Comparing Effectiveness of Duloxetine and Desipramine in Patients With Chronic Pain: A Pragmatic Trial Using Point of Care Randomization

Statistical Analysis Plan

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Statistical Analysis. The initial sample size calculation determined that 107 participants per group would provide 90% power to detect a one-unit between-group difference in the NRS pain score (SD=2.25) at α=0.05. However, the study was prematurely stopped due to most referred patients having prior experience with duloxetine or, less frequently, desipramine. As a result, we enrolled 38 patients in the desipramine group and 48 in the duloxetine group. With this sample size, we could detect a difference of 1.37–1.58 in NRS pain reduction with 80–90% power.

Participants were eligible if they completed at least one survey before being assigned a study medication and at least one follow-up survey. The baseline assessment was defined as the most recent survey before treatment assignment. Participants without follow-up surveys or those lost to follow-up were excluded. The primary analysis followed modified intention-to-treat (ITT) principles. However, within the first day of treatment assignment, five individuals switched from desipramine to duloxetine. To account for these switches, a per-protocol (PP) analysis was conducted, categorizing individuals based on the medication they took. For consistency, survey data (research and clinical surveys) were evaluated up to 52 weeks post-baseline when available.

Baseline demographic and clinical characteristics were summarized using three comparative analyses. First, a “per-protocol” approach was applied to compare demographic and clinical characteristics between the desipramine and duloxetine groups. Second, differences were assessed between participants who completed the full course of medication and those who discontinued early. Third, participants who achieved a clinically meaningful (≥30%) pain reduction were compared to those who did not. Categorical variables were analyzed using Pearson’s Chi-square or Fisher’s Exact tests, while continuous variables were assessed using t-tests or Mann-Whitney U tests depending on normality.

Longitudinal changes in pain intensity, physical function, and psychological function were analyzed using linear mixed-effects models (LMMs). Dependent variables included pain intensity (average and worst), PROMIS Pain Interference, PROMIS Anxiety, PROMIS Depression, and PROMIS Physical Function (Upper Extremity, Mobility, and Composite) scores. The primary independent variables were medication group (desipramine vs. duloxetine) and its interaction with time (weeks since baseline) to assess differential treatment effects. Baseline pain intensity was included as a covariate. A random intercept for each participant accounted for within-subject correlations. Various model structures were evaluated using Akaike Information Criterion and Bayesian Information Criterion, with final models selected based on model fit and diagnostic assessments. Model fit was evaluated using residual plots, Q-Q plots, histograms, and Variance Inflation Factor analyses. Bonferroni correction was applied to account for multiple comparisons. LOESS (Locally Estimated Scatterplot Smoothing) predicted values with 95% confidence intervals were plotted to visualize longitudinal trends stratified by medication group.

Kaplan-Meier survival analysis was used to evaluate medication adherence over time, conducted separately for both the intention-to-treat and per-protocol analyses. Time to discontinuation was calculated as the number of days between treatment initiation and discontinuation. Participants who completed the full course of medication were censored at the maximum observed follow-up duration. Kaplan-Meier survival curves were generated for each medication group, and the log-rank test was used to compare groups with 95% confidence intervals. A Kaplan-Meier survival analysis was also conducted to compare the time to achieving a ≥30% reduction in average pain intensity from baseline between medication groups. A binary indicator variable was created to determine whether a participant met the pain reduction threshold at any follow-up point, with time-to-event defined as the earliest occurrence of this reduction. Participants who did not achieve the threshold were censored at 52 weeks. Kaplan-Meier survival curves were plotted separately for desipramine and duloxetine, with the log-rank test used for group comparisons.

To assess the relationship between medication adherence and the likelihood of achieving meaningful pain reduction, a chi-square test was conducted. The proportion of participants who achieved a ≥30% pain reduction was compared between those who completed the full course of medication and those who discontinued early