Retrospective Cohort Study

Mexiletine Usage in a Chronic Pain Clinic: Indications, Tolerability, and Side Effects

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Background: Background: Intravenous lidocaine has multiple applications in the management of acute and chronic pain. Mexiletine, an oral lidocaine analogue, has been used in a number of chronic pain conditions although its use is not well characterized.

Objectives: To report our experience using mexiletine in a chronic pain population, specifically looking at tolerability, side effects, and EKG changes.

Study Design: Retrospective, cohort study.

Setting: Multiple pain clinic locations in an integrated multispecialty health system.

Methods: All patients who had a mexiletine prescription between August 2015 and August 2016 were queried via the electronic medical record. Each chart was examined for demographics, QTc changes on EKG, length of use, and reasons for stoppage.

Results: There were 74 total patients identified in the chronic pain management clinics as receiving at least 1 mexiletine prescription over the 1-year time period. Twice as many women as men received mexiletine prescriptions. Neuropathic pain was the most common primary diagnosis (64%) which included diabetic neuropathy, radiculopathy, and others. Fibromyalgia was the next most common primary diagnosis (28%). A QTc change on the EKG showed a mean decrease of 0.1 ms and median increase of 1.5 ms. At 6 months (180 days), approximately 30% of the patients remained on mexiletine therapy, and 28% remained on the therapy at 1 year (360 days). Median duration of use was 60 days and the mean was 288 days. Neurologic and gastrointestinal side effects were the most commons reason for stoppage. All side effects were mild and resolved with stoppage. After side effects, lack of response, or loss of efficacy, were the next most common reasons for stoppage.

Limitations: Pain relief and outcomes were not specifically examined due to confounding factors including interventional treatments and multiple treatment modalities. This was a retrospective, cohort study limited to our specific clinic population with a relatively high loss to follow-up rate.

Conclusion: Mexiletine is rarely a first line option for chronic pain management and is often used when multiple other modalities have failed. By reporting our experience, we hope other clinicians may have more familiarity with the drug's use in a chronic pain practice. It appears reasonably tolerable, may not require frequent EKG monitoring, and can be an appropriate adjunct in the chronic pain population. More research is needed regarding efficacy and dose titration for mexiletine in chronic pain.

Key Words: Chronic pain, mexiletine, IV lidocaine, pain, neuropathic pain, neuropathy, fibromyalgia, QTc, tolerability

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Intravenous lidocaine infusions have found applications for pain management in multiple settings including neuropathic pain, fibromyalgia (1,2), perioperative pain (3), burn care (4), and the adolescent population (5).

Mexiletine was initially developed as a cardiac

antiarrhythmic as an oral analogue of lidocaine. It has been used as an adjuvant in neuropathic pain, fibromyalgia, headache, and erythromelalgia (6-8). However, it is not frequently prescribed by physicians for this purpose. This could be due to lack of efficacy, unfamiliarity with the drug's safety profile regarding cardiac conduction, or patient intolerability.

Our pain management clinic currently uses lidocaine and mexiletine therapy in the treatment of chronic pain, primarily neuropathic pain and fibromyalgia. Our protocol involves use of 2 successful lidocaine infusions followed by mexiletine initiation. Our protocol requires an EKG and assessment of the QTc interval prior to the initiation of the lidocaine infusion and with each subsequent mexiletine dose adjustment. There is a concern that mexiletine effects on cardiac conduction may result in an arrhythmia (9). The mexiletine dose is started at 150 mg daily and titrated up every 2 weeks to 150 mg 3 times a day.

This retrospective cohort study aims to report our experience with mexiletine by looking at the safety and tolerability by patients in our clinic. Specifically, we examine the effect of mexiletine on QTc, the rate of mexiletine tolerance and dropout, and reasons for discontinuation.

Methods

Following Institutional Review Board approval, we conducted a retrospective review via our electronic medical record (EMR). We reviewed patient records that were prescribed mexiletine in our multi-physician, 3-location chronic pain practice. Using our EMR, all patients who were prescribed mexiletine during the period of August 2015 to August 2016 were queried. Each patient's chart was then reviewed to collect demographic data, diagnosis, QTc changes, reason for stoppage, and length of use. Data points included: gender, age, diagnosis, QTc intervals before mexiletine initiation and on maximum dosage, presence of prior lidocaine infusion, date of initiation, date of stoppage or last follow-up date, and reason for stoppage. Length of use and dropout excluded those patients who never started mexiletine, or those who were already on mexiletine at the start of the study period. Chart review occurred in August 2017 to ensure at least 1 year had passed for all queried patients.

