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TITLE: 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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CONTRACTING ORGANIZATION: University of Miami

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13. SUPPLEMENTARY NOTES

14. ABSTRACT
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.

15. SUBJECT TERMS
Nothing listed

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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: Dec 11, 2014**

1d. Obtain final project approval (month 6) **Completed for Miami site and 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; Completed for Detroit sites March 2015.**

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. Participant recruitment for Detroit site started September 2015.**

3a. Screening and recruitment of participants (months 6-40**) ongoing at Miami sites, ongoing at Detroit sites**

3b. Portable polysomnography completion (months 6-40) **ongoing at Miami sites, ongoing at Detroit sites**

3c. Polysomnography scoring and interpretation (months 6-40) **ongoing at Miami sites, ongoing at Detroit sites**

3d. Computer generated randomization (months 6-40) **Completed**

3e. Completion of baseline sleep and neuro-cognitive questionnaires (months 6-40) **ongoing at Miami sites, ongoing at Detroit sites**

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

3g. Medical record review to determine participant co-morbidities, and medications (months 6-40) **ongoing at Miami sites, ongoing at Detroit sites**

3h. Obtaining baseline blood and urine samples (6-40) **ongoing at all sites**

3i. Processing and storing of samples (6-40) **ongoing at all sites**

3j. Entry of results into de-identified study database (months 6-40) **ongoing at all sites**

Task 4. Cognitive, Sleep, Quality of Life, and Cardiovascular Outcomes (months 7-44) **ongoing at all sites**

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

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

4c. Processing and storing of follow-up samples (months 10-44) **ongoing at all sites**

4e. Entry of follow-up results into de-identified study database (months 7-44) **ongoing at all sites**

Task 5. Data Analysis, Presentations, and Manuscripts (months 40-48) **These tasks are for year 4..**

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) **Year 4 and beyond**

5c. Manuscript preparation and presentations (months 44-48) **Year 4 and beyond**

- **What was accomplished under these goals?**
  - Screening, recruitment and enrollment of participants ongoing at Miami sites (UM and VAH).
  - Screening and recruitment of participants is ongoing at Detroit sites (Wayne State and VAH).
  - Database data entry is in progress in Miami and Detroit sites.
  - PI and Detroit Site PI Meetings ongoing.
  - Miami site visit for the expert study consultant Dr. Berlowitz was completed during the time period of Monday October 4th – October 9th, 2015.
  - Portable polysomnography ongoing at Miami sites (UM and VAH) and Detroit sites (Wayne State University and Detroit VAH).

- Polysomnography scoring and interpretation ongoing at Miami sites (UM and VAH) and Detroit sites (Wayne State University and Detroit VAH).

- Computer generated randomization task completed and research participants are currently being randomized per study protocol at UM and VAH and Detroit sites (Wayne State University and Detroit VAH).

- Completion of baseline sleep and neuro-cognitive questionnaires, 1 month and final four month sleep and neuro-cognitive questionnaires ongoing at Miami sites (UM and VAH) and Detroit sites (Wayne State University and Detroit VAH).

- Baseline and 4 month follow up blood and urine samples ongoing at Miami sites (UM and VAH) and Detroit sites (Wayne State University and Detroit VAH).

- Processing and storing of samples ongoing at Miami sites (UM and VAH).

To date, a total of 58 individuals [paraplegia (n=32) and tetraplegia (n=26)] at the Miami sites, satisfied the study inclusion criteria and have been consented and enrolled in the study. Six of the 58 participants were Veterans recruited through the Miami VAH. Six of the 58 participants withdrew from the study or were excluded. One participant was dropped from the study due to imprisonment, one subject withdrew because he "was no longer interested in participating" and one subject were lost to study follow up. Two subjects from the Miami VA were excluded by study PI, after enrollment, due to change in medical status and hospitalization during the baseline testing period. The change in medical condition/ hospitalization was not study related.

