

AWARD NUMBER: W81XWH-17-1-0426

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

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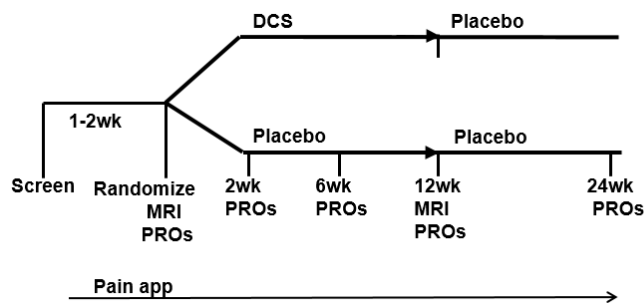
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14. ABSTRACT Chronic low back pain constitutes the major form of chronic pain, with a prevalence as high as 70-85% in adults at some time in their lives. This 26-week, double blind, randomized, placebo controlled two-arm parallel-group study will evaluate 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.						
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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) – 52.0% complete

Milestone Achieved: All data collected (Goal – Month 42) – 37.7% 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 third year have been completed to the extent possible due to continued challenges posed by the ongoing COVID-19 pandemic. Specifically, there was a stay-at-home order for the state of Illinois from March 21, 2020, through May 31, 2020, during which Northwestern University instituted a policy that placed a hold on all non-essential clinical research, including enrollment of new participants, during this period. Human subjects research was finally allowed to resume on June 29, 2020. Participants who were already enrolled in clinical research trials during the March-June period could continue in these studies with data collected electronically whenever possible. In addition, all University research facilities, such as imaging, were not functioning during this time. However, all regulatory approvals have been maintained during the past reporting year. This included modifications to collect data electronically from actively enrolled subjects during the stay-at-home order period and to subsequently implement a hybrid of conducting virtual and in-person visits based on the needs of the schedule of evaluations per protocol to minimize the risk of COVID-19 infection to all research staff and participants once human subjects research was allowed to resume.

Screening and enrollment of participants (Specific Aim 1, Major Task 3) is ongoing. 127 participants have been randomized and treated. 92 participants have completed the final

Week 24 follow-up visit, 28 have withdrawn or been lost to follow-up, and 7 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. Safety is being continually monitored by collection of adverse events for review by the investigators and the medical monitor during data safety monitoring committee meetings at intervals directed by protocol. No safety concerns have been identified and there have been no unapproved significant changes in the study proposed.

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

Two post-doctoral fellows have been actively involved in this study, focusing primarily, at this point, on brain imaging data collection. Their involvement in this study has been beneficial for their professional development. There also has been training opportunities for a new coordinator and research assistant in a variety of instruments for collection of pain measures (e.g., NIH Toolbox, PROMIS).

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

Nothing to report at this time.

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

The goal for the next reporting period will be enrollment of participants into the trial, retention and data collection. Since resuming enrollment in July 2020 after a 3-month pause due to Illinois' stay-at-home order, we plan to continue to gradually increase 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 have included restarting our social media campaign which had been scaled back and placed on hold until we could resume enrollment. Our enrollment rate has not yet returned to our pre-COVID-19 level but we have identified new clinics and clinical practices from which we plan to recruit participants. We have made contact with the physicians involved and will work with their staffs as well as involve our recruitment manager to a greater extent in these efforts.

With respect to conducting study visits and collecting data, we have implemented changes to resume in-person visits only as necessary to complete certain required evaluations and assessments (i.e. imaging, physical exam, labs, etc.) and to conduct virtual visits which allow for remote electronic collection of data when possible. We will continue to employ this hybrid approach to obtain all data as outlined in the study protocol while maintaining the safety and well-being of study participants and staff.

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 faced and that continues to pose a challenge is the COVID-19 pandemic and its effects on our site's operations. From March-June 2020, the State of Illinois was under a stay-at-home order which required that we cancel all new in-person activities; however, follow-up visits were remotely completed to the extent possible with all active subjects who were previously enrolled into the study up until that point. Some data could not be collected for these subjects which included their MR imaging scheduled at 3 months as they were unable to come in and our imaging facility was likewise closed. However, we attempted to capture the critical data for the primary outcome of the trial, the participants' pain ratings, which is being collected via our study pain diary website. Thus, participants continued to complete pain ratings through our study pain diary website and we are conducting surveys electronically. We also sent medication, as appropriate, to participants to allow them to continue in the study. AEs were also being collected for safety.

