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

Statistical Analysis Plan

NCT03548454

April 24, 2018

Data collection: The participants will receive monthly electronic surveys similar to their routine clinical care. These surveys are going to be abbreviated to include average and worst Numerical Rating Scale (NRS) of pain; National Institute of Health (NIH) Patient Reported Outcomes Measurement Information System (PROMIS) measures for function, depression and pain interference; and questions about medication compliance, dose and adverse events. Data about use of other analgesics and medications, and pain interventions will also be recorded at these intervals from participants' electronic health records. If the participants do not complete the surveys within five days of receipt of the survey link, they will be contacted to be reminded of the survey. We will also record participants' baseline characteristics including age, sex, main pain diagnosis, other pain diagnoses, psychological comorbidities, medical comorbidities, medication use, and education.

Statistical Analysis: We will test the hypotheses that:

1. Duloxetine is more effective than desipramine in decreasing NRS pain scale in patients with chronic pain.
2. Duloxetine is more effective than desipramine in improving function, depression and pain interference in patients with chronic pain.

We will use repeated measure linear regression for this comparison. The primary comparison is between the mean scores at six months, which we will estimate by fitting a longitudinal model that includes all monthly observations. We will fit a linear mixed effects model with random slope and intercept and contrast the expectations at 6 months between the treatment groups. We will also use a Generalized Least Squares regression model with an unstructured symmetric correlation matrix to check for model dependence. These methods allow missing outcomes, subject to the assumption of missing at random conditional on the observed data.

3. Participants continue taking duloxetine longer than desipramine.

We will use Cox proportional hazards model for this comparison.

Our null hypotheses are similarity of measures. We will perform a two-sided hypothesis testing with accepted type I error of 0.05. We will compare baseline characteristics using t-test for continuous variables and chi-square for categorical variables. We will adjust for the variables that are different between the groups in our final regression model. We will then perform subgroup analysis based on participants' sex and primary pain diagnoses: fibromyalgia, neuropathic pain, musculoskeletal pain, and headache. We will perform Bonferroni correction for multiple analyses.

Our primary analysis is going to be based on intention to treat. We will try to separate adherence to medication from our data collection. We will try to continue collecting data even if the participants decide to stop study medication. We anticipate minimal difficulty considering that these participants are our clinic patients with ongoing treating relationship. We will also report a secondary analysis based on participants who adhere to study protocol.

Sample Size Consideration: The highest standard deviation of NRS pain scale in our clinic is 2.25 based on prior publications.[7-12] Accepting type I error of 0.05 with 90% power, we will require 107 participants per group to detect one unit between-group difference in NRS pain scale. We are proposing a more conservative (larger) sample size to: (1) preserve power if the effect size is underestimated secondary to low medication adherence; and (2) preserve power for our subgroup analyses. We will therefore add 50% to our sample size to a total of 160 patients in each arm. Correlation between repeated measure will decrease variance and increase the power of the proposed study.

Timeline: Our center provides around 20,000 clinic visits per year. Considering that our center is a tertiary referral center, we expect less than 20% of our patients to be novices to these treatments. Considering potential patient refusal and the fact that all remaining patients are not candidates for treatments with anti-depressants, we expect to complete our recruitment phase in less than a year. Subsequently, follow-up for the last patients will end by 18 months after initiation of the trial. We will then complete the statistical analysis and report our results.