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TITLE: D-Cycloserine for the Treatment of Chronic, Refractory Low Back Pain

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Northwestern University, 633 Clark St., Evanston, IL 60208-0001

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14. ABSTRACT

Chronic low back pain constitutes the major form of chronic pain, with a prevalence as high as 70-85% in adults at some time in their lives. This 26-week, double blind, randomized, placebo controlled two-arm parallel-group study will evaluate 244 participants to determine if treatment with d-cycloserine in individuals with chronic, refractory low back pain will demonstrate greater reduction in pain compared to individuals treated with placebo. After a two-week screening period, individuals are randomized to receive either 12 weeks of d-cycloserine or placebo and then followed for an additional 12 weeks to evaluate persistence of benefit at study endpoint, 24 weeks after randomization. Follow-up visits and data collection will occur at baseline and 2, 6, 12, and 24 weeks after randomization to assess general health, pain, proper treatment use, and side effects. Pain and safety will also be assessed at 16 and 20 weeks after randomization by phone calls.

15. SUBJECT TERMS
Chronic pain, low back pain, d-cycloserine

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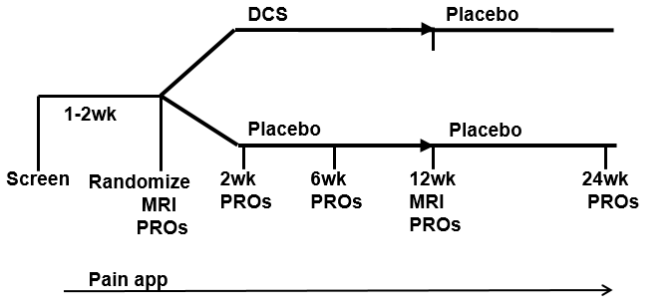
1. Introduction

Chronic low back pain constitutes the major form of chronic pain, with a prevalence as high as 70-85% in adults at some time in their lives. This 26-week, double blind, randomized, placebo controlled two-arm parallel-group study will evaluate 244 participants to determine if treatment with d-cycloserine in individuals with chronic, refractory low back pain will demonstrate greater reduction in pain compared to individuals treated with placebo. After a two-week screening period, individuals are randomized to receive either 12 weeks of d-cycloserine or placebo and then followed for an additional 12 weeks to evaluate persistence of benefit at study endpoint, 24 weeks after randomization. Follow-up visits and data collection will occur at baseline and 2, 6, 12, and 24 weeks after randomization to assess general health, pain, proper treatment use, and side effects. Pain and safety will also be assessed at 16 and 20 weeks after randomization by phone calls.



2. Keywords

Chronic pain, low back pain, d-cycloserine

3. Accomplishments

- **What were the major goals of the project?**

  Specific Aim 1: Determine the efficacy and safety of DCS compared to placebo to reduce pain in people with chronic low back pain

  Major Task 1: Obtain Regulatory Approvals
  Milestone Achieved: Local IRB approval (Goal – Month 3) – 100% complete
  Milestone Achieved: HRPO Approval (Goal – Month 6) – 100% complete

  Major Task 2: Complete Site Preparation Start-up Activities
  Subtask 1. Prepare required documents and databases – 100% complete
  Subtask 2. Prepare medication – 100% complete
  Subtask 3. Develop recruitment plan – 100% complete
  Milestone Achieved. Site prepared to screen participants (Goal – Month 6) – 100% complete

Major Task 3: Execute RCT and Data Collection
Milestone Achieved: 1st participant consented and enrolled (Goal – Month 8) – 100% complete
Milestone Achieved: 50% of participants enrolled (Goal – Month 24) – 100% complete
Milestone Achieved: 100% of participants enrolled (Goal – Month 39) – 83% complete
Milestone Achieved: All data collected (Goal – Month 42) – 100% complete