Results

Figure 1 is a flowchart examining the patients prescribed mexiletine in our study. There were 74 total patients identified in the chronic pain management clinics as receiving at least 1 mexiletine prescription over the one-year time period. Table 1 describes the age, gender, and primary diagnoses of the 74 patients prescribed mexiletine. Neuropathic pain was the most common primary diagnosis (64%) which included diabetic neuropathy, radiculopathy, and others. Fibromyalgia was the next most common primary diagnosis (28%). More

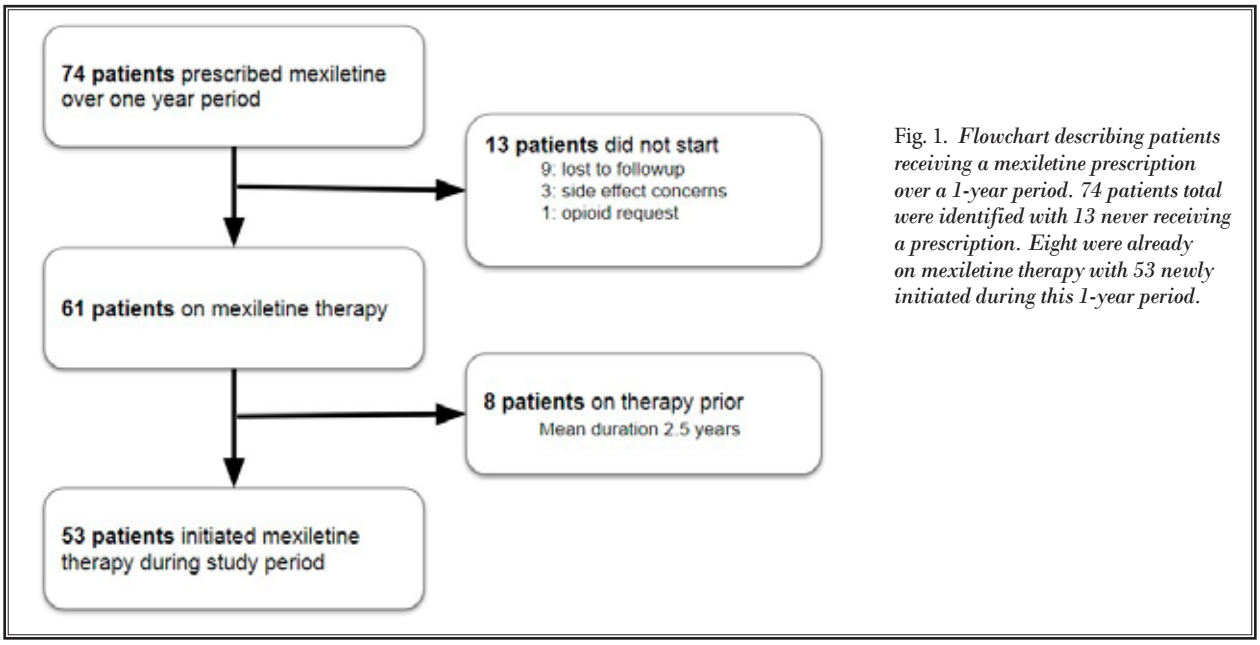

Fig. 1. *Flowchart describing patients receiving a mexiletine prescription over a 1-year period. 74 patients total were identified with 13 never receiving a prescription. Eight were already on mexiletine therapy with 53 newly initiated during this 1-year period.*

than twice as many women were prescribed mexiletine as compared to men.

Thirteen of the 74 patients never actually started the mexiletine. Nine were lost to follow-up, 3 had concerns over side effects, and one specifically requested opioid therapy. From the 61 remaining patients, 8 were already on mexiletine therapy at the start of the study. The average duration of treatment for these 8 patients was 2.5 years. QTc changes on the EKG were examined in this group of 61 patients. QTc change on EKG showed a mean decrease of 0.1 ms and median increase of 1.5 ms as shown in Table 2.

