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

PRINCIPAL INVESTIGATOR: Thomas J. Schnitzer, MD, PhD

CONTRACTING ORGANIZATION: Northwestern University, Evanston, IL

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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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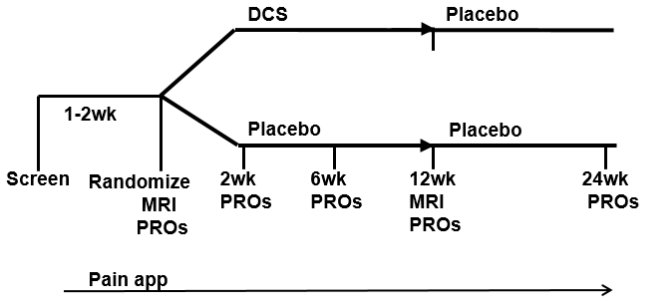
1. Introduction

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) – 78.3% complete
Milestone Achieved: All data collected (Goal – Month 42) – 73.8% 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?**

All objectives outlined in the Statement of Work to be completed during the fourth year have been completed to the extent possible due to continued challenges posed by the ongoing COVID-19 pandemic. Subject recruitment is on-going and we have fine-tuned our social media campaign to maximize exposure in our geographic reach. We have also continued to receive weekly reports of all new back pain patients seen at Northwestern Medicine and reach out to them on an on-going basis. Though we have resumed in-person screening and subsequent enrollment and follow-up as approved by our institutional IRB before the COVID-19 pandemic, we maintain the ability to also conduct virtual visits with remote data collection as needed.

Screening and enrollment of participants (Specific Aim 1, Major Task 3) is ongoing. 191 participants have been randomized and treated at the end of this reporting period. 136 participants have completed the final Week 24 follow-up visit, 44 have withdrawn or been lost to follow-up, and 11 are currently active in the study. Data are being obtained and entered into the study database (Specific Aim 1, Major Task 3). As the investigators remain blinded to allocation of treatment assignment, efficacy data will not be available until all participants have completed the study, the database is cleaned and locked, and

analyses completed.

All regulatory approvals have been maintained during the past reporting year, including FDA annual report submission. There have been no unapproved significant changes. Safety is being 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. Two DSMC meetings were held during this reporting year with no safety concerns identified.

- **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 enrollment of participants into the trial, retention and data collection. We plan to continue our recruitment and enrollment efforts while observing institutional and governmental COVID-19 guidelines and recommendations to maintain the safety and well-being of study participants and staff. These efforts include continuing our social media campaign to maximize exposure in our geographic reach and reaching out to more patients seen in our medical system.

  With respect to conducting study visits and collecting data, we have returned to a normal schedule among our research staff and resumed in-person participant visits while maintaining the ability to conduct virtual visits which allow for remote electronic collection of data when needed. We will continue to maintain all regulatory approvals to allow for this hybrid approach when needed to obtain all data as outlined in the study protocol while maintaining the safety and well-being of study participants and staff. Regarding study drug availability, we have established a relationship with an external pharmacy that has been reformulating d-cyloserine into the protocol-specified study drug dosage and dispensing it to our study participants. We have sufficient supply of study drug to complete the trial without further purchases.

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 continues to pose a challenge is the COVID-19 pandemic and its effects on our site's operations. We have largely returned to a normal schedule both in the clinic and with respect to screening and following participants in the study. We have made good progress with our staff being in the office on a regular schedule, 5 days/week with safety protocol in place. However, we have continued to experience reluctance on the part of participants to come to the clinic with a high no-show rate. We have thus increased our outbound calls and are scheduling more people than before, but many are simply not showing up. Our enrollment rate has been fairly stable over the past 1-2 years; however, it remains down to approximately 50% of our pre-pandemic rate of enrollment.

  In this reporting period, we have had changes to our Lead Coordinator, Byron Yip, who was the project lead coordinator since its beginning. Mr. Yip left in January 2022. Ms. Narina Simonian who has substantial experience with coordinating DOD-funded studies, took over oversight of the study and managing regulatory affairs. Dr. Rahia Shuaib took over the clinical aspects of the study. Dr. Shuaib seamlessly picked up the study and increased monthly enrollment, achieving one month with 5 people randomized. Prior to Dr. Shuaib' leave for a residency program, she thoroughly trained our new post-doctoral fellow, Dr. Santiago Espinosa-Salas. Dr. Espinosa-Salas is continuing Dr. Shuaib's recruitment efforts and averaging an enrollment rate of 3 participants per month. Ms. Simonian is continuing overseeing the study's regulatory affairs.

As noted above, we are enhancing our outreach efforts both via social media and by utilizing the electronic database from our health system. These efforts are time- and personnel-intensive but have worked previously and we believe they will be effective in reaching our enrollment goal.