Major Task 4: Data Completion and Analysis
Milestone Achieved: Database Lock (Goal – Month 43) – 0% complete
Milestone Achieved: Pre-specified analyses completed (Goal – Month 46) – 0% complete
Milestone Achieved: Abstract and/or manuscript submitted (Goal – Month 48) – 0% complete

Specific Aim 2: Develop a self-report measurement tool to predict the probability of CBP patients responding to DCS and/or placebo

Major Task 1: Develop models of self-report measurement tool
Milestone Achieved: Initial model developed (Goal – Month 30) – 0% complete

Major Task 2: Collect data after database lock and refine final model
Milestone Achieved. Measurement tool developed (Goal – Month 46) – 0% complete
Milestone Achieved. Abstract and/or manuscript submitted (Goal – Month 48) – 0% complete

- **What was accomplished under these goals?**

During the fifth year, we have concluded enrollment into the study. Recruitment has been completed to the extent possible due to continued challenges posed by the COVID-19 pandemic. Screening and enrollment of participants (Specific Aim 1, Major Task 3) was completed in the second quarter with 203 participants randomized and treated. 164 participants completed the primary endpoint/Week 12 visit, 150 completed the final/Week 24 visit, and 53 withdrew or were lost to follow-up. All data has been obtained and entered into the study database (Specific Aim 1, Major Task 3).

As previously reported to the DOD, local IRB, and FDA, during this reporting year, an error was discovered in pharmacy drug allocation. The compounding pharmacy dispensed an incorrect study treatment to some participants. All these participants still received one of two study treatments: DCS or placebo. Due to a low study drug supply and to fix the imbalance in the number of participants assigned to the two study treatments, the PI prospectively assigned the next cohort of participants to a single treatment.

This event was reported to the local IRB in February 2023. Since the report, NU IRB held two panel reviews and requested multiple action items which the study team has fulfilled. Per the IRB's request, an independent study statistician reviewed this situation and determined that the study data collected from those participants who were not

randomized per protocol are still evaluable. The IRB has required that all participants who were incorrectly assigned were to be notified of the event and their written consent is obtained prior to using their collected study data in the study analysis.

In the last quarter of this reporting period, the statistical analysis plan has been revised by the independent statistician and received IRB approval. We have mailed out letters to all affected participants and received some of the written consents, now waiting for the rest to be mailed back to us. Once it is determined which participants are to be included in the analysis, the database will be cleaned and locked, and study analyses will be initiated.

All regulatory approvals have been maintained during the past reporting year, including FDA annual report submission. While participants were active in the study, safety was continually monitored by collection of adverse events for review by the investigators and the medical monitor during data safety monitoring committee (DSMC) meetings at intervals directed by protocol. No safety concerns have been identified at the DSMC meetings held during this reporting year

- **What opportunities for training and professional development has the project provided?**

  Four post-doctoral fellows have been actively involved in this study, two focusing primarily on brain imaging data collection and two serving as lead study coordinators. Their involvement in this study has been beneficial for their professional development.

- **How were the results disseminated to communities of interest?**

  Portions of the data collected to date have been presented at the 2021 Society for Neuroscience annual meeting. Data has also been published in PAIN and in Pain and Therapy (see section 6). The data included in these publications were baseline data from study subjects. No data was unblinded and all was deidentified.

- **What do you plan to do during the next reporting period to accomplish the goals?**

  The goal for the next reporting period will be to complete a database lock, all data analyses, and prepare a manuscript to submit to a scientific journal. We will continue to maintain all regulatory approvals and then close out the study with our local IRB and submit a close out report to the DOD. We also plan to publish the study results on ClinicalTrials.gov.

4. Impact

- **What was the impact on the development of the principal discipline(s) of the project?**

  Nothing to report at this time.

- **What was the impact on other disciplines?**

  Nothing to report at this time.

- **What was the impact on technology transfer?**

  Nothing to report.

- **What was the impact on society beyond science and technology?**

  Nothing to report at this time.