After removing the patients who were already on mexiletine therapy, 53 patients remained who were initiated on the mexiletine treatment. These patients were reviewed for tolerability and treatment dropout. Figure 2 shows the Kaplan Meier curve for length of treatment of mexiletine. At 6 months (180 days), approximately 30% of patients remained on therapy, and 28% remained on therapy at 1 year (360 days). Regard-

Table 1. *Age, gender, and primary diagnosis of all 74 patients receiving a mexiletine prescription.*

Average age	48 (range 22-82)
Gender	
Female	50 (68%)
Male	24 (32%)
Diagnosis	
Fibromyalgia	21 (28%)
Neuropathic pain	47 (64%)
Other	6 (8%)

Table 2. *QTc changes on EKG of the 61 patients on mexiletine therapy.*

Average change (ms)	-0.1
Median change (ms)	1.5
Standard deviation (ms)	21.7

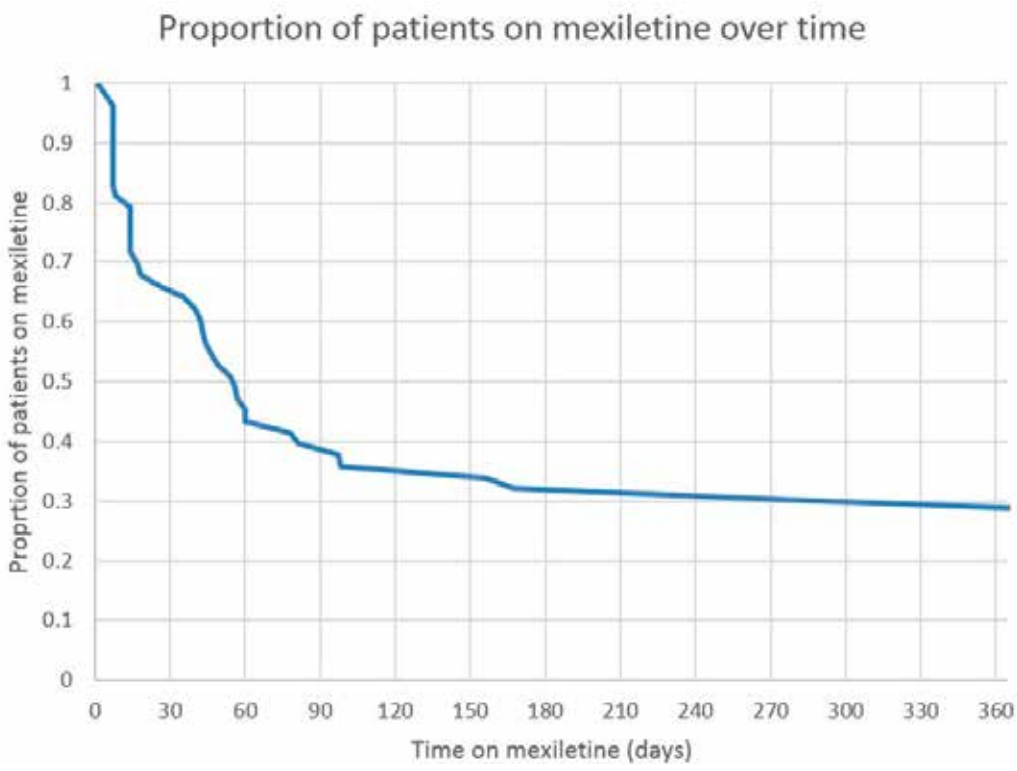

Fig. 2. *Kaplan Meier curve of those initiated on mexiletine during the study period, with minimum of one year follow-up. This includes 53 patients, excluding those who never started mexiletine and those already initiated on it during the study time period.*

ing duration of use, the median was 60 days and the mean 288 days.

Table 3 summarizes presence of previous successful lidocaine infusion. Regarding prior lidocaine infusion, 41 of 53 (77%) patients who initiated mexiletine during the study period had successful prior lidocaine infusions. Those that did not were primarily due to insurance coverage issues. Of these maintained on mexiletine for at least 6 months, 13 of 16 (81%) had a previous infusion, and of those maintained at one year, 12 of 15 (80%) had a previous infusion.

Table 4 describes reasons for discontinuation. Of 61 patients on mexiletine therapy, 45 (74%) stopped it at some point and 19 (31%) of these stopped it within 30 days. Neurologic and gastrointestinal side effects were the most commons reason for stoppage. Neurologic side effects included dizziness, lightheadedness, confusion, and anxiety. Gastrointestinal side effects included nausea, vomiting, and dry mouth. Cardiac side effects included feelings of palpitations.

