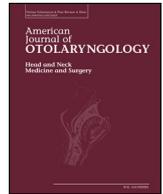




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Transdermal lidocaine as treatment for chronic subjective tinnitus: A pilot study

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ABSTRACT

Objective: To assess the efficacy of transdermal lidocaine as a treatment for chronic subjective tinnitus as measured by the Tinnitus Functional Index (TFI).

Study design: Pilot, prospective efficacy trial.

Setting: Tertiary care hospital.

Patients: Men and women, over the age of 18 with chronic subjective tinnitus for > 6 months.

Intervention: Daily application of commercially available transdermal lidocaine patch.

Outcome measure: Change in the TFI.

Results: The average pre-treatment TFI score was 56.2. After 1 month the average TFI decreased to 41 ($p < 0.05$). The scores dropped to 34 and 35 after 2 and 3 months of treatment respectively. Despite improvement in symptoms of tinnitus, most patients did not continue the study after the first month, dropping out due to the size, discomfort, and appearance of the lidocaine patch, failure to follow-up and lack of perceived benefit from treatment.

Conclusions: In this preliminary study, 5% transdermal lidocaine appears to be a potential treatment for chronic subjective tinnitus. The majority of subjects who completed 1 month of treatment had clinically significantly improved tinnitus. These findings are confounded however by the small sample size and significant drop out rate.

1. Introduction

Frequent or prolonged tinnitus is a common problem among adults, with an incidence of 7.9% in the United States and 10% in the UK [1,2]. Tinnitus is the conscious experience of sound that originates internally within the perceiver's own head or mind [3]. There are many anatomic and physiologic causes of tinnitus, however neither cause nor adequate treatment can often be identified for an individual's tinnitus. Many theories have been developed for the underlying source of chronic subjective tinnitus [4,5]. One theory of tinnitus is due to relative hypoactivity or hyperactivity of a central auditory pathway [4]. The specific process of neurotransmission is still unknown, but the proposed afferent auditory path from the cochlea to the brain stem is believed to be mediated by a number of stimulator and inhibitory neurotransmitters [5]. In part due to the multitude of theories in regard to the cause of tinnitus, as well as its likely multifactorial etiology, treatments have varied, and pharmacologic intervention has been difficult to identify.

One of the few interventions that has been relatively successful for tinnitus is lidocaine.

The first report of an amide anesthetic relieving tinnitus was from nasal application of procaine in 1935 [6]. Lidocaine, acetamide, 2-(diethylamino)-N-(2,6-dimethylphenyl), is an amide anesthetic and antiarrhythmic whose use in treatment of tinnitus has been well studied [7]. In investigations of lidocaine as a treatment, tinnitus suppression was observed at 1 µg/mL, and most relief with subjective titration found between 1.5 and 2.5 µg/mL [8]. The therapeutic window is small with concentrations > 2.0 µg/mL leading to side effects, which include but are not limited to dazed sensation and tongue parenthesis [9]. Lidocaine is believed to affect the central pathway of tinnitus. This hypothesis was tested by Baguley et al., where lidocaine was shown to relieve subjective tinnitus in individuals following resection of the cochlear nerve [10]. Class 1 antiarrhythmics, such as lidocaine, are known to interfere with fast gated sodium channels. Other drugs known to inhibit fast gated ion channels, including other antiarrhythmics and

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antiepileptics, have not shown nearly the same aptitude for alleviating tinnitus as lidocaine. In response to this finding, Davies et al. proposed the possibility that lidocaine may have special affinity for an unknown channel, may work through some other central pathway, or both [11]. Lidocaine does have an affinity for many other receptors essential for human hearing, but the relationship of these receptors with tinnitus is unknown [12,13]. These findings, as well the finding of tinnitus generation at large doses of lidocaine, support the theory of physiologic imbalance between stimulatory and inhibitory pathways as a cause for chronic subjective tinnitus [11,13].

