

Predictors of Chronic Pain Relief by Fixed-Site High-Frequency Transcutaneous Electrical Nerve Stimulation

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INTRODUCTION

About 100 million people in the U.S. have chronic pain. Many people with chronic pain also have low quality sleep, anxiety, depression, and poor overall health. Prescription opioids are frequently used for chronic pain despite concerns about adverse events. There is a need for nonpharmacological treatments for chronic pain.

Transcutaneous electrical nerve stimulation (TENS) is the delivery of electric current across the intact surface of the skin to activate sensory nerve fibers, primarily for pain relief. Fixed-site high-frequency TENS (FS-TENS) is a form of TENS in which the stimulator is designed for a predetermined location rather than for co-localization with the patient's pain. A single target site enables design of small wearable devices that may be used while active and sleeping.

Previous studies have demonstrated that 50-80% of FS-TENS users with chronic lower extremity or low back pain experience clinically meaningful pain relief. The objective of this study was to determine predictors of a positive FS-TENS response.

METHODS

Study Design and Subject Selection. This retrospective, observational study evaluated users of a FS-TENS device to treat chronic pain over a 10-week period (Quell®, NeuroMetrix, Waltham, MA). The device is worn on the upper calf and semi-continuously stimulates sensory. The device and a companion smartphone app monitors utilization (Number of therapy sessions with 30+ minutes of stimulation) and collects demographics, painful health conditions, pain sites, weather sensitivity, pain intensity and interference with sleep, activity and mood on an 11-point NRS. All data are stored in a cloud database and a snapshot of the database was taken on August 5th 2018.

Inclusion criteria were users 1) providing demographic/clinical information, 2) having pain characteristics indicative of chronic pain, 3) reporting pain intensity and interference ratings at baseline and 10 week of FS-TENS use, and 4) consenting to use of anonymized data for research. The primary study outcome was the baseline to 10-week change in composite pain (average of pain intensity and interference with sleep, activity and mood).

Users were defined as a responder or comparator based on changes of their composite pain: responder $\geq 15\%$ decrease; comparator $\geq 15\%$ increase

Data Analysis. Generalized linear model with probit link function is used. Stepwise forward regression adds a new predictor ($p < 0.05$) in each iteration among all candidate predictors (see Figure in middle column) to determine independent predictors of responders of statistical significance. All analyses were performed with STATA Version 15.1 (StataCorp, College Station, TX, USA).

