AWARD NUMBER: W81XWH-17-1-0426

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

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REPORT DATE: October 2019

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
October 2019	Annual	30Sep2018 - 29Sep2019

4. TITLE AND SUBTITLE

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

5a. CONTRACT NUMBER
W81XWH-17-1-0426

5b. GRANT NUMBER
PR160108

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

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.

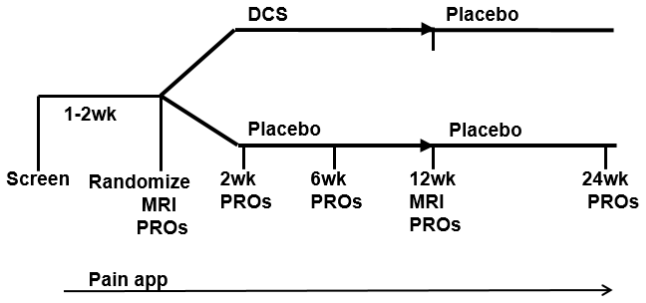
15. SUBJECT TERMS
Chronic pain, low back pain, d-cycloserine

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	11	19b. TELEPHONE NUMBER *(include area code)*

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) – 78.7% complete
Milestone Achieved: 100% of participants enrolled (Goal – Month 39) – 39.3% complete
Milestone Achieved: All data collected (Goal – Month 42) – 21.3% 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 second year have been completed. All regulatory approvals have been maintained. Screening and enrollment of participants (Specific Aim 1, Major Task 3) is ongoing. 96 participants have been randomized and treated. 52 participants have completed the final Week 24 follow-up visit, 16 have withdrawn or been lost to follow-up, and 28 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. We would like to enhance the enrollment rate to a minimum of 6-7 participants/month and ideally more. To this end, 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. We also will be adding additional staff to handle the increased recruitment outreach, screening and data collection activities.

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 been maintained at a steady rate with good progress, but we would like to enhance this further. As noted above, in order to accomplish this 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. We also will be adding additional staff to handle the increased recruitment outreach, screening and data collection activities.

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

  As a consequence of the somewhat slower than planned enrollment rate, we have had a lower rate of expenditures for participants' costs as well as reduced effort for research staff. This has allowed us to conserve funds to ensure that adequate funding will be present to allow for full enrollment over what is now foreseen as a longer enrollment period extending for an additional year.

- **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:	*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:	*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:	*6*
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:	*Diane Reckziegel*
Project Role:	*Post-doctoral fellow*
Researcher Identifier:	*n/a*
Nearest person month worked:	*6*
Contribution to Project:	*Dr. Reckziegel will assist with analyzing MRI data being collected from the brain imaging.*

Name:	*Tiana Zdravkovich*
Project Role:	*Study Coordinator*
Researcher Identifier:	*n/a*
Nearest person month worked:	*3*
Contribution to Project:	*Ms. Zdravkovich has been assisting Mr. Yip in*

	screening and collecting data

Name:	*Ethan Taira*
Project Role:	*Research Assistant*
Researcher Identifier:	*n/a*
Nearest person month worked:	*6*
Contribution to Project:	*Mr. Taira has been assisting with recruitment and collecting data.*

- **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) 09/01/2018 - 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

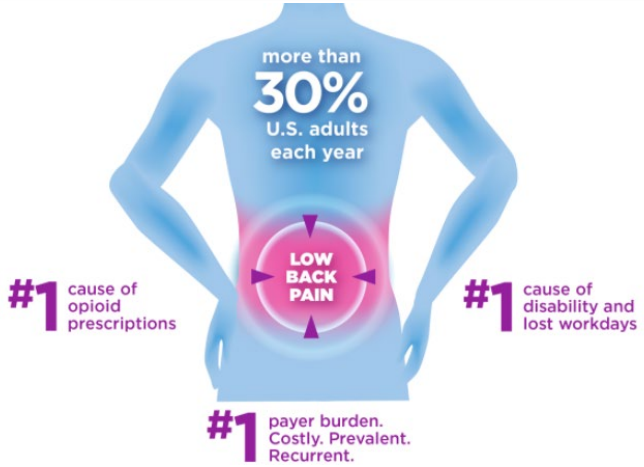
PI: Dr. Thomas J. Schnitzer **Org:** Northwestern University Feinberg School of Medicine **Award Amount: $4,883,210**

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. 374 participants have been screened, 176 consented and 96 randomized. Recruitment rate is steady and study continues on track with projected recruitment to be complete at end of Year 4.

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

Recruitment remains steady at 6 participants/month. Adding another coordinator and clinic to attempt to increase enrollment rate while staying on track to complete enrollment by end of Year 4. Expenditures reduced to allow for additional time for recruitment.

Budget Expenditure to Date:

Projected Expenditure: $2,373,904
Actual Expenditure: $1,343,213

Updated: 15 October 2019