Lidocaine is one of the few available pharmacologic treatments for tinnitus. The primary route of administration for lidocaine has been intravenous (IV) infusion. The risks associated with IV lidocaine administration include arrhythmia, paresthesia, disequilibrium, and worsening of tinnitus. These side effects are attributed to the rapid absorption and rapid escalation of plasma concentrations during infusion [7]. Following infusion, the beneficial effects on tinnitus are often short lived, secondary to the drug's half-life of 107 ± 22 min [14]. Commercially available lidocaine patches, which have a steady and controlled release of lidocaine, are safely used on an outpatient basis and do not require regular outpatient monitoring for cardiac or neurologic changes. There has been a case report of topically applied lidocaine, via these commercially available transdermal lidocaine patches, leading to temporary resolution of tinnitus [15]. The transdermal lidocaine 5% patch, when used as directed, provides continuous administration of lidocaine for up to 12 h, with a peak serum concentration of 0.13 ± 0.06 $\mu\text{g}/\text{mL}$. This concentration is well below the noted treatment threshold for lidocaine infusion of 1.5 to 2.5 $\mu\text{g}/\text{mL}$. The effects noted in the aforementioned case study may be due to improper use of the transdermal lidocaine patch or some still unknown pathway inhibited by prolonged, low dose lidocaine exposure.

One of the difficulties with investigating tinnitus is measuring a subjective experience. Many different questionnaires and surveys exist for measuring tinnitus, and even more evaluations exist for related depression and disability. Historically, the surveys used to evaluate tinnitus were not designed in order to evaluate interventions or to monitor for changes in symptoms. One survey known as the Tinnitus Functional Index (TFI) was developed specifically for research purposes and was validated against other quality-of-life measures of tinnitus, depression, and disability. Through this comparison with previously validated surveys, the TFI was found to be both valid and reliable in evaluating tinnitus interventions. The TFI is composed of 25 questions followed by a 0–10 Likert Scale. Each question falls into one of eight subscales related to the impact of tinnitus on the individual's life, including: intrusiveness, loss of sense of control, cognitive impairment, sleep dysfunction, auditory impact, difficulty with relaxation, decreased quality of life, and emotional distress. The final score is scaled from 0 to 100. In the validation of this index, the investigators found that individuals who felt their tinnitus was a small problem scored from 10 to 20, a moderate problem from 30 to 40, a big problem from 40 to 60, and a very big problem from 60 to 90. The investigators also defined a significant clinical change as a reduction in 13 points, or half the reported standard deviation of 24 points [16,17].

There are currently no published studies on the use of the transdermal lidocaine patch for the acute treatment of tinnitus, nor any studies investigating the long term effectiveness of low dose lidocaine on tinnitus. As such, we undertook this study to determine if transdermal lidocaine is a plausible treatment for chronic subjective tinnitus. Our hypothesis is that patients will have a significant improvement in their perception of tinnitus as measured by the TFI with minimal toxicity.

2. Methods

This study is a single center, un-blinded, quasi-experimental protocol designed to determine if transdermal lidocaine is a feasible

treatment for chronic subjective tinnitus, defined as non-fluctuating tinnitus for at least 6 months that could not be attributed to anatomic or physiologic cause. This study was registered on ClinicalTrials.gov (NCT02088866) and approved by the University of California, Davis Institutional Review Board (515576-3) as was the use of transdermal lidocaine as an off-label drug. The intervention used was commercially available transdermal lidocaine, (5%, 700 mg obtained from Endo or Actavis Pharmaceuticals). Patients were responsible for purchasing lidocaine patches and vouchers were provided to offset the cost of the intervention if insurance coverage was not available. No funding, benefits or contact was had between the study team and the manufacturers of the study intervention.

2.1. Inclusion criteria

Eligible participants were English speaking, aged 18 years or older, and had chronic (longer than 6 months) subjective tinnitus without known vascular, neurologic, neoplastic or traumatic causes. All patients underwent complete history and physical exam, including otologic exam. Patients also had a pre-treatment audiogram as part of the standard tinnitus workup. Patients were excluded for history of heart disease, arrhythmia, previous reaction to lidocaine, poor kidney function. Women who were pregnant, could become pregnant and were unwilling to use contraception, and breastfeeding mothers were excluded.