All side effects were mild and resolved with stoppage. After side effects, lack of response, or loss of efficacy were the next most common reasons for stoppage with 13 patients (21%) overall and 2 patients (3%) within 30 days. A significant number stopped therapy for unknown reasons with 9 patients (15%) overall and 7 patients (11%) within 30 days. The majority of these were lost to follow-up.

Table 3. *Percentage of patients with prior lidocaine infusion for those initiated on mexiletine during study period.*

Total patients	41 of 53 (77%)
Mexiletine at 6 months	13 of 16 (81%)
Mexiletine at one year	12 of 15 (80%)

Table 4. *Reason for discontinuation of mexiletine. This is broken down into overall discontinuation rate during the entire study period, and for the first 30 days only. Neurologic side effects included dizziness, lightheadedness, confusion, and anxiety. Gastrointestinal side effects included nausea, vomiting, and dry mouth. Cardiac side effects included feelings of palpitations.*

Reason for discontinuation	30 days: n (%)	Overall: N (%)
Side effects		
Neurologic	4 (7%)	11 (18%)
Gastrointestinal	2 (3%)	5 (8%)
Cardiac	2 (3%)	3 (5%)
Ineffective	2(3%)	13 (21%)
Other	2 (3%)	4 (7%)
Unknown	7 (11%)	9 (15%)
Total	19 (31%)	45 (74%)

Discussion

Lidocaine has been studied in both the perioperative and chronic pain settings. Due to its high first-pass metabolism, it is only used in intravenous form. Mexiletine, a class IB sodium channel blocker that inhibits the Phase 0 of the action potential, is an oral analogue of lidocaine. One study showed lidocaine and mexiletine decrease the excitability of dorsal horn sensory neurons in rats by inhibiting sodium and potassium current (10). Another study suggests that axonal persistent sodium currents are increased in neuropathic pain and may be suppressed by mexiletine (11).

Our clinic generally starts mexiletine at 150 mg daily after 2 successful lidocaine infusions and titrates up to a maximum of 150 mg 3 times a day. We acquired a new EKG to monitor QTc for every dose change. Mean change was a 0.1 ms decrease in QTc while median change was a 1.5 ms increase. This is likely clinically insignificant, although standard deviation was 21.7 ms. There is a report in the literature of suspected Torsades de pointes due to mexiletine toxicity and is mentioned in the drug labeling (9,12). However, to our knowledge, this is the only report in the literature of mexiletine provoking arrhythmia or increasing the QTc, and in fact more recent sources suggest mexiletine may decrease QTc or even be used in the treatment of QT prolongation (12-14). Based on this, regular EKG monitoring may not be necessary for QTc monitoring.

Given its indicated use for ventricular arrhythmia, there is potential concern for drug interactions. The CYP2D6 and CYP1A2 enzymes are involved in its metabolism and consequently drugs altering these enzymes will affect mexiletine plasma levels. For example, use of phenytoin, rifampin, or phenobarbital has been shown to decrease mexiletine plasma levels while use of propafenone or cimetidine have been shown to increase mexiletine plasma levels in some patients (12). Interestingly, studies looking at mexiletine use with several antiarrhythmics and antihypertensives including propafenone, quinidine, propanolol did not result in changes in EKG intervals or increase arrhythmic activity, with some evidence showing enhanced antiarrhythmic activity (12). Nonetheless, cardiology consultation should still be considered for those at increased risk for arrhythmia.

One potential interaction of concern to pain physicians is the concurrent use of methadone with mexiletine given methadone's potential for QTc prolongation. While some of our population is on methadone and we did not note any adverse interactions, we did not track this specifically during our study. We believe these drugs can be used safely simultaneously given that mexiletine is antiarrhythmic and thought to actually decrease QTc interval. To our knowledge, no studies have examined the interaction between methadone and mexiletine, but there is potential of increased levels of both of these drugs due to their pharmacokinetics. We expect cutaneous lidocaine (patch, cream, or gel) can be used safely as well with mexiletine given the relatively low systemic uptake of the cutaneous formulation.

