Therapeutic Mechanisms of Epidural Spinal Cord Stimulation
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STATISTICAL DESIGN AND POWER

Specific Aim 1. Test the hypothesis that spinal cord stimulation decreases peripheral measures of autonomic tone in patients with chronic pain. ***Aim 1a*** *will repeatedly measure cardiovascular markers of autonomic tone (blood pressure, heart rate variability, baroreflex sensitivity, 24-hour blood pressure).* ***Aim 1b*** *will correlate acute and chronic changes in multi-domain measures of pain via NIH PROMIS patient reported outcomes with changes in measures of autonomic tone.*

Statistical Analysis (Specific Aim 1 – Aim 1a and 1b):

Clinical, laboratory, and sudomotor measures will be compared between patients with or without co-morbid hypertension and across the four time points (baseline (V1), V2, V3, and V4, where "V" represents visit). Repeated measurements of pain, autonomic function, and blood pressure will be obtained on patients who proceed through a spinal cord stimulation (SCS) trial and permanent SCS implantation. This will consist of baseline testing (V1), 2 visits (V2, V3) during acute SCS trial stimulation based upon waveform use (non-paresthesia inducing and paresthesia inducing waveform), and one chronic, 3-month post-SCS implantation visit (V4).

Key outcome markers of autonomic tone are systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP). Key outcome markers for pain are the NIH PROMIS patient reported outcomes (PROs). Note that all PROMIS measures will be scored and then converted into T-scores prior to statistical analysis.

Descriptive statistics, such as means and standard deviations (SDs) for continuous variables and frequencies and proportions for categorial variables, will first be obtained for all study measures, including all outcome variables. Each of the continuous outcome variables will then be assessed for a normal distribution using statistical and graphical techniques such as box plots, normal probability plots, and tests for normality. Variables that are not normally distributed will be transformed prior to analysis or will be analyzed using nonparametric methods (such as the Wilcoxon rank-sum test and the Wilcoxon signed rank test). Statistical tests will be two-sided and will be performed using a significance level of 5%. Statistical analyses will be performed using SAS, version 9.4 or later.

Baseline differences between groups (e.g., patients with hypertension, patients without hypertension) will be examined using the two-group test (or the Wilcoxon rank-sum test, if needed), or analysis of covariance when performing comparisons that include potential confounders (refer to the list of confounders below). *Exploratory cross-sectional changes* between two time points will be assessed using the paired t-test (or the Wilcoxon signed-rank test, if needed). Our *primary method of analysis* will consist of the use of general linear mixed effect models, *primarily repeated measures linear mixed effects models* (the specific analysis is also referred to as mixed models repeated measures analysis). This analysis method will allow us to examine differences between the study groups and changes among the time points within each study group simultaneously. The specific covariance matrix (e.g., compound symmetry, autoregressive, unstructured) will be selected based upon the final data. The Tukey-Kramer *multiple comparisons method* will be used for post hoc pairwise comparisons of means. These repeated measures linear mixed effects models will allow us to assess the between-group effect, the within-group effect, and the group by time interaction simultaneously. *Potential confounders* that will be included in some of our analyses as covariates include age, sex, use of antihypertensive medications, baseline pain score, and baseline MAP. Correlation analysis will be used to test the strength of the association between the obtained measurements and the potential confounders. Bivariate linear regression analysis and Pearson's correlation analysis (or Spearman's correlation analysis, if needed) will be used to test the strength of association between the obtained measurements and pain ratings, age, sex, and other parameters of interest (Specific Aim 1b only). Categorical data will be analyzed using the chi-square test, or Fisher's exact test when the assumptions for the chi-square test are not tenable. Secondary data analysis will examine sex differences (men vs. women) using the same statistical methods as above; however, this study is not specifically powered to detect statistically significant sex differences.

Missing data that are not rectified through ongoing review of source documents may be managed with multiple imputation (especially if the data are determined as being not missing at random). Missing data analysis will not be performed on variables with small amounts (<5%) of missing data since the use of these methods may

introduce a statistical bias that will be larger than any bias obtained using complete case analysis (an analysis including only participants who have complete data). The influence of the missing data will be assessed with sensitivity analyses. The sensitivity analyses will include performing a complete case analysis using the statistical analysis techniques described above.