Patients who met inclusion criteria gave informed consent prior to initiating treatment. To evaluate the severity of tinnitus, the Tinnitus Functional Index (TFI) was used. At the initial visit, informed consent was obtained and patients filled out a pre-treatment TFI. This score was recorded and the patient was started on 1 patch of 5% transdermal lidocaine, either Lidoderm (Endo Pharmaceuticals) or Transdermal Lidocaine (Actavis Pharmaceuticals) to be applied to the skin for 12 h on, and 12 h off. This treatment was continued for 1 month, and the patient was contacted by phone for a follow-up. At the second month, a TFI was filled out, these scores were recorded and the patient was given the option to increase the dose to 2 patches per day, continue on 1 patch, or stop treatment. The desired treatment was continued for one more month, again the TFI was repeated and an increase in dose (to the maximum of 3 patches per day), decrease in dose, maintenance or withdrawal was allowed. After 3 months of treatment, the patient was evaluated, a final, post-treatment TFI was administered and the results were analyzed. After the patients completed the study, they were given the option of maintaining their lowest effective dose or stopping treatment.

2.2. Statistics

The sample size was determined using power analysis with the Southwest Oncology Group's (SWOG) statistical tool center, using the one sample normal, single sided analysis. The analysis assumed a power of 90%, an alpha of 0.05, and an assumed dropout rate of 25%. Using a single armed approach we assessed that we would need a minimum of 28 patients, and 34 for a two arm analyses. We initially intended to recruit 43 patients, however due to unforeseen circumstances, primarily loss of study personnel to other health systems, we were limited to 30 participants who were analyzed on an intention to treat basis.

Statistical analysis was performed using RStudio Version 0.98 (RStudio IDE, Boston, Massachusetts). Means are reported with the standard deviation (SD). The data set was evaluated using the paired student's *t*-test due to the dependence of the variables. Significance was determined with *P* values < 0.05.

3. Results

A total of sixty-four patients were evaluated for inclusion in the study. Of these patients, thirty-four did not meet inclusion criteria,

Table 1
Patient characteristics. The average age of the patients enrolled in the study was 59.8 years with a standard deviation of 9.4 years.

	No. (%) of patients	Average age (st dev)
All enrolled patients	30 (100%)	59.8 (9.4)
Male	13 (43.3%)	60.6 (7.9)
Female	17 (56.7%)	59.2 (10.6)

usually due to underlying cardiac disease. 30 patients were enrolled in the study. Equal numbers of male and female participants were recruited with an average age of 60 years. Demographic information is presented in Table 1.

One-third of enrolled patients completed the trial, while the majority of patients completed at least one month of treatment (n = 24, 80%) (see Fig. 1). 6 patients dropped out from the study before completing one month. These patients dropped out for a variety of reasons, the most common being patch irritation or skin reactions, followed by lack of insurance coverage for medication and inability to comply with the study regulations (see Table 2).

The average pre-treatment TFI score was 56.2. After one month of treatment the average TFI score dropped to 41, a difference of 15

Table 2
Reasons for not completing the study. Of the 21 patients that did not complete the study, 11 patients were lost to follow up and 10 patients dropped out. Patients dropped out due to inability to afford patches because their insurance would not cover the off-label usage, due to lack of subjective improvement of their tinnitus, and due to adverse reactions.

No. (%) of patients	N = 30 patients
Lost to follow-up	11 (33.3%)
Dropped out	10 (33.3%)
Insurance coverage issues	4 (36.7%)
No subjective improvement of tinnitus severity	2 (14.3%)
Adverse reactions	7 (53.8%)
Skin rash/skin irritation	3 (23.1%)
Worsened tinnitus	3 (23.1%)
Poor cosmesis	1 (7.7%)

(p < 0.01). After 2 months the average score was 34, an improvement of 22 points from pre-treatment (p < 0.01), and at the conclusion of the study, the average TFI score was 35, an overall improvement of 21 points (p < 0.05) (see Figs. 2 and 3).

