribed mexiletine were included in the analysis. Patients were referred for IV lidocaine infusions based on findings suggestive of neuropathic pain, including hyperalgesia, allodynia, hypoesthesia, and hyperesthesia.

### Lidocaine Infusions

Patients had an IV catheter placed. Then, during approximately one hour, they received a stepwise, computer-controlled lidocaine infusion to a targeted plasma level of 5 mcg/mL

using a paradigm previously developed in our institution.<sup>9</sup> At the time of the infusion, a record was completed for all patients documenting initial and final Numerical Rating Scores (NRS) of pain. Blood pressure and pulse oximetry were monitored continuously throughout the infusions.

### **Post-Lidocaine Oral Therapy**

Patients without an analgesic response to lidocaine were not offered mexiletine. Patients with any decrease in NRS following lidocaine infusions were offered ongoing treatment with oral mexiletine or other analgesics at the discretion of the treating physician. All patients prescribed mexiletine were given an identical standard clinic dosing titration schedule, which guided dose escalation to the minimum effective dose over one month, starting at 150 mg/day and not exceeding 900 mg/day of mexiletine.

### **Data Collection and Independent Variables**

Lidocaine infusion records included initial and final NRS. Lidocaine response was defined as  $(\text{initial NRS} - \text{final NRS}) / \text{initial NRS}$ . Independent variables analyzed to predict subsequent oral regimen success were obtained from clinic intake forms filled out by the patients prior to their infusions at the time of their initial evaluation in the pain clinic. Independent variables examined included patient's age, gender, pain location, duration of pain problem, previous trials of anticonvulsants, tricyclic antidepressants, venlafaxine, duloxetine, antiarrhythmics, opioids, and nonsteroidal anti-inflammatory drugs (NSAIDs).

### **Primary Outcome**

Our primary outcome was time to discontinuation of subsequent oral therapy with mexiletine. Patient charts were reviewed for prescriptions of mexiletine started following lidocaine infusions. Initial prescription dates were obtained from the prescriptions. Date of discontinuation was ascertained from clinic notes, pharmacy records, and patient interviews for all patients prescribed mexiletine. Discontinuation dates could not be ascertained for three patients.

### **Analysis**

Cox proportional hazard models and Kaplan-Meier survival curves were used to examine predictors of discontinuation of oral therapy. Model selection was performed by stepwise reduction from the full model until overall model strength was maximized, as assessed by Akaike information criteria. SAS version 9.1 (SAS Institute, Cary, NC) was used for all analysis.

## **Results**

### **Patient Identification**

We screened 635 alphabetically sequential charts of patients currently treated at the Stanford Pain Management Clinic. Our goal was to identify 100 patients who had undergone IV lidocaine infusions from whom to identify people subsequently given mexiletine. We actually identified 99 patient infusions, following which 37 patients had been given a prescription for mexiletine. All identified patients who underwent lidocaine infusions, and were subsequently prescribed mexiletine were included. All 37 patients prescribed mexiletine had undergone an IV lidocaine infusion first, and had written concurrent records of their analgesic response to lidocaine. Patient characteristics are displayed in Table 1.

## Overall Acceptance of Mexiletine

Patient acceptance of chronic mexiletine therapy was poor (Fig. 1). Median time until discontinuation of mexiletine was 43 days (95% confidence interval 26–73 days), and fewer than 20% of patients who started on mexiletine continued the therapy past a year.

## Factors Contributing to Patient Acceptance of Mexiletine Therapy

Cox proportional hazard models demonstrate that the degree of analgesia during lidocaine infusions, gender, and age each significantly contributes to patient acceptance of mexiletine therapy.

In contrast, a history of failed treatment with opioids, antineuropathic agents, and NSAIDs did not predict failure of mexiletine, nor did duration of the patients' pain or concurrent use of other antineuropathic pain medications.