Sample Size Justification / Statistical Power (Specific Aim 1 – Aim 1a and 1b):

Our center performs approximately 30-40 SCS trial/implants annually. This is projected to grow to 45-50 annually over the data collection period. With an expected enrollment rate of 80% and an approximate dropout rate of 10%, our goal is to enroll approximately 60 total participants over the 1.5-year data collection period. With an expected rate of co-morbid hypertension in the chronic pain patient group being 40%, we expect to internally enroll approximately 24 participants with and 36 participants without co-morbid hypertension.[1,2]

Power calculations were performed using nQuery, version 9.3.1. We obtained estimates of the SD of 10 mm Hg for DBP, 10 mm for MAP, and of 14 mm Hg for SBP, from our previous work.[3] The SD of 10 for the T-score metric for PROMIS measures are described in Section 1.3 of the Research Strategy. For comparisons of two participant groups, assuming group sizes of 24 and 36 participants, a two-sided two-group t-test, and a significance level of 5%, we will have 80% power to detect differences in the means of 7.6 mm Hg in DBP, of 7.6 mm Hg in MAP, of 7.6 in the T-score metric (for PROMIS measures), and of 10.6 mm Hg in SBP (all with effect size of 0.751), between two groups as being statistically significant. In our prior research, we have obtained between-group differences in means for these parameters that are of similar or larger magnitude. For within-group comparisons, assuming group sizes of 24 and 36 participants, a two-sided paired t-test, and a significance level of 5%, we will have 80% power to detect within-group changes (between any two time points) in the means of 6.0 mm Hg in DBP, of 6.0 mm Hg in MAP, of 6.0 in the T-score metric (for PROMIS measures), and of 8.4 mm Hg in SBP (all with effect size of 0.597) for the group of 24, and of 4.9 mm Hg in DBP, of 4.9 mm Hg in MAP, of 4.9 in the T-score metric (for PROMIS measures), and of 6.8 mm Hg in SBP (effect size of 0.480) for the group of 36, as being statistically significant. In our prior research, we have obtained within-group changes in means for these parameters that are of similar or larger magnitude. Given these results, we will be able to detect moderate effect sizes within groups as being statistically significant and moderate-to-large effect sizes between groups as being statistically significant. These estimates are conservative as we will use statistical methods that are more sophisticated than those assumed for these power calculations.

Specific Aim 2. Test the hypothesis that spinal cord stimulation-evoked electrophysiology associated with pain relief correlates with decreased sympathetic tone. ***Aim 2a*** *will describe SCS-induced spinal cord (ECAP) and cortical (EEG) responses (alpha and theta power shifts) associated with acute pain relief during routine trial stimulation.* These data will expand knowledge on how SCS interacts with local spinal cord and more distant cortical circuits, both of which could serve as a candidate biomarkers for efficacy. ***Aim 2b*** *will correlate the SCS responses with longitudinal autonomic tone and NIH PROMISE measures at 3 months.*

Statistical Analysis (Specific Aim 2 – Aim 2a and 2b):

The statistical analysis methods that will be used here in Specific Aim 2 are the same as those described above for Specific Aim 1, with some of the methods to be used in Specific Aim 2 applied a little differently. Our primary method of analysis will still consist of the use of general linear mixed effect models, primarily repeated measures linear mixed effects models, to examine differences between the study groups and changes across time points within each study group simultaneously.

The proposed research involving the SCS-induced spinal cord responses (ECAP) and the cortical responses (EEG) is exploratory. As such, results obtained from the statistical analyses that include ECAP responses and/or EEG responses must be viewed as preliminary and hypothesis-generating.

We will determine the correlation between the SCS-induced spinal cord responses (ECAP) and the SCS parameters. We will also determine the correlation between the cortical responses (EEG) and the SCS parameters. For example, in one analysis, the ECAP amplitude will be the outcome measure, the stimulus type and the EEG location will be crossed, fixed effects, and the participants will be included as the random

intercept; our primary interest will be in detecting differences between the two stimulus types. In another analysis, the alpha power, theta power, and alpha:theta ratio (the ratio of the alpha power bands to the theta power bands) representing the EEG responses will be the outcome measure. The stimulus type and the EEG location will be crossed, fixed effects, and the participants will be included as the random intercept; our primary interest will be in detecting differences between the two stimulus types.