Of the participants, four patients elected to increase their dose after the first month. 3 of the 4 had worsening tinnitus and reverted back to

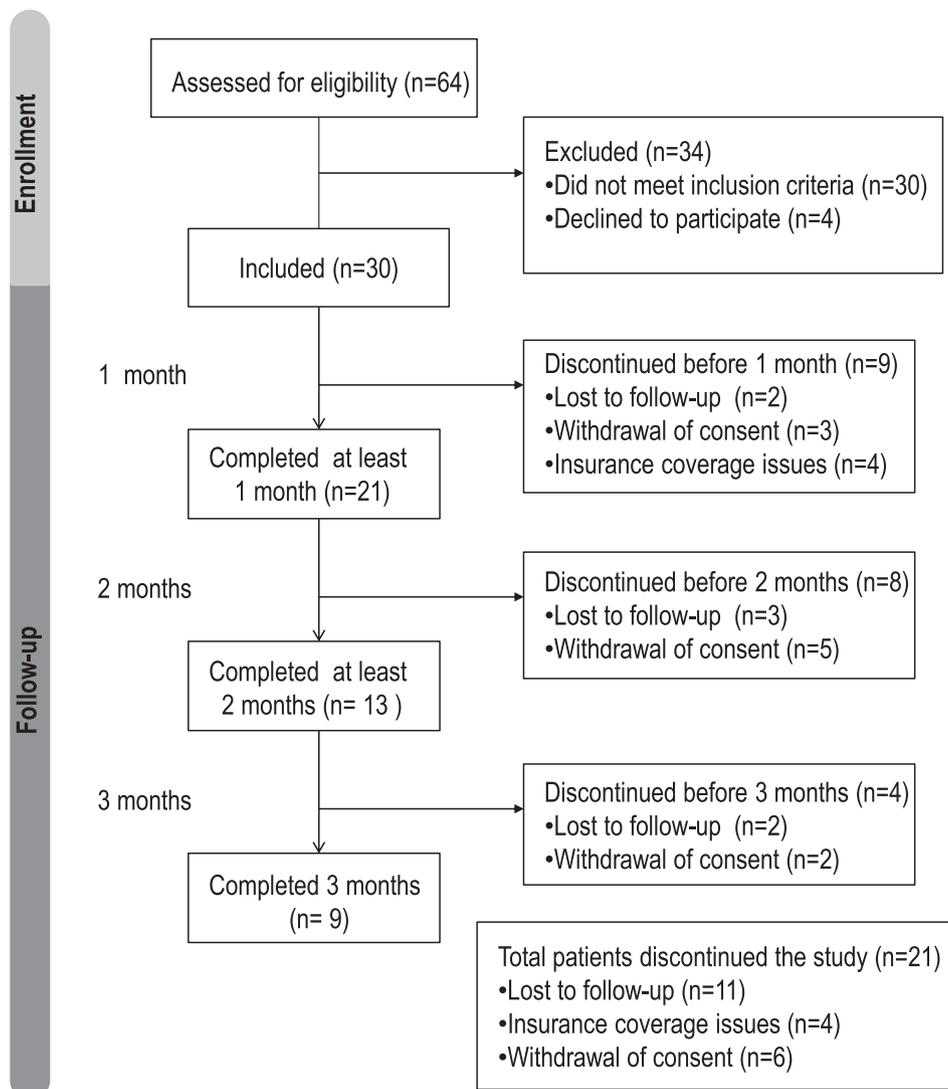


Fig. 1. Patient Flow Diagram. Of the 64 patients, 30 were enrolled into the study. The most frequent reason for screening failure was cardiac problems. All patients were administered the TFI on enrollment. 9 patients discontinued before the first month, 8 discontinued before the second month, and 4 discontinued before the third month.