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

  Our enrollment rate has not yet returned to our pre-COVID-19 level. Consequently, we have increased our spending on social media outreach, which was successful pre-pandemic, and reaching out to more patients seen in our medical system. We have posted flyers throughout the Northwestern Medical Campus and utilizing our research registry for identifying study candidates.

  We anticipate that enrollment will continue for an additional 3-4 months, limited by the need for a 6 month duration of the study, thus leaving approximately 3 months for final data collection, locking the database, data analysis and preparation of a manuscript. . We had reduced our personnel effort during the pandemic in order to have adequate funding. We have requested a second year of no-cost extension to allow for further progress of the study and anticipate that the funding available from this award will be adequate for this period of time.

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

  As a consequence of the slower enrollment rate, 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).

- **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:	*Byron Yip*
Project Role:	*Lead Study Coordinator*
Researcher Identifier:	*n/a*
Nearest person month worked:	*3*
Contribution to Project:	*Mr. Yip has completed preparatory work and is currently enrolling participants and collecting data.*

Name:	*Kathlyn Craigie*
Project Role:	*Recruitment Manager*
Researcher Identifier:	*n/a*
Nearest person month worked:	*6*
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:	*2*
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:	*6*
Contribution to Project:	*Dr. Huang will work to analyze the MRI data being collected from the brain imaging.*

Name:	*Michael Tam*
Project Role:	*Physician Assistant*
Researcher Identifier:	*n/a*
Nearest person month worked:	*2*
Contribution to Project:	*Mr. Tam performed physical examinations and assisted with reviewing labs and adverse events.*

Name:	*Amanda Murphy*
Project Role:	*Nurse Practitioner*
Researcher Identifier:	*n/a*
Nearest person month worked:	*3*
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:	*2*
Contribution to Project:	*Ms. Yan assist in screening and collecting data.*

Name:	*Leila Yazdanbakhsh*
Project Role:	*Research Assistant*
Researcher Identifier:	*n/a*
Nearest person month worked:	*2*
Contribution to Project:	*Ms. Yazdanbakhsh is assisting with recruitment efforts.*

Name:	*Graeme Witte*
Project Role:	*Research Assistant*
Researcher Identifier:	*n/a*
Nearest person month worked:	*2*
Contribution to Project:	*Mr. Witte is assisting with recruitment efforts.*

Name:	*Meghan Ford*
Project Role:	*Study Coordinator*

Researcher Identifier:	*n/a*
Nearest person month worked:	*2*
Contribution to Project:	*Ms. Ford assists in screening and collecting data.*

Name:	*Rahia (Laila) Shuaib, MD*
Project Role:	*Lead Study Coordinator*
Researcher Identifier:	*n/a*
Nearest person month worked:	*8*
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*
Researcher Identifier:	*n/a*
Nearest person month worked:	*5*
Contribution to Project:	*Dr. Espinosa-Salas is recruiting and enrolling patients.*

- **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

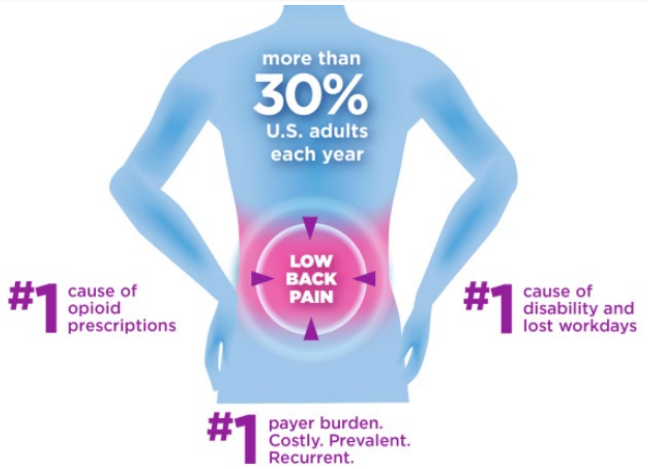
PI: Dr. Thomas J. Schnitzer **Org:** Northwestern University Feinberg School of Medicine **Award Amount: $4,883,210**

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. IP has been reformulated and is available. 415 participants have been consented and screened and 191 randomized. Recruitment has improved considerably, and we anticipate maintaining this rate of enrollment until the study is closed during the next fiscal year.

Timeline and Cost

Activities CY	17	18	19	20	21	22	23
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

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

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. With almost 80% of participants enrolled, we plan to continue recruitment efforts during the second no-cost extension year to get as close to our enrollment target as possible.

Budget Expenditure to Date: (through end of September, 2022)
Projected Expenditure: $4,883,210
Expenditures: $3,742,668

Updated: 14 October 2022