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

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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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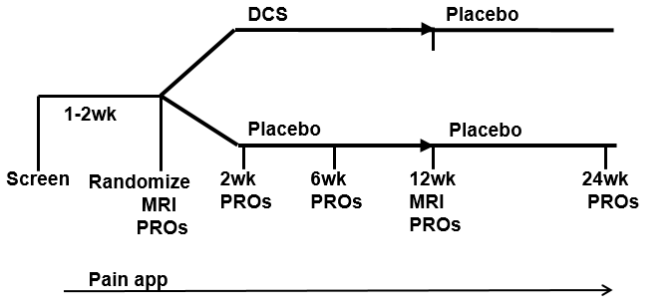
Table of Contents

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) – 28% complete
Milestone Achieved: 100% of participants enrolled (Goal – Month 39) – 14% complete
Milestone Achieved: All data collected (Goal – Month 42) – 0.4% 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 first year have been completed. All regulatory approvals have been maintained. Screening and enrollment of participants (Specific Aim 1, Major Task 3) is ongoing. 34 participants have been randomized and treated. One (1) participant has completed the final Week 24 follow-up visit, 3 have withdrawn or been lost to follow-up, and 30 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 in brain imaging data collection. Their involvement in this study has been beneficial for their professional development. There also has been training opportunities for the lead coordinator 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 on enrollment of participants into the trial, retention and data collection. Enrollment has slowed during the past 1-2 months, and 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.

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**

  There have been no changes at this time.

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

  Enrollment has slowed during the past 1-2 months, and 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.

- **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.

- **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/Inventions, Patent Applications, and/or Licenses

- **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:	*Dr. Thomas Schnitzer*
Project Role:	*Principal Investigator (Northwestern University)*
Researcher Identifier:	*n/a*
Nearest person month worked:	*2*
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:	*12*
Contribution to Project:	*Mr. Yip has completed preparatory work and is currently enrolling participants and collecting data.*

Name:	*Darwin Tse*
Project Role:	*Recruitment Manager*
Researcher Identifier:	*n/a*
Nearest person month worked:	*6*
Contribution to Project:	*Mr. Tse will be 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:	*Diane Reckziegel*
Project Role:	*Post-doctoral fellow*
Researcher Identifier:	*n/a*
Nearest person month worked:	*6*
Contribution to Project:	*Dr. Reckziegel will 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.*

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

  The PI has obtained funding as a co-investigator in the project noted below:

  P50 DA044121-01A1 Apkarian (PI) 090/01/2018-06/30/2023
  NIH/NIDA
  Center for Chronic Pain and Drug Abuse
  The goal of the Northwestern University Center for Chronic Pain and Drug Abuse is to address two critical challenges regarding chronic pain and its treatment: 1) Unravel the interaction between development of chronic pain, and opiate analgesia and opiate addiction; and 2) pursue molecular and circuit targets underlying the maladaptive plasticity that controls the interaction between chronic pain and opiate exposure, to discover potential novel minimally-addictive or non-addictive therapies for chronic pain.
  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

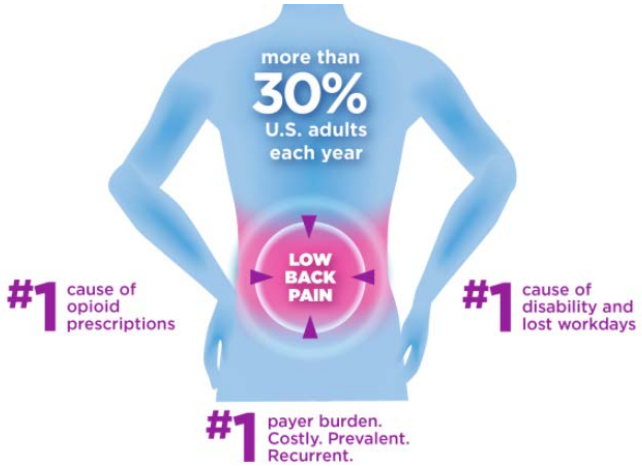
PI: Dr. Thomas J. Schnitzer **Org:** Northwestern University Feinberg School of Medicine **Award Amount: $4,883,210**

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. All study start-up activities have been completed. 39 participants have been consented and 19 randomized. Recruitment and the study are on track.

Timeline and Cost

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

completed projected

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 – Complete subject enrollment and data collection
CY21 Goals – Complete data collection; Complete analysis of clinical and brain imaging data; develop self-report tool.

Comments/Challenges/Issues/Concerns

Recruitment was on track through 30June 2018. Has slowed since then and additional clinic sites added with good results. Expenditures reduced to allow for additional time for recruitment.

Budget Expenditure to Date:

Projected Expenditure: $1,077,034
Actual Expenditure: $ 526,692

Updated: 11 October 2018