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

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CONTRACTING ORGANIZATION: Northwestern University, Evanston, IL

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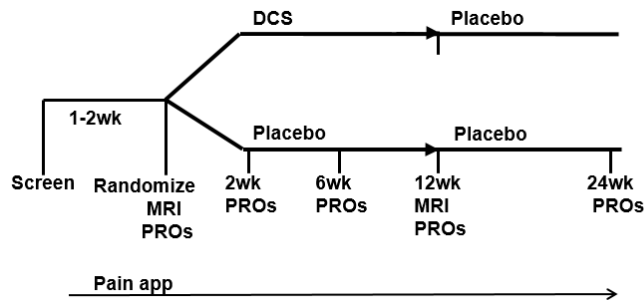
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14. ABSTRACT Chronic low back pain constitutes the major form of chronic pain, with a prevalence as high as 70-85% in adults at some time in their lives. This 26-week, double blind, randomized, placebo controlled two-arm parallel-group study will evaluate 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) – 66.0% complete

Milestone Achieved: All data collected (Goal – Month 42) – 61.1% 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. 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 monthly reports of all new back pain patients seen at Northwestern Medicine and reach out to them on an on-going basis. All regulatory approvals have been maintained during the past reporting year. Though we have resumed single visit 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 with the pandemic still ongoing.

Screening and enrollment of participants (Specific Aim 1, Major Task 3) is ongoing. 161 participants have been randomized and treated. 118 participants have completed the final Week 24 follow-up visit, 31 have withdrawn or been lost to follow-up, and 12 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?**

Portions of the data collected to date have been utilized for an abstract accepted for presentation at the upcoming 2021 Society for Neuroscience annual meeting and for a publication in Pain and Therapy.

- **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. We plan to continue to 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 fine-tuning our social media campaign to maximize exposure in our geographic reach. Our enrollment rate has not yet returned to our pre-COVID-19 level. Consequently, we are increasing 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 and will be testing other local advertising approaches (free newspaper in Chicago, public transit advertising, etc.).

With respect to conducting study visits and collecting data, we have returned to a more normal schedule among our research staff and have largely 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 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 were successful in obtaining a new shipment of drug which will again be formulated at our pharmacy and we anticipate that this supply will allow us 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. Since our last report, we have largely returned to a more 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 now being in the office on a regular schedule, 5 days/week. 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. The vaccination rate in our area has been relatively successful but the city of Chicago lags behind the state of Illinois overall with just over half the population being fully vaccinated and under 60% having received at least one shot. Thus, there remains a high level of concern among the population at large. We continue to have safety protocols in place and are hoping we can get back to pre-pandemic levels of activity. During the last reporting period our enrollment rate has decreased somewhat, down to approximately 50% of our pre-pandemic rate of enrollment. 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 again.

It remains difficult to estimate what additional impact the ongoing pandemic will have on recruitment and enrollment of participants. However, we remain hopeful that we can continue enrollment and reach higher numbers than in the past year.

- **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 are increasing 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 and will be testing other local advertising approaches (free newspaper in Chicago, public transit advertising, etc.).

We anticipate that enrollment will require a minimum of an additional 12 months and possibly 18 months. We had reduced our personnel effort during the pandemic in order to have adequate funding to allow for at least an additional 18 months of study conduct, anticipating the 12-month delay and a 6-month period for final data collection, cleaning and analysis. If enrollment continues for 18 months, we may need and will request a second year of no-cost extension to allow for completion of the study though some degree of cost-sharing may be required as it is doubtful that the funding available from this award will be fully adequate.

- **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 full 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.

- **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. Accepted poster presentation at the upcoming 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:	<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,</i>

	<i>assist with reviewing labs and adverse events, and be responsible for collecting the brain imaging data.</i>
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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>

Name:	<i>Michael Tam</i>
Project Role:	<i>Physician Assistant</i>
Researcher Identifier:	<i>n/a</i>
Nearest person month worked:	<i>2</i>
Contribution to Project:	<i>Mr. Tam will perform physical examinations and assist with reviewing labs and adverse events.</i>

Name:	<i>Elizabeth Yan</i>
Project Role:	<i>Study Coordinator</i>
Researcher Identifier:	<i>n/a</i>
Nearest person month worked:	<i>6</i>
Contribution to Project:	<i>Ms. Yan will assist Mr. Yip in screening and collecting data.</i>

Name:	<i>Zachary Feldman</i>
Project Role:	<i>Research Assistant</i>
Researcher Identifier:	<i>n/a</i>
Nearest person month worked:	<i>6</i>
Contribution to Project:	<i>Mr. Feldman will assist with recruitment and collecting data.</i>

- **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



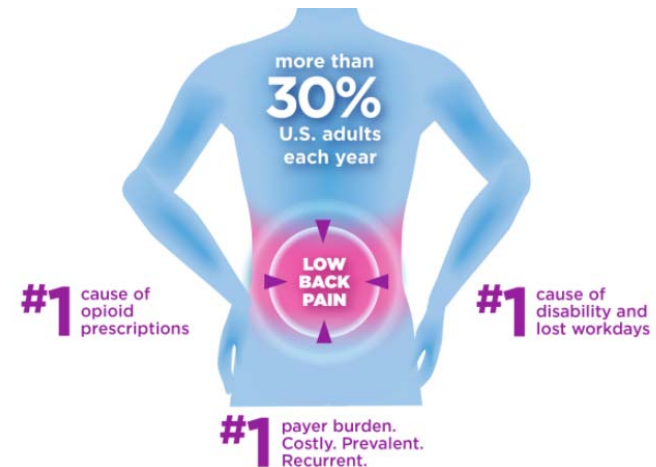
PI: Dr. Thomas J. Schnitzer Org: Northwestern University Feinberg School of Medicine Award Amount: \$4,883,210

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. 340 participants have been consented and screened and 161 randomized. Recruitment has continued but we anticipate the currently ongoing COVID-19 pandemic which began in early 2020 to delay full enrollment by 12-18 months.

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** – Continue recruitment and enrollment
- CY22 Goals** – Complete subject enrollment and 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. We will need at least another 18 months to reach enrollment targets. Additional financial support for the unforeseen personnel time will be available for at least an additional 12 months.

Budget Expenditure to Date: (through end of September 2021)
 Projected Expenditure: \$4,601,987
 Actual Expenditure: \$2,972,956 (does not include encumbrances)

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