5. Changes/Problems

- **Changes in approach and reasons for change**

  The major problem we have faced and that continued to pose a challenge to our recruitment was the COVID-19 pandemic and its effects on our site's operations. We made multiple adjustments in our outreach and how we conducted our study visits, which resulted in our enrollment rate to be fairly stable over the past 2-3 years; however, it still remained approximately 50% less of our pre-pandemic rate of enrollment.

  At the beginning of this reporting period, our Lead Coordinator, Dr. Espinosa-Salas trained another post-doctoral fellow Leila Bagherzadeh to help with recruitment and data collection efforts. Together, they completed enrollment and all data collection. Ms. Simonian continued overseeing the study's regulatory affairs and corresponding with regulatory agencies about the errors in randomization allocation, allowing the study coordinators to continue to remain blinded.

- **Actual or anticipated problems or delays and actions or plans to resolve them**

  Although recruitment and enrollment increased significantly after the Covid pandemic, we requested and received two full year extensions to the study to permit further accrual of participants. We had adequate funding to allow for these additional activities, having reduced our expenditures on this project during the pandemic when enrollment was much slower. We targeted to enroll 200 participants by the end of December 2022 and were close to reaching that goal, enrolling 197 participants. We continued enrolling and were able to reach and surpass our n=200 enrollment goal, completing enrollment in early February 2023 with 203 participants.

  Due to our IRB's directives to conclude participation of participants who were affected by the randomization allocation error, the number of potentially completed study visits was decreased. In addition, if some of these participants do not consent to have their data be included in the final analysis, our sample size will also be slightly affected. Nevertheless, we still have a robust sample size and anticipate obtaining meaningful results about efficacy of the study drug in patients with chronic low back pain. We hope

to publish the study results, whether positive or negative, in a relevant medical journal and also present the data at scientific conferences.

- **Changes that had a significant impact on expenditures**

  As a consequence of the slower enrollment rate during the study, we have had a lower rate of expenditures for participants' costs. We have also attempted to conserve funds as much as possible in order to ensure that adequate funding will be present to allow for higher enrollment in the event that it takes longer than originally planned (see above). We requested and were granted two no-cost-extensions.

- **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

  Nothing to report.

- **Significant changes in use or care of human subjects**

  Nothing to report.

- **Significant changes in use or care of vertebrate animals**

  Not applicable.

- **Significant changes in use of biohazards and/or select agents**

  Not applicable.

6. Products

- **Publications, conference papers, and presentations**

  - **Journal publications**

    Wakaizumi K, Vigotsky AD, Jabakhanji R, Abdallah M, Barroso J, Schnitzer TJ, Apkarian AV, Baliki MN. Psychosocial, functional, and emotional correlates of long-term opioid use in patients with chronic back pain: a cross-sectional case-control study. Pain Ther. 2021 Jun;10(1):691-709. doi: 10.1007/s40122-021-00257-w. Epub 2021 Apr 12.

    Pinto CB, Bielefeld J, Barroso J, Yip B, Huang L, Schnitzer TJ, Apkarian AV. Chronic pain domains and their relationship to personality, abilities, and brain networks. PAIN: April 20, 2022. doi: 10.1097/j.pain.0000000000002657

  - **Books or other non-periodical, one-time publications**

Nothing to report.

- **Other publications, conference papers, and presentations**

  Bonin Pinto C, Bielefeld J, Barroso J, Yip BK, Huang L, Baliki MN, Schnitzer TJ, Apkarian AV. Constituent dimensions of chronic pain domains and their relationship to psychology and brain connectivity. Poster presentation at the Society for Neuroscience Annual Meeting, Chicago, USA, November 8-11, 2021.

- **Website(s) or other Internet site(s)**

  Nothing to report.

- **Technologies or techniques**

  Nothing to report.

- **Inventions, patent applications, and/or licenses**

  Nothing to report.

- **Other Products**

  Nothing to report.