Regarding tolerability, one study (15) found a median time to discontinuation of mexiletine therapy for neuropathic pain at 43 days with fewer than 20% continuing at 1 year. This was thought to be due to both efficacy and tolerability. One of the predictive factors they note is success of a prior lidocaine infusion. Our study showed somewhat higher median time to discontinuation (60 days) and maintenance at 1 year (28%), although we did not initiate mexiletine for the majority of our patients unless they had successful prior lidocaine infusions. Our regular practice usually consists of mexiletine initiation after successful lidocaine infusion unless the patient declines or insurance refusal. Of note, the retention rate at 6 months (30%) was nearly the same as at 1 year (28%).

Our experience regarding tolerability and side effects is in line with the package label insert for mexiletine in that gastrointestinal and neurologic side effects are the most common reason for discontinuation (12). In this labeling, 10-40% of patients are noted to have gastrointestinal side effects which generally resolve within 4 weeks and are decreased with food. We didn't specifically measure total side effects, but 23% of patients overall discontinued mexiletine due to gastrointestinal or neurologic side effects.

The most important reason for mexiletine initiation - pain relief, was not specifically examined in this study, other than at diagnosis. This was a retrospective cohort study looking at the tolerability of mexiletine. Due to multiple treatment modalities including medication and procedures for the patients studied, reporting pain scores would be confounded by these other factors, and questionnaires describing disability and function were not consistently available. Based on the duration of treatment, mexiletine is presumed to provide pain relief in those patients with longer duration as continuation was contingent on adequate relief as determined by clinical assessment. However, there is no quantification of pain relief or function. The variability in diagnoses is another limitation of this study. "Neuropathic" is a very broad term and while the majority included diagnoses of diabetic neuropathy and radiculopathy, more uncommon diagnoses such as trigeminal neuralgia were also included. Fibromyalgia also presents with high variability. Comorbid conditions such as depression and anxiety as well as other treatment modalities including interventions were not examined and could have influenced reasons or rates of mexiletine discontinuation. Other limitations include applicability as this was limited to our specific clinic population and a relatively high loss to follow up rate.

The literature regarding efficacy of mexiletine is mixed. A randomized, controlled trial (RCT) showed mexiletine to be superior to placebo in diabetic neuropathy (16). This study was limited to 16 patients and used higher doses than we typically do (10mg/kg per day). Another RCT study looked at mexiletine for post-amputation pain and found it was slightly better than placebo but not as good as morphine (17). This study used a mean dose of mexiletine of 933 mg/day. Multiple other RCTs have shown a positive response for diabetic neuropathy (18,19), or no difference with placebo in multiple forms of neuropathy and spinal cord injury (20-23). Dosing regimens are different among these studies and no clear effective dosage appears to exist.

We list our revised mexiletine protocol in Fig. 3. Patients who are considered for therapy are generally those with neuropathic pain or fibromyalgia of long-standing duration refractory to or recurrent after other treatments. This includes patient education, physical therapy, pain psychologist referral, interventions if appropriate, and other pharmacotherapy. Pharmacotherapy includes but is not limited to gabapentinoids, tricyclic antidepressants, and serotonin and norepinephrine reuptake inhibitors. A screening EKG is done, if not available within the past 2 years. It is the treating providers' discretion if changes or abnormalities warrant cardiac evaluation. A lidocaine infusion of 5mg/kg (450 mg maximum) is done over 60 minutes in our clinic with a nurse with EKG, pulse oximetry, and blood pressure monitoring. If the patient experiences >50% pain relief on VAS, a repeat infusion is done 1-2 weeks later. If the patient again experiences >50% relief, then mexiletine 150 mg daily is started. The patient is reas-