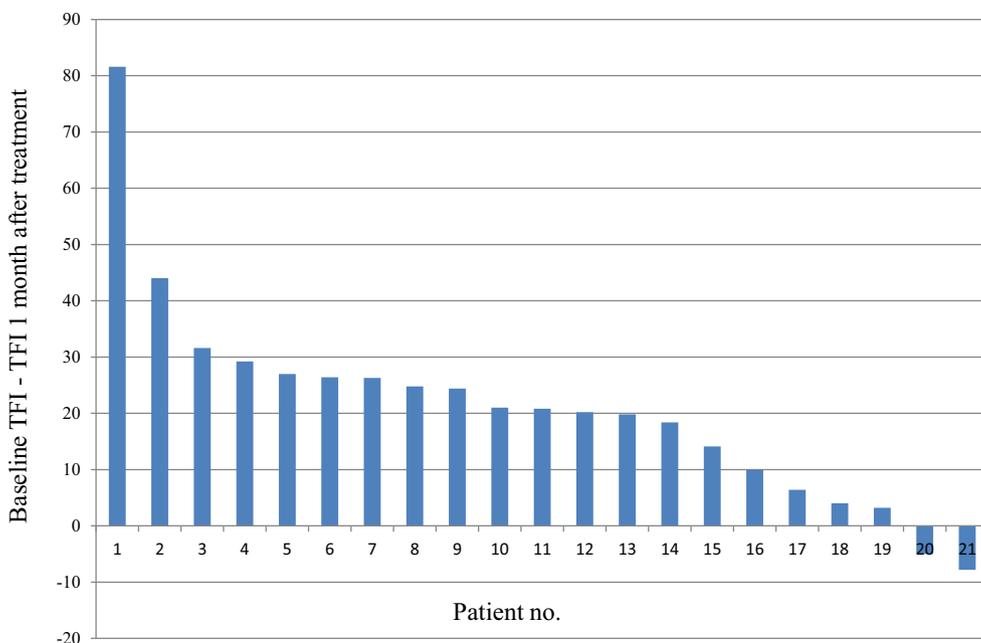


Fig. 2. Change in Tinnitus Functional Index after 1 month of treatment. The change in TFI was calculated by subtracting the TFI score measured one month after treatment from the baseline TFI before lidocaine patches were started. A positive delta indicates an improvement in TFI, with a delta > 13 indicating significant improvement. Two patients had a negative delta, indicating a worsened TFI.

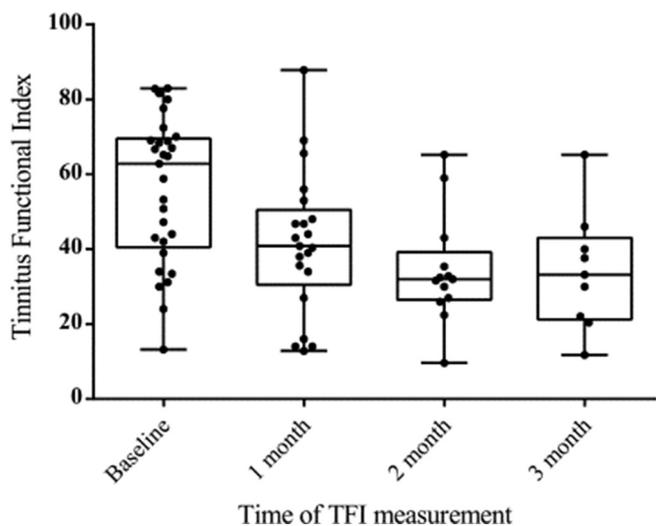


Fig. 3. Changes in TFI after treatment. The box and whisker plots show the distribution of measured TFIs at baseline before treatment, after one month of treatment with lidocaine patches, after two months of treatment, and three months of treatment. The boxes extend from the 25th and 75th percentiles. The whiskers extend to the minimum and to the maximum TFI, and each plot shows each individual TFI superimposed on the graph.

one patch. The remaining patients used one patch throughout their treatment.

Of the patient who did not complete the full 3 months of the study (n = 20), the majority completed at least one month of treatment. Major reasons for not completing the study included patch related issues (35%), patients being lost to follow-up (26%), and insurance related issues (13%).

4. Discussion

Tinnitus is a frustrating condition for both patients and frustrating for clinicians. It is frustrating for patients because it can be so intrusive into and upon their daily lives, impacting them most during the quiet times. It is challenging for clinicians because in most cases there is no clear cause of the tinnitus other than hearing loss and the majority of

treatments are aimed at symptomatic relief. The gold standard of treatment is tinnitus retraining [18]. Tinnitus retraining is a type therapy directed towards reducing the impact of tinnitus on an individual's life [19–21]. Tinnitus retraining requires a significant amount of time and disposable resources since it is rarely covered by health insurance. Other more novel approaches include transcranial magnetic therapy [22–24]. These studies, while promising, have many of the same limitations of this study including limited sample size and long term efficacy. Other pharmaceutical inquires such as the AM-101 series looking at intratympanic injection of esketamine hydrochloride gel (Auris Medical AG, Basel, Switzerland) has had promising results [25–28]. These studies however have been limited to known inciting event and in patient who have only had tinnitus for a maximum of 90 days. One of the most promising approaches uses a computer based model of tinnitus retraining with concurrent pharmacotherapy [29]. Despite the promise of this treatment it has similar limitations of tinnitus retraining without pharmacotherapy in that it requires time and resources that patient may not have the ability to access. As such, we hoped to find an additional therapy for tinnitus in transdermal lidocaine.