7. Participants & Other Collaborating Organizations

- **What individuals have worked on the project?**

Name:	*Dr. Thomas Schnitzer*
Project Role:	*Principal Investigator (Northwestern University)*
Researcher Identifier:	*n/a*
Nearest person month worked:	*4*
Contribution to Project:	*Dr. Schnitzer has been providing oversight of regulatory and recruitment activities and drug acquisition/preparation.*

Name:	*Kathlyn Craigie*
Project Role:	*Recruitment Manager*
Researcher Identifier:	*n/a*
Nearest person month worked:	*2*
Contribution to Project:	*Ms. Craigie is responsible for developing and implementing programs to identify appropriate participants.*

Name:	*A. Vania Apkarian*
Project Role:	*Co-Investigator*
Researcher Identifier:	*n/a*
Nearest person month worked:	*1*
Contribution to Project:	*Dr. Apkarian will supervise brain imaging*

Name:	*Prakash Jayabalan*
Project Role:	*Co-Investigator*
Researcher Identifier:	*n/a*
Nearest person month worked:	*1*
Contribution to Project:	*Dr. Jayabalan will perform physical examinations and assist with reviewing labs and adverse events.*

Name:	*Joana Barroso*
Project Role:	*Post-doctoral fellow*
Researcher Identifier:	*n/a*
Nearest person month worked:	*1*
Contribution to Project:	*Dr. Barroso will perform physical examinations, assist with reviewing labs and adverse events, and be responsible for collecting the brain imaging data.*

Name:	*Lejian Huang*
Project Role:	*Senior Post-doctoral fellow*
Researcher Identifier:	*n/a*
Nearest person month worked:	*4*
Contribution to Project:	*Dr. Huang will work to analyze the MRI data being collected from the brain imaging.*

Name:	*Amanda Murphy*
Project Role:	*Nurse Practitioner*
Researcher Identifier:	*n/a*
Nearest person month worked:	*4*
Contribution to Project:	*Mrs. Murphy performs physical examinations and assists with reviewing labs and adverse events.*

Name:	*Elizabeth Yan*
Project Role:	*Study Coordinator*
Researcher Identifier:	*n/a*
Nearest person month worked:	*1*
Contribution to Project:	*Ms. Yan assisted in screening and collecting data.*

Name:	*Leila Yazdanbakhsh*
Project Role:	*Research Assistant*
Researcher Identifier:	*n/a*

Nearest person month worked:	*1*
Contribution to Project:	*Ms. Yazdanbakhsh assisted with recruitment efforts.*

Name:	*Graeme Witte*
Project Role:	*Research Assistant*
Researcher Identifier:	*n/a*
Nearest person month worked:	*1*
Contribution to Project:	*Mr. Witte assisted with recruitment efforts.*

Name:	*Meghan Ford*
Project Role:	*Study Coordinator*
Researcher Identifier:	*n/a*
Nearest person month worked:	*1*
Contribution to Project:	*Ms. Ford assisted in screening and collecting data.*

Name:	*Leila Bagherzadeh, MD*
Project Role:	*Post-Doctoral Fellow*
Researcher Identifier:	*n/a*
Nearest person month worked:	*5*
Contribution to Project:	*Dr. Shuaib recruited and enrolled participants and collected data.*

Name:	*Narina Simonian, CCRC*
Project Role:	*Project Manager*
Researcher Identifier:	*n/a*
Nearest person month worked:	*3*
Contribution to Project:	*Mr. Simonian provides regulatory oversight.*

Name:	*Santiago Espinosa-Salas, MD*
Project Role:	*Lead Study Coordinator/Post-Doctoral Fellow*
Researcher Identifier:	*n/a*
Nearest person month worked:	*8*
Contribution to Project:	*Dr. Espinosa-Salas recruited and enrolled patients.*

Name:	*Adin-Christian Andrei, PhD*
Project Role:	*Independent Statistician*
Researcher Identifier:	*n/a*
Nearest person month worked:	*1*
Contribution to Project:	*Dr. Andrei is assisting with data analysis.*

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

  Nothing to report at this time.