Analgesic response to IV lidocaine—defined as (initial NRS – final NRS)/initial NRS—strongly predicted increased patient acceptance of oral mexiletine therapy (see Table 2). Each 20% decrease in analgesic response to lidocaine increased the rate of mexiletine discontinuation by 30% ( $P < 0.03$ ). A full report on the distribution and predictors of lidocaine analgesia is reported elsewhere.<sup>10</sup>

Gender also had a significant impact on patient acceptance of mexiletine therapy. Men discontinued mexiletine at a rate that was 67% lower than among women ( $P < 0.02$ ). Advancing age had a deleterious effect on patient acceptance of mexiletine therapy. Each additional decade of advancing age was associated with a 43% increase in the rate of mexiletine discontinuation ( $P < 0.05$ ).

## Discussion

Previous studies of oral mexiletine treatment have focused on analgesic endpoints without assessing the degree to which its limited efficacy and prominent side effects limit its real world performance. Tremont-Lukats et al. recently confirmed mexiletine's analgesic efficacy for neuropathic pain in a meta-analysis.<sup>2</sup> However, the mean decrease on a 100-point VAS score was only 11, leading experts to question mexiletine's clinical use and specifically call for an integrated assessment of mexiletine's efficacy and side effects.<sup>3</sup> However, historically there has been no consensus on how to evaluate the overall clinical performance of an analgesic drug such as mexiletine, one that has inconsistent analgesia and common overwhelming side effects.

We present a novel approach for evaluating chronic oral analgesic drug performance using time until drug discontinuation. Time to discontinuation recently has been espoused as a clinically relevant, discrete composite endpoint of drug efficacy and side effects,<sup>6,8</sup> and experts have specifically advocated using time to discontinuation to evaluate analgesic drug performance.<sup>1,7</sup> We used time to discontinuation as a broader measure of mexiletine's performance that integrates factors both promoting and curtailing continued use of mexiletine. Our ability to identify three separate factors that independently predict patient acceptance of chronic mexiletine therapy in a multivariate model demonstrates the power of this type of analysis.

Using the techniques of survival analysis to analyze these data eliminates problems associated with other types of longitudinal data analysis associated with missing data and patient dropout. In particular, it avoids using common statistical techniques, such as the "last observation carried forward" technique, to impute values for missing data that result in bias and the appearance of greater accuracy than actually exists.<sup>6</sup>

Our results quantify for the first time the natural history and limitations of chronic mexiletine therapy for neuropathic pain. Analyzing time to mexiletine discontinuation uncovers important limitations in mexiletine's clinical performance missed by studies with conventional endpoints such as change in pain score. We describe the magnitude of clinical failure with mexiletine: 50% of the patients discontinued treatment within 43 days, and fewer than 20% continued treatment for a year. A small minority of patients chose to continue on long-term mexiletine therapy, suggesting it may have a clinical niche. Our study is the first to identify patient characteristics that can be used to help target mexiletine to this minority population. Our data indicate that younger patients, men, and those with more profound analgesic lidocaine responses are the most likely to continue chronic mexiletine therapy. To our knowledge, this is the first study defining the factors that predict patient continuation of any pharmacotherapy in the treatment of neuropathic pain.

In this study, IV lidocaine response strongly predicted patient acceptance of chronic mexiletine therapy. One previous pilot study with nine patients with neuropathic pain found a positive correlation in relief of spontaneous pain between IV lidocaine and oral mexiletine.<sup>4</sup> Another group reported a positive correlation in relief of mechanical allodynia in a cohort of 13 patients with peripheral nerve injury.<sup>5</sup> Data from the cardiac arrhythmia literature also suggest that IV lidocaine predicts mexiletine efficacy.<sup>11</sup> We extend these findings and show that more profound IV lidocaine analgesic responses predict diminished rates of mexiletine discontinuation in the clinical setting. These data support the use of lidocaine infusions to target appropriate populations with mexiletine therapy.