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

The COVID-19 pandemic has had and continues to have a significant impact on our ability to enroll new subjects into this trial. In essence, we have lost approximately 6 months of enrollment activity due to the total shutdown of new clinical research activities and the slow ramp-up allowed subsequently by our university in order to maximize safety for research staff. Only during the past 2-3 weeks have we begun to reach levels of study visits similar to those prior to the pandemic that were on target for our completing

enrollment as planned. Having said that, at this very time there appears to be a marked increase in new viral infections in the community, and the impact of that on our work is unknown. It is clear that there is a marked reluctance on potential study subjects to come in for visits, meaning that we have to devote more resources to recruitment now than ever before. There is also the possibility that if another wave of infections occur that the city, state or university could mandate that we discontinue new research participant visits. What we are doing at this stage is, as noted, devoting more resources to recruitment, identifying new recruitment sites, and attempting to identify and screen as many people as quickly as possible. We have identified several new clinics and clinical practices from which we plan to recruit participants. We have made contact with the physicians involved and will work with their staffs as well as involve our recruitment manager to a greater extent in these efforts.

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

One of the consequences of the pandemic and its impact on our research unit as described above, has been on our overall expenditures in study progress. Due to the shutdown of new research activities, we continued to incur costs of study staff who were involved with continuing to collect data from on-going research participants, but we were not able to simultaneously enroll new participants. As a consequence, for us to achieve full enrollment, we will need a minimum of 6-9 months of additional personnel time and costs, over and above the situation we were in pre-pandemic. We had attempted to conserve funds as much as possible in order to ensure that some funding would be present to allow for full enrollment, but at this point even that funding will likely not be adequate given the delays we have experienced.

- **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**

Nothing to report at this time.

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

Nothing to report.

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

Nothing to report

- **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:	<i>Dr. Thomas Schnitzer</i>
Project Role:	<i>Principal Investigator (Northwestern University)</i>
Researcher Identifier:	<i>n/a</i>
Nearest person month worked:	<i>2</i>
Contribution to Project:	<i>Dr. Schnitzer has been providing oversight of regulatory and recruitment activities and drug acquisition/preparation.</i>

Name:	<i>Byron Yip</i>
Project Role:	<i>Lead Study Coordinator</i>
Researcher Identifier:	<i>n/a</i>
Nearest person month worked:	<i>12</i>
Contribution to Project:	<i>Mr. Yip has completed preparatory work and is currently enrolling participants and collecting data.</i>

Name:	<i>Kathlyn Craigie</i>
Project Role:	<i>Recruitment Manager</i>
Researcher Identifier:	<i>n/a</i>
Nearest person month worked:	<i>6</i>
Contribution to Project:	<i>Ms Craigie will be responsible for developing and implementing programs to identify appropriate participants.</i>

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

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

Name:	<i>Joana Barroso</i>
Project Role:	<i>Post-doctoral fellow</i>
Researcher Identifier:	<i>n/a</i>
Nearest person month worked:	<i>6</i>
Contribution to Project:	<i>Dr. Barroso will perform physical examinations, assist with reviewing labs and adverse events, and be responsible for collecting the brain imaging data.</i>

Name:	<i>Lejian Huang</i>
Project Role:	<i>Senior Post-doctoral fellow</i>
Researcher Identifier:	<i>n/a</i>
Nearest person month worked:	<i>6</i>
Contribution to Project:	<i>Dr. Huang will work to analyze the MRI data being collected from the brain imaging.</i>

musculoskeletal and post-surgical pain, as part of the NIH-led Acute to Chronic Pain Signatures (A2CPS) program. The DIRC will work closely with omics centers specifically tasked with omics analyses, as well as the clinical coordinating center and multi-site data collection centers.

Role: Co-Investigator

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

During the first year we have not involved other institutions. We are actively involved currently with plans to involve Shirley Ryan AbilityLab (formerly Rehabilitation Institute of Chicago) as a 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. 313 participants have been screened, 251 consented and 127 randomized. Recruitment was on hold from mid-March through end of June 2020 but has resumed. We are anticipating this will delay full enrollment by at least 6 months.

Timeline and Cost

Activities	CY	17	18	19	20	21	22
Study Start-Up Activities		■					
Participant Enrollment			■	■	■	■	
Data Collection and Entry			■	■	■	■	■
Data Analysis					■	■	■
Estimated Budget (\$K)		\$269	\$1,150	\$1,387	\$1,322	\$720	\$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 Goals** – Continue recruitment and enrollment
- CY21 Goals** – Complete subject enrollment and data collection
- CY22 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 this hold will require additional time for enrollment. The rate of new enrollment during the pandemic is hard to predict but we should have a better idea by next quarter. Financial consequences also will be better understood then.

Budget Expenditure to Date: (through end of September 2020)
 Projected Expenditure: \$3,758,322
 Actual Expenditure: \$2,313,167 (does not include encumbrances)