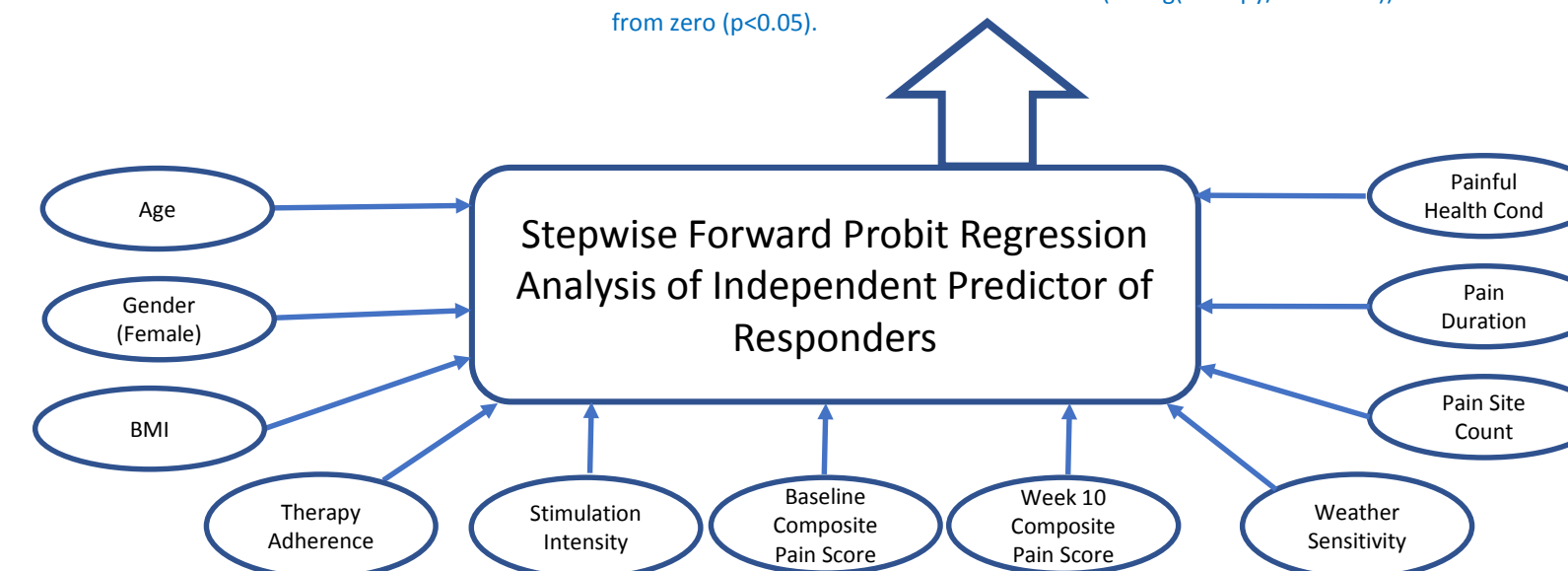
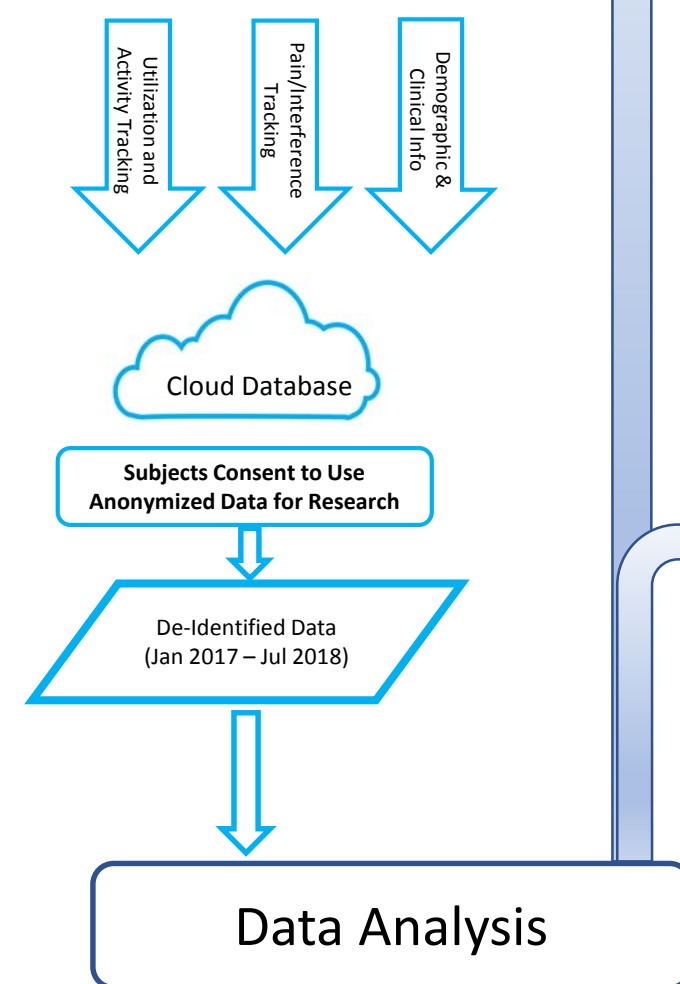
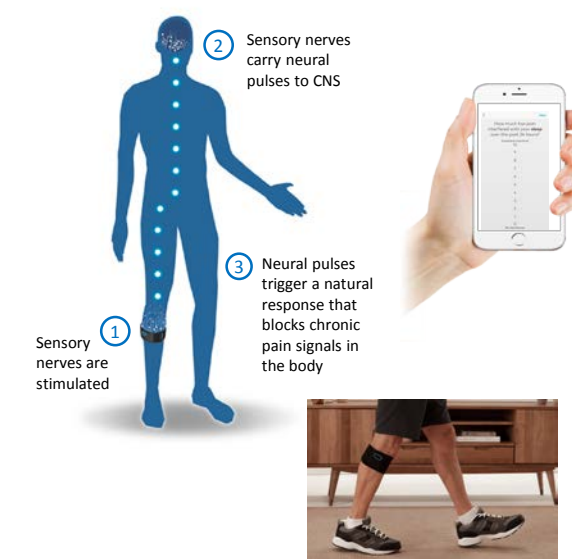


