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Sleep-Disordered Breathing in Chronic SCI: A Randomized Controlled Trial of Treatment Impact on Cognition, Quality of Life, and Cardiovascular Disease

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14. ABSTRACT This study addresses the widely recognized and heretofore incompletely managed cognitive, and cardiovascular (CV) secondary complications in military veterans and non-veterans with SCI. In this prospective randomized controlled trial, we will objectively measure sleep disordered breathing (SDB) in chronic SCI patients using portable sleep studies, and systematically evaluate the association between SDB, cognitive performance, mood, pain, and CV measures. We will randomize participants to 4 months of PAP or placebo. We will re-evaluate cognitive measures, quality of life, sleep quality, mood and CV outcomes after 4 months of therapy to determine whether PAP therapy has improved baseline impairments. There is minimal risk to study participants and significant potential for immediate and lasting benefits. In the first year of the study, we have completed the manual of study operations, designed a secure study database for data gathering, obtained local IRB approval at all study sites, and DoD approval for the University of Miami and Miami VA sites. Study equipment has been purchased. Research coordinators have been trained and we have enrolled 15 subjects at approved sites. Our first subject will be randomized shortly.					
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Annual Report 2013-2014

1. INTRODUCTION:

There is a paucity of information on the impact of sleep disordered breathing (SDB) and its treatment in chronic spinal cord injury (SCI). Despite the increased prevalence reported in the literature, screening for SDB and its treatment are not yet standard of care. To enable change in practice, well designed randomized placebo-controlled trials (RCT) are needed to demonstrate the importance of SDB and its treatment on the health of this population. The central hypothesis of this study is that the treatment of SDB with positive airway pressure (PAP) will improve cognitive impairment, sleep quality, quality of life, and cardiovascular disease (CVD) surrogate measures in persons with chronic SCI. The Specific Aims are: 1) Determine the associations between SDB and cognitive impairment and evaluate the impact of PAP therapy on cognitive measures, and 2) Determine the impact of PAP therapy on surrogate CV biomarkers, sleep quality, quality of life, mood, and pain, in a cohort with chronic SCI and SDB.

This is a four year multi-center double blinded, placebo controlled RCT. We will objectively measure SDB in chronic SCI participants using portable unattended polysomnography, and randomize those with SDB to four months of therapeutic PAP vs. sham PAP (placebo). We will measure cognitive performance (memory, attention, and executive function) using a battery of standardized neuro-cognitive tests (PASAT-primary outcome). Additionally, we will measure surrogate CVD biomarkers. All measurements will be done at baseline and four month follow-up.

2. **KEYWORDS:** Spinal cord injury, Sleep disordered breathing, Positive airway pressure, Randomized controlled Trial, Cognition, Quality of life, Sleep Quality, Polysomnography

3. ACCOMPLISHMENTS:

- **What were the major goals of the project?**

Study Tasks

Task 1. Regulatory Approval (months 1-6)

1a. Obtain IRB approval University of Miami and Miami VA (months 1-3) **Completed**

1b. Obtain IRB approval Wayne State University and Detroit VA (months 1-3) **Completed**

1c. Obtain DoD regulatory approval (months 1-6) **Miami site Feb 25, 2014; Miami VA site**

April 11, 2014, Wayne State and Detroit VA pending

1d. Obtain final project approval (month 6) **Completed for Miami site not for Detroit site**

Task 2. Elaborating Study Protocol, Training, Purchasing Equipment, and Database Design (months 1-5)

2a. Finalizing a detailed study manual explicitly outlining inclusion/exclusion criteria, protocols for recruitment, questionnaire administration, performing portable polysomnography, scoring of questionnaires, and scoring of sleep studies (months 1-5) **Completed**

2b. Design of study database (months 1-2) **Completed**

2c. Training of Research Associates in study protocol, recruitment strategies, administration of sleep and cognitive questionnaires, hook up of portable sleep study, and maintaining database (months 3-5) **Completed**

2d. Purchasing portable PSG units, auto PAP units, testing, and ensuring accurate operation (month 4-5) **Completed for University of Miami and Miami VA sites; will be ordered for Detroit sites once DoD approval is received**

Task 3. Participant Recruitment, Portable Polysomnography, Randomization, Baseline Outcome Measures (months 6-40). **Participant recruitment at University Miami started in March 2014 and at the Miami VA in July 2014.**

3a. Screening and recruitment of participants (months 6-40) **ongoing at Miami sites, not started at Detroit sites- awaiting DoD approval**

3b. Portable polysomnography completion (months 6-40) **ongoing at Miami sites, not started at Detroit sites- awaiting DoD approval**

3c. Polysomnography scoring and interpretation (months 6-40) **ongoing at Miami sites, not started at Detroit sites- awaiting DoD approval**

3d. Computer generated randomization (months 6-40) **Completed, first patient will be randomized the week of November 1, 2014**

3e. Completion of baseline sleep and neuro-cognitive questionnaires (months 6-40) **ongoing at Miami sites, not started at Detroit sites- awaiting DoD approval**

3f. Scoring of questionnaires (months 6-40) **ongoing at Miami sites, not started at Detroit sites- awaiting DoD approval**