Analyses will include measures of autonomic and pain changes obtained in Specific Aim 1 as outcome measures in various repeated measures linear mixed effects models. The markers for pain will again be represented by the PROMIS pain score. As in Specific Aim 1, all PROMIS measures will be scored and then converted into T-scores prior to statistical analysis. We will determine the correlation between the PROMIS pain score and the ECAP amplitude. We will also determine the correlation between the PROMIS pain scores and the (EEG) alpha:theta ratio. For these models, the PROMIS pain score will be the outcome variable. We expect that PROMIS pain score improvements during paresthesia-inducing SCS correlates with maximum ECAP amplitude, whereas we expect pain score improvements from non-paresthesia SCS correlate with shifts in EEG frontal alpha power, theta power, and alpha:theta power.

For the above analyses, we will again adjust for multiple comparisons using the Tukey-Kramer method. Missing data will be handled as previously described in Specific Aim 1.

Sample Size Justification / Statistical Power (Specific Aim 2 – Aim 2a and 2b):

All 60 participants enrolled into Specific Aim 1 will proceed to Specific Aim 2. The sample size in each of the groups will remain the same, with approximately 24 participants with and 36 participants without co-morbid hypertension. As described above, the proposed research involving the SCS-induced spinal cord responses (ECAP) and the cortical responses (EEG) is exploratory. As such, we do not information available with which to perform specific power calculations for the electrophysiological parameters (ECAP, EEG).

However, we can perform a power analysis that examines the correlation between changes in patient reported outcomes (PROs), or for that matter, changes in any two distinct continuous variables. Assuming a two-sided test of the correlation coefficient, a significance level of 5%, and a sample size of 60 participants, we will have more than 80% power to detect correlation coefficients of 0.36 and greater between changes in any two distinct PROs as being statistically significant. Assuming a two-sided test of the correlation coefficient, a significance level of 5%, and group sample sizes of 24 participants and 36 participants, respectively, we will have more than 80% power to detect correlation coefficients of 0.55 and greater between changes in any two distinct PROs for the group of 24, and of 0.46 and greater between changes in any two distinct PROs for the group of 36, as being statistically significant. Therefore, for the entire group of 60 participants, we have adequate power to detect small, moderate, and large correlations as being statistically significant between changes in any two distinct continuous variables; for the groups of 24 participants and 36 participants, we have adequate power to detect moderate and large correlations between changes in any two distinct continuous variables as being statistically significant.

For comparisons of the PROMIS scores, the SD of 10 for the T-score metric for PROMIS scores are described in Section 1.3 of the Research Strategy. For comparisons of two participant groups, assuming an SD of 10 for the T-score metric for PROMIS scores, group sizes of 24 and 36 participants, a two-sided two-group t-test, and a significance level of 5%, we will have 80% power to detect differences in the means of 7.6 in the T-score metric (effect size of 0.751), for PROMIS scores, between two groups as being statistically significant. In our prior research, we have obtained between-group differences in means for PROMIS scores that are of similar or larger magnitude. For within-group comparisons, assuming an SD of 10 for the T-score metric for PROMIS scores, group sizes of 24 and 36 participants, a two-sided paired t-test, and a significance level of 5%, we will have 80% power to detect within-group changes (between any two time points) of 6.0 in the T-score metric (effect size of 0.597), for PROMIS scores, for the group of 24, and of 4.9 in the T-score metric (effect size of 0.480), for PROMIS scores, for the group of 36, as being statistically significant. In our prior research, we have obtained within-group changes in means for PROMIS scores that are of similar or larger magnitude. Given these results, we will be able to detect moderate effect sizes within groups as being statistically significant and moderate-to-large effect sizes between groups as being statistically significant.

Estimates provided above are conservative as we will use statistical methods that are more sophisticated than those assumed for these power calculations.

1. Fayaz A, Ayis S, Panesar SS, Langford RM, Donaldson LJ. Assessing the relationship between chronic pain and cardiovascular disease: A systematic review and meta-analysis. *Scand J Pain*. Oct 2016;13:76-90. doi:10.1016/j.sjpain.2016.06.005
2. Fayaz A, Watt HC, Langford RM, Donaldson LJ. The Association Between Chronic Pain and Cardiac Disease: A Cross-sectional Population Study. *Clin J Pain*. Dec 2016;32(12):1062-1068. doi:10.1097/AJP.0000000000000359
3. Holwerda SW, Holland MT, Green AL, Pearson ACS, Pierce GL. Dissociation between reduced pain and arterial blood pressure following epidural spinal cord stimulation in patients with chronic pain: A retrospective study. *Clin Auton Res*. Apr 2021;31(2):303-316. doi:10.1007/s10286-020-00690-5