Table 1. Demographics and Baseline Pain Characteristics

	Responder (N=451)	Comparator (N=263)	P-Value*
Female (%)	54.1	52.1	0.603
Age (Yrs)	57.3 ± 13.0	55.3 ± 13.8	0.047
BMI (kg/m ²)	30.4 ± 7.2	31.0 ± 7.5	0.310
No. Pain Sites	4.6 ± 2.4	4.6 ± 2.4	0.987
No. Painful Health Cond	3.4 ± 1.9	3.5 ± 2.0	0.553
Pain Duration > 10 Yrs (%)	39.0	35.0	0.282
Constant Pain (%)	50.8	42.2	0.027
Daily Pain (%)	97.1	97.3	0.863
Weather Sensitive (%)	59.0	63.9	0.196
Baseline Pain, 0—10 NRS			
Pain Intensity	6.5 ± 1.9	5.4 ± 1.8	0.000
Sleep Interference	5.5 ± 2.9	3.8 ± 2.6	0.000
Activity Interference	6.9 ± 2.3	5.4 ± 2.2	0.000
Mood Interference	6.4 ± 2.6	5.1 ± 2.7	0.000

* Statistical significance of group differences determined by two-group t-test for continuous variables and Pearson's chi-squared test for categorical variables.

Table 2. Independent Predictors of Responders from Probit Regression

Predictor	Coefficient
Age (Yrs)	0.01
Baseline Composite Pain (0—10)	0.27
Headache or Migraine	-0.37
Diabetes	-0.33
Weather Sensitivity	-0.22
Adherence (%)	0.01
Stimulation Intensity (dB)	0.02
Constant	-2.36

Adherence, % of days with at least 30 minutes of stimulation. Stimulation Intensity, ratio of therapeutic stimulation to sensation threshold in decibels ($20 \log(\text{therapy/sensation})$). All coefficient are different from zero ($p < 0.05$).

RESULTS

Demographics and Baseline Pain Characteristics (Table 1). A total of 714 users met the inclusion criteria. 451 (63%) were responders and 263 (37%) were comparators. Responders were slightly older (57.3 yrs vs. 55.3 yrs, $p=0.047$) and a higher percentage had constant pain (50.8% vs. 42.2%, $p=0.027$). All other demographics and clinical characteristics were similar. Responders had higher baseline pain intensity and pain interference ($p < 0.001$).

Independent Predictors of Responders (Table 2). Independent predictors were age, baseline composite pain, adherence, stimulation intensity, headaches/migraine, diabetes and weather sensitivity. Age, baseline composite pain, regular therapy (adherence), and higher stimulation intensity (in relation to sensation threshold) positively predicted responders. Headache or migraine, diabetes, and weather sensitivity negatively predicted responders.

The area under the ROC curve was 0.76 (95% confidence interval: 0.72 – 0.79).

CONCLUSIONS

FS-TENS users in this study cohort were more likely to report a 15% or more reduction in composite pain scores when they were older, had a higher baseline pain scores, carried out FS-TENS therapies in more days within the 10-week study period, and used a higher stimulation intensity (with respect to their sensation threshold). Users with headache or migraine, diabetes, or weather sensitivity were less likely to report a composite pain score reduction.

Prediction of FS-TENS effectiveness, based on baseline pain characteristics and TENS dosage factors, was moderately accurate.

REFERENCES

- Gozani SN. Fixed-site high-frequency transcutaneous electrical nerve stimulation for treatment of chronic low back and lower extremity pain. *Journal of Pain Research*. 2016;9:469-479.
- Kong X and Gozani SN. Effectiveness of fixed-site high-frequency transcutaneous electrical nerve stimulation in chronic pain: a large-scale, observational study. *Journal of Pain Research*. 2018;11:703-714.
- Gozani SG and Kong X. Real-world evidence for the widespread effects of fixed-site high-frequency transcutaneous electrical nerve stimulation in chronic pain. *Journal of Pain & Relief*. 2018; 7:329. doi: 10.4172/2167-0846.1000329