- **What other organizations were involved as partners?**

  The Shirley Ryan AbilityLab (formerly Rehabilitation Institute of Chicago) has acted as an additional site for recruitment of participants.

8. Special Reporting Requirements

- **Collaborative Awards**

  Nothing to report.

- **Quad Charts**

  Quad chart: attached.

9. Appendices

None.

D-Cycloserine for the Treatment of Chronic, Refractory Low Back Pain

Proposal Log Number PR160108; Award # W81XWH-17-1-0426; HRPO Log A-20364

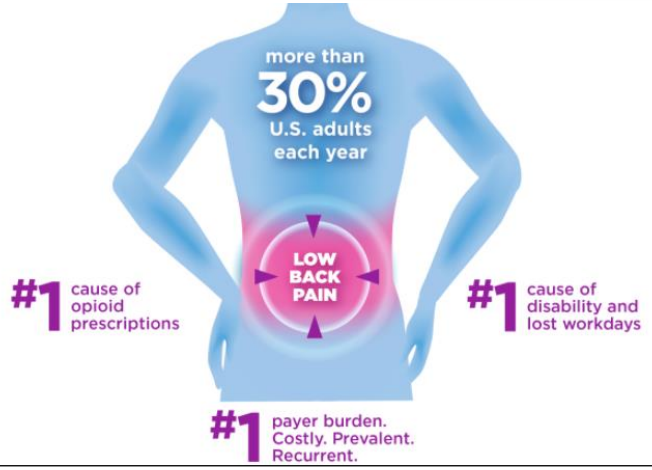
PI: Dr. Thomas J. Schnitzer **Org:** Northwestern University Feinberg School of Medicine **Award Amount: $4,883,210**

Study/Product Aims

- Determine the efficacy and safety of DCS compared to placebo to reduce pain in people with chronic low back pain
- Define brain biomarkers that will allow prediction of people who will respond to specific intervention, placebo or DCS, in this population
- Develop a self-report measurement tool to predict the probability of CBP patients responding to DCS and/or placebo.

Approach

Participants will be enrolled in this randomized, double-blind parallel-group study of d-cycloserine 200mg bid and placebo. Pain-related data will be collected throughout the 6 months of treatment (3 months double-blinded active/placebo; 3 subsequent months single-blinded placebo); brain imaging will occur at baseline and 3 months.



All regulatory approvals have been received. 436 participants have been consented and screened and 203 randomized. All participant visits have concluded during this reporting year as has all data collection. Data clean up is currently in progress.

Timeline and Cost

Activities CY	17	18	19	20	21	22	23	24
Study Start-Up Activities								
Participant Enrollment								
Data Collection and Entry								
Data Analysis								
Estimated Budget ($K)	$269	$1,150	$1,387	$1,322	$720	$0	$0	$0

completed initial projection updated projection

Goals/ Milestones

CY17 Goals – Begin study start-up. Regulatory approval at NU obtained.
CY18 Goals – Start-up completed. Recruitment begun and on-going.
CY19 Goals – Continue recruitment and enrollment
CY20-22 Goals – Continue recruitment and enrollment and data collection
CY23 Goals – Complete data collection; complete analysis of clinical and brain imaging data; develop self-report tool
CY24 Goals – Complete database lock, data analysis, submit for publication

Comments/Challenges/Issues/Concerns

The pandemic resulted in a hold on continued enrollment from March 2020-end of June 2020. Research has since resumed but at a reduced pace. Recruitment has concluded this reporting period with 83% (203/244) of participants enrolled. No active participants remain.

Budget Expenditure to Date: (through Sept 30, 2023)
Projected Expenditure: $4,883,210
Expenditures: $4,795,912

Updated: 30 Sep 2023