In this study we assessed whether or not transdermal lidocaine as a vector for delivering low dose lidocaine is a plausible treatment for tinnitus. Our results demonstrate that is a plausible treatment, with minimal toxicity and showed the potential for significant benefit in patient with tinnitus. The data show that patients treated with lidocaine patches had a clinically significant reduction in their tinnitus symptoms, as determined by the TFI. Most patients did not have an adverse reaction to the patch, with most noting that they had skin irritation at the patch site, a known side effect. Interestingly, despite this reduction in tinnitus and minimal symptoms, most patients decided to not continue the patch beyond the first month of the study. What this finding suggests is that despite the improvement as reported in the TFI, patients did not find significant benefit to outweigh the cost of the patches.

While the study was not powered to assess this finding, the patients that did persist in the trial beyond the first month had further improvement in the reported TFI score. This result may be from further improvement while on the patch, but is most likely due to self-selection as those who did not respond dropped out from the study. Of further note, while the FDA has found that up to three patches at a time is safe for use, we had very few patient increase their dose beyond one patch. Those that did increase their dose had proportionate worsening of their

side effects, without improvement of their TFI scores. Anecdotally, of these patients who persisted, they noted improvement of their tinnitus, often regardless of the change of the TFI. This occurrence, with the dichotomous findings of clinically significant improvement as measured by the TFI with a high dropout rate, raises the question of whether the TFI is an accurate tool in the case of this study. Wilson et al. published pilot data regarding how we may better assess tinnitus in the future [30]. In this study, participants responded to TFI based questions using their smartphones. Using this method they were able to evaluate their patients' more frequently than we were in this study. They found significant inter-patient and intra-patient variability in these patients experience of their tinnitus on a daily if not more frequent basis, which contradicts previous investigations using the Tinnitus Handicap Index. As such, a survey like the TFI on a monthly or weekly basis may not appreciate a patient's burden of disease.

4.1. Limitations

Not many conclusions can be drawn from this single center, non-blinded, non-funded study due to its design. It was built to determine if further study of transdermal lidocaine in individuals with chronic tinnitus was worth pursuing, and as such accomplished this goal. No placebo was used in this study, therefore it is difficult to assess if the results of this study are secondary to placebo effect or the impact of lidocaine itself. There is a known psychologic component to tinnitus, including a high rate of comorbid psychiatric disorder [31,32]. Due to the psychologic aspect of tinnitus, there is the potential for a significant placebo effect. Furthermore, this study was performed in a single center among patients who self-presented. While there was a national call, and this study was listed on ClinicalTrials.gov, the ability for patients and for the study team to involve patients outside of the Sacramento and surrounding areas was limited. Further still, since this study required the participants to self-pay for all study medications, whether via insurance or privately, there is the potential for even further bias. In order to address these biases a larger, blinded, randomized and placebo controlled study would be of greatest benefit.

5. Conclusion

Tinnitus is a common problem affecting 50 million people in the United States alone. While there are multiple ongoing studies for the treatment of tinnitus, there is no current therapy for chronic subjective tinnitus. In this single center, un-blinded study we investigated the feasibility and efficacy of commercially available transdermal lidocaine as a treatment for tinnitus. We found that after a month of therapy, the majority of patients had a statistically significant reduction of tinnitus. Despite this result, only a small subset of patients chose to continue therapy due to known side effects of therapy, cost of therapy, or unmet expectations. This preliminary study should serve as a basis for future investigations of transdermal lidocaine as a treatment for chronic subjective tinnitus.

Conflict of interest disclosures

O'Brien was partially by NIH 5TL1TR000133-08 T32 grant during the course of this study. No other conflicts of interest.

Previous presentation

Part of this data set was presented at the American Academy of Otolaryngology Annual Meeting.

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