3g. Medical record review to determine participant co-morbidities, and medications (months 6-40) **ongoing at Miami sites, not started at Detroit sites - awaiting DoD approval**

3h. Obtaining baseline blood and urine samples (6-40) **will start after randomization**

3i. Processing and storing of samples (6-40) **will start after randomization**

3j. Entry of results into de-identified study database (months 6-40) **ongoing at Miami sites, not started at Detroit sites- awaiting DoD approval**

Task 4. Cognitive, Sleep, Quality of Life, and Cardiovascular Outcomes (months 7-44) **These tasks will start after randomization**

4a. Completion of follow-up sleep, HRQoL, and neuro-cognitive questionnaires at 1 month (selected measures) and 4 month follow-up (months 7-44)

4b. Obtaining blood and urine samples at four month follow-up (months 10-44)

4c. Processing and storing of follow-up samples (months 10-44)

4e. Entry of follow-up results into de-identified study database (months 7-44)

Task 5. Data Analysis, Presentations, and Manuscripts (months 40-48) **These tasks are for years 2 onwards.**

5a. Interim baseline data accuracy and safety review (quarterly, months 6-44) **Baseline data on patients enrolled to date has been reviewed for safety and accuracy**

5b. Final data analysis (months 40-48)

5c. Manuscript preparation and presentations (months 44-48)

- **What was accomplished under these goals?** Study procedure manual, training of research associates, creation of secure study database, and purchasing of equipment (for Miami site) has been completed. To date, we have enrolled 15 subjects from the University of Miami and Miami VA sites. All baseline questionnaires and cognitive evaluations have been completed. Baseline portable polysomnography has been completed for 8 and scheduled for the remaining 7 subjects in the coming weeks. Of the 7 with baseline polysomnography completed, 5 have obstructive sleep apnea and are eligible for randomization. They have been contacted and will be randomized during the week of November 1. Subject recruitment is ongoing at the Miami sites.
- **What opportunities for training and professional development has the project provided?** Nothing to report
- **How were the results disseminated to communities of interest?** Nothing to report

- **What do you plan to do during the next reporting period to accomplish the goals?**
- During the next year, we anticipate that the Detroit sites will be approved and start participating in subject recruitment. Randomization will begin, as well as 1 month, and four month follow-up post randomization. We anticipate close to 60 subjects randomized by next reporting period.

4. **IMPACT:**

- **What was the impact on the development of the principal discipline(s) of the project?**
 - Nothing to Report
- **What was the impact on other disciplines?** Nothing to Report
- **What was the impact on technology transfer?** Nothing to Report
- **What was the impact on society beyond science and technology?** Nothing to Report

5. **CHANGES/PROBLEMS:**

- **Changes in approach and reasons for change** Nothing to report
- **Actual or anticipated problems or delays and actions or plans to resolve them.** There was an initial delay in funding/project approval due to sequestration and changes in DoD regulatory personnel assigned to project. The project was approved for funding Sept 30, 2014. DoD approval of the University of Miami site occurred Feb 25, 2014 and Miami VA site April 11, 2014. Recruitment from the Miami VA was initially slower than anticipated but that has now been resolved by establishing closer contacts with the health care team responsible for both inpatient and outpatient SCI patients at the Miami VA and participating in their weekly care meetings.
- The Detroit sites have not been approved yet by DoD. Changes to their consent forms were requested and these were approved by the Wayne State and Detroit VA IRBs and recently submitted to DoD for approval.
- **Changes that had a significant impact on expenditures** Nothing to report
- **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.** Nothing to report
- **Significant changes in use of biohazards and/or select agents** Nothing to report

6. **PRODUCTS:** Nothing to report

7. **PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

▪ **What individuals have worked on the project?**

▪

Name:	<i>Shirin Shafazand</i>
Project Role:	<i>PI</i>
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	3 months
Contribution to Project:	<i>PI, design study, responsible for overseeing all aspects of study, interpreting sleep studies</i>
Funding Support:	

Name:	<i>Patricia Burns</i>
Project Role:	<i>Research Associate</i>
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	6 months
Contribution to Project:	<i>Study coordinator, subject recruitment, responsible for conducting cognitive testing and sleep studies, data entry</i>
Funding Support:	

Name:	<i>Mark Nash</i>
Project Role:	<i>Co-investigator</i>
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1 month
Contribution to Project:	<i>Assisted in study design, finalizing operations manual, database design</i>
Funding Support:	

Name:	<i>Douglas Johnson Greene</i>
Project Role:	<i>Co-investigator</i>
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1 month
Contribution to Project:	<i>Training of research associates in cognitive testing, overseeing accuracy of cognitive testing</i>
Funding Support:	

Name:	<i>Safwan Badr</i>
Project Role:	<i>Co-investigator; Wayne state PI</i>
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1 month
Contribution to Project:	<i>responsible for overseeing regulatory overview at Detroit sites and coordinating study procedures with Miami sites</i>
Funding Support:	

- **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
- **What other organizations were involved as partners?** Nothing to report. Wayne state University and Detroit VA were 2 other sites listed previously on this multi-site proposal and that has not changed.

8. SPECIAL REPORTING REQUIREMENTS

- **COLLABORATIVE AWARDS:** Not applicable

9. APPENDICES: Not applicable