There are significant limitations to this study. We hypothesized that IV lidocaine response would predict acceptance of mexiletine therapy. However, age and gender were found to influence patient acceptance in an exploratory analysis rather than through hypothesis-driven research. Therefore, these findings need to be replicated in further studies.

This study is retrospective and subject to bias inherent in such studies. Selection and respondent bias were minimized by including all patients among the 635 charts screened who were started on mexiletine following a lidocaine infusion. To minimize observer bias, all lidocaine infusion data and information regarding pain severity, duration, gender, age, and medication use were ascertained from concurrent records recorded at the time of the infusions or initial clinic visit. There was nonrandom assignment of who was given mexiletine. We refrain from contrasting those given mexiletine to those patients not prescribed mexiletine following the lidocaine infusion specifically because that assignment (at the discretion of the treating physician) was not random and would introduce selection bias invalidating any subsequent *between-group* comparisons. It is for this specific reason that this is not a cohort study of the subsequent oral therapy of 99 patients who underwent a lidocaine infusion, but rather is a cohort study of the 37 patients assigned to mexiletine therapy following a lidocaine infusion. We limit our conclusions to those that can be validly derived from the *within-group* comparisons among those given mexiletine.

It is conceivable that patients might discontinue a medication due to symptom resolution. In our study, of the 37 patients started on mexiletine only one had resolution of symptoms—following surgical decompression of thoracic outlet syndrome. We do not know if the others who discontinued mexiletine therapy did so due to overwhelming side effects, inadequate efficacy, or both. We were not able to pair discontinuation data with concurrent subjective assessments of pain relief and side effects. As a result, we cannot infer whether age, gender, and lidocaine response predict mexiletine's analgesia, side effects, or both. Future work would be strengthened by pairing this *objective* behavioral endpoint (time to discontinuation) with patient reports of their *subjective* unobservable internal experience of analgesia and side effects.

Further work needs to be done to confirm and expand predictors of mexiletine acceptance and evaluate prospectively if other drugs are better accepted than mexiletine. Furthermore, the methodology of using time to discontinuation to evaluate real world performance of analgesics should be considered as a possible way of assessing which of the many promoted medications for neuropathic pain is most effective. Results from such analysis would speak directly to the clinician's current dilemma of which initial therapy for neuropathic pain is best.