Forty-eight of the 52 participants completed baseline testing and polysomnography analysis; the remaining four are in the process of completion of baseline testing. Of the 48 participants analyzed via polysomnography, 24 individuals (50%) had objective clinical evidence of obstructive sleep apnea when undergoing portable home based polysomnography with AHI ≥ 5 [paraplegia (n=11) and tetraplegia (n=13)]. One of the 24 participants diagnosed with SDB did not wish to be randomized and withdrew. Twenty-three participants diagnosed with SDB have been randomized to the four-month treatment with auto-PAP or fixed PAP set at 3 cmH20 (sham PAP).

Nineteen of the 23 participants have completed 4-month study follow-up and are discharged from the study. One participant died two days after being randomized, prior to initiation of study treatment. The death was not study related; a report was submitted to the local IRB and the

DOD was informed via email. Three participants are presently in the intervention phase (4-month treatment phase) of the study. One month and four-month follow-up testing and data collection is currently in progress. Subject recruitment is ongoing at the Miami sites and potential subjects have been identified to be enrolled at the beginning of next quarter.

The Detroit site has enrolled and randomized a total of 8 subjects. Four of whom have completed the study.

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?**
- We are also trying to increase enrollment at Miami sites by reaching out to support groups. We anticipate close to 40 subjects randomized by next reporting period. We have had several discussions with Detroit site in an effort to increase recruitment. They will continue advertising at their support groups. However, if there is no improvement in recruitment by Dec 2016, we will end the sub-contract with Detroit (by Feb 2017) and re-budget remaining funds, with DOD approval to allow for increased recruitment at Miami sites. Including reimbursing subject travel costs.

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,

2013. DoD approval of the University of Miami site occurred Feb 25, 2014 and Miami VA site April 11, 2014. Recruitment from the Miami VA is slower than anticipated and we are trying to rectify the situation by advertising study at support groups. One of the barriers to recruitment has been transportation difficulties for subjects.

- The Detroit site started enrollment in Sept/Oct 2015 and will be increasing recruitment this year.
- **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:	*Shirin Shafazand*
Project Role:	*PI*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	2.5 months
Contribution to Project:	*PI, design study, responsible for overseeing all aspects of study, interpreting sleep studies*
Funding Support:	

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

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

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

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

9. **APPENDICES:**

As requested a flow chart of study enrollment is provided. This flowchart reflects study flow to Jan 2017.

Table 1 outlines baseline characteristics of all consented participants at Miami sites and interim data analysis of measured sleep variables.

Table 1: Baseline Demographic and Sleep Characteristics

Baseline Characteristic	**All Participants N = 59**
Age, yrs*	43±13
Gender, Male, n (%)	49 (83)
BMI, kg/m^2*	26±6
Level of Injury, n (%)	
C4-C7	26 (44)
T1-T5	14 (24)
T6-T12	12 (20)
Other	7 (12)
Marital Status, n (%)	
Married/Partner	13 (22)
Other (Single, Divorced, Widow)	46 (78)
Ethnicity, Hispanic or Latino, n (%)	32 (54)
Race, White, n (%)	40 (68)
Education, n (%)	
≤ Grade 8	0 (0)
Some High School or Diploma	16 (27)
Some College or College Degree	37 (63)
Professional Degree	6 (10)
Employment, n (%)	
Employed	14 (24)
Unemployed	5 (9)
Other (Retired, Disability, Housewife)	37 (63)
Co-Morbidities, n (%)	
Myocardial Infarction	6 (10)
Stroke	4 (7)
Diabetes	9 (15)
Chronic Kidney Disease	1 (2)
Anxiety and/or Depression	21 (36)
Previous History of Malignancy	2 (3)
Beck Depression Inventory *	8.8±10.1
Beck Anxiety Inventory *	6.8±7.1
Insomnia (AIS)	7.1 ± 5.1
AHI *, events/hr	12 ±15
Daytime Sleepiness (ESS)	7 ±4
Sleep Quality, n (%)	
Very Good	8 (14)
Fairly Good	28 (48)
Fairly Bad	16 (27)
Very Bad	6 (10)

Figure 1: Study Enrollment to Jan 2017