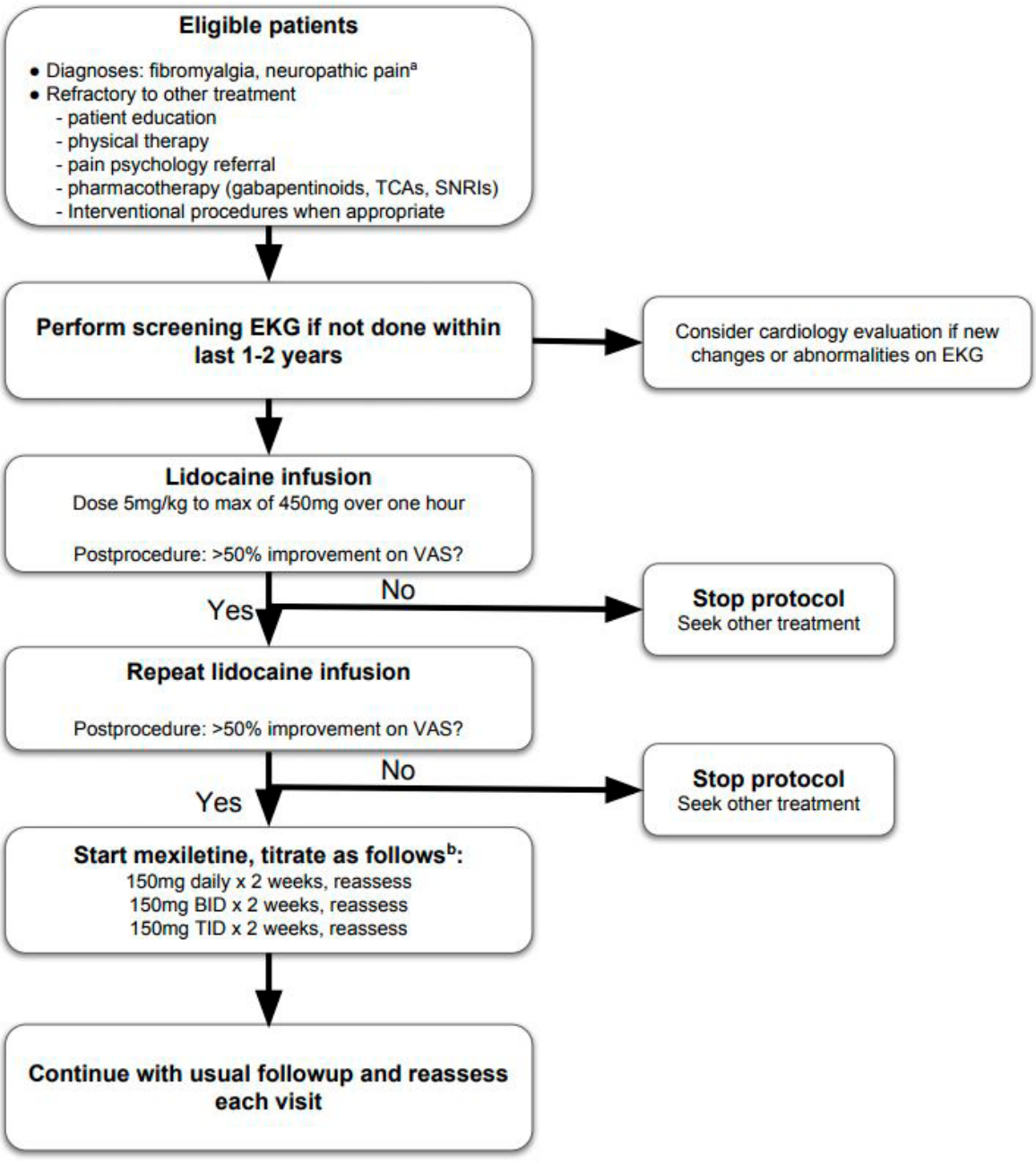

Fig. 3. *Flow chart of our revised clinic protocol for mexiletine initiation.*
a Neuropathic pain may include a number of entities such as diabetic neuropathy, trigeminal neuralgia, post-stroke pain, and others.
b Titration is based on patient response and side effects. At the physician's discretion, we sometimes go as high as mexiletine 200mg TID.
Abbreviations: TCA, tricyclic antidepressant; SNRI, serotonin and norepinephrine reuptake inhibitor; EKG, electrocardiogram; BID, twice a day; TID, three times a day.

sessed every 2 weeks to determine titration up in dose, maintenance, or discontinuation based on response. If the dose is not changed, then the patient is seen for regular follow-up thereafter.

Mexiletine is rarely a first line option for chronic pain management and is often used when multiple other modalities have failed. Mexiletine may be considered early in a treatment algorithm to neuropathy or fibromyalgia as part of a multimodal, opioid-sparing approach. By reporting our experience, we hope other clinicians may have more familiarity with the drug's use in a chronic pain practice. It appears reasonably tolerable, may not require frequent EKG monitoring, and can be an appropriate adjunct in the chronic pain population. More research is needed regarding efficacy and dose titration for mexiletine in chronic pain.

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