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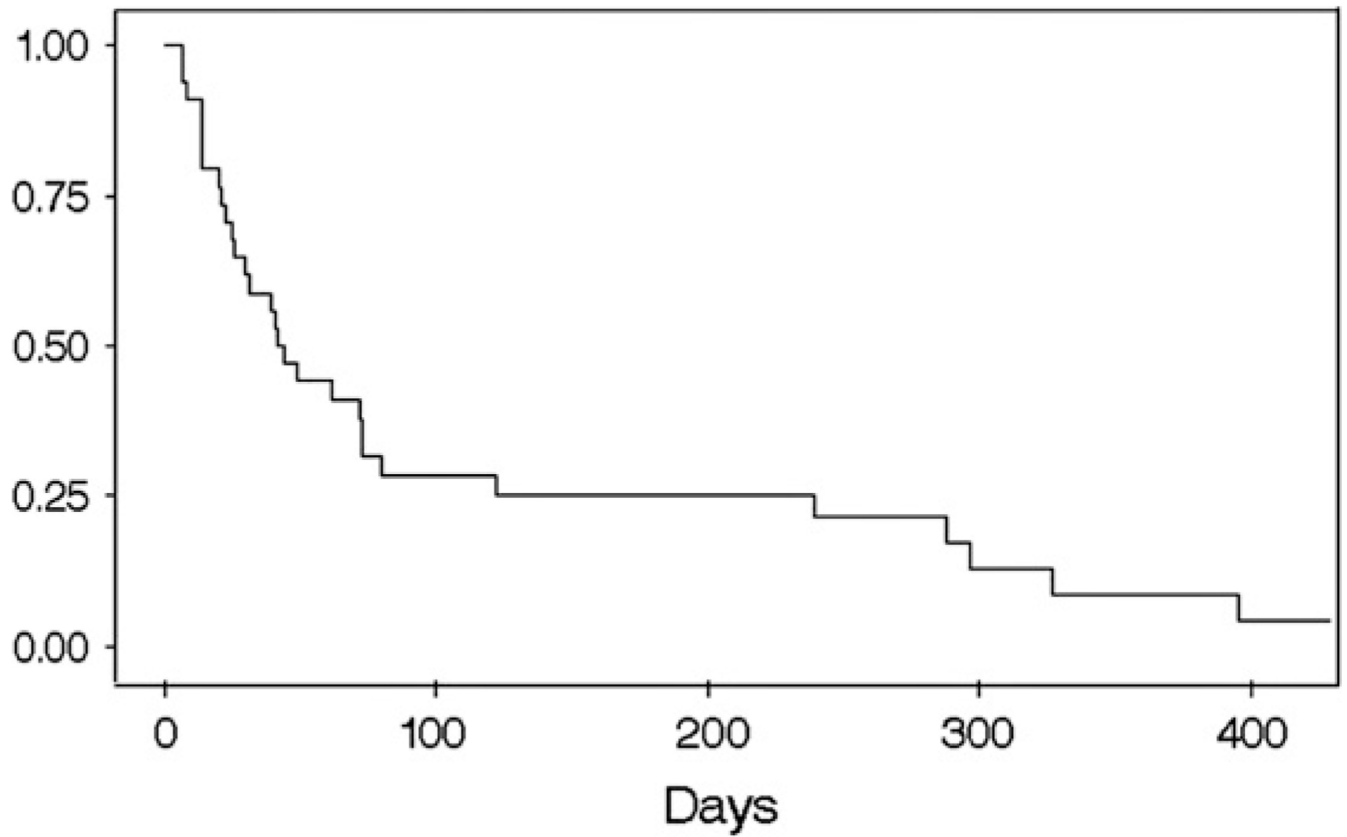
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## Proportion of Patients Continuing Mexiletine



**Fig. 1.** Discontinuation of mexiletine is rapid and highly prevalent. Median time to discontinuation is 43 days (95% confidence interval 26–73 days).

**Table 1**

## Patient Characteristics at Baseline

| Characteristic                         | Mean   | Range |
|--|--------|-------|
| Age                                    | 49.3   | 16–78 |
| Gender (percent male)                  | 39.2   |       |
| Baseline Pain Score <sup>a</sup>       | 6.3    | 3–10  |
| Duration (years)                       | 6.6    | 1–42  |
| Previous antineuropathics <sup>b</sup> | 1.3    | 0–8   |
| Previous opiates                       | 2.9    | 0–8   |
| Previous NSAIDs                        | 2.1    | 0–6   |
| Diagnosis                              | Number |       |
| Radiculopathy                          | 15     |       |
| Complex regional pain syndrome         | 6      |       |
| Central pain                           | 3      |       |
| Spinal stenosis                        | 2      |       |
| Other                                  | 15     |       |

<sup>a</sup>Pain Score are verbal Numerical Rating Score, report from 0 to 10.

<sup>b</sup>Antineuropathics included anticonvulsants, antiarrhythmics, tricyclic antidepressants, venlafaxine, and duloxetine.



**Table 2**

## Factors Promoting Mexiletine Discontinuation

| <b>Factor</b>           | <b>Hazard Ratio</b> | <b>P-Value</b> |
|-------------------------|---------------------|----------------|
| IV Lidocaine response   | 0.70                | 0.03           |
| Male gender             | 0.33                | 0.02           |
| Age                     | 1.43                | 0.05           |
| Number of opiates tried | 0.87                | 0.31           |

Cox proportional hazards presented per 20% change in lidocaine response and decade of age.