

PARTNERS HUMAN RESEARCH COMMITTEE DETAILED PROTOCOL

Version: March 8, 2017

Title: Pharmacologically improving the pharyngeal muscle activity during sleep: implications for the novel treatment of obstructive sleep apnea.

Principal Investigator: David Andrew Wellman, MD, PhD

I. BACKGROUND AND SIGNIFICANCE

Obstructive sleep apnea (OSA) is characterized by repetitive collapse or ‘obstruction’ of the pharyngeal airway during sleep. Over the last decade, and particularly in the last few years, research has shown that a number of pathogenic factors, or traits, contribute to the development of OSA (1-4). These include: 1) an anatomically small, collapsible upper airway; 2) an oversensitive respiratory control system leading to ventilatory overshoots and undershoots, i.e., instability; 3) a loss of pharyngeal muscle tone or responsiveness during sleep; and 4) a low respiratory arousal threshold, i.e., premature arousal to respiratory stimuli.

Despite our improved understanding of the pathogenesis of OSA, it has not led to improved therapy. Continuous positive airway pressure (CPAP) is still the only viable treatment for most patients, and it is usually effective because it mechanically splints the upper the airway open. The problem, however, is that many patients cannot use CPAP because they find it intolerable. This represents a significant health concern, as OSA is known to cause a number of adverse cardiovascular (5-12), neurocognitive (13), and daytime functioning (14) consequences.

One possible approach to finding alternative treatments for OSA is to continue searching for a single drug or agent that, like CPAP, has a large enough effect size to override the various causes of OSA. This approach has proven difficult, and while we hold out hope for such a drug, in the meantime we have adopted another (possibly equally effective) tactic, which is to target the relevant upstream mechanisms or individual traits with one or more drugs in an individual patient. The rationale for this approach is that non-CPAP therapies have tended to have small effect sizes and proven, by themselves, marginally effective at fully correcting OSA in many patients. Another reason stems from the manner in which most major medical disorders are treated. Rarely is a single drug used to treat, for example, congestive heart failure, hypertension, asthma, etc., unless the condition is mild. In our view, a similar approach should be taken for managing OSA.

Regardless of whether single or multidrug therapy is ultimately used, the search for alternative treatments has been lacking a very important ingredient – a drug to stimulate the pharyngeal muscles. While a host of oral devices and surgeries have been developed to address the anatomical predisposition to collapse, and our group has made significant headway in dealing with ventilatory control sensitivity (15, 16), drugs that activate the pharyngeal muscles are needed. Interestingly, new research in animals has improved our understanding of the state-dependent neurotransmitters involved in pharyngeal muscle activation during sleep. Importantly, the loss of noradrenergic activity is now thought to play the key role in the sleep-related hypotonia of pharyngeal muscles.

Chan and colleagues (17) showed in rats that the noradrenergic antagonist terazosin substantially reduced genioglossus (a major muscle of the upper airway) activity (EMG_{GG}) during wakefulness and produced REM-like atonia during NREM sleep, illustrating the importance of noradrenergic mechanisms. Other studies (18, 19) also support the notion that progressive withdrawal of noradrenergic tone, from wakefulness to NREM and REM sleep, is the major mechanism causing sleep-related pharyngeal hypotonia. While noradrenergic withdrawal is thought to be the main cause of pharyngeal hypotonia in NREM sleep, there are additional mechanisms that cause further reduction in REM sleep. Chan and colleagues (17) failed to reverse REM atonia with alpha-1 receptor agonists applied to the hypoglossal

PARTNERS HUMAN RESEARCH COMMITTEE

DETAILED PROTOCOL

Version: March 8, 2017

nucleus, suggesting that another, possibly inhibitory, mechanism is at work. Horner and colleagues have identified this inhibitory process as muscarinic by demonstrating restoration of EMG_{GG} activity during REM sleep with the muscarinic antagonist scopolamine (20, 21). More recently, these researchers found that the multiple state-dependent adrenergic, serotonergic and muscarinic systems produce suppression of EMG_{GG} activity during sleep via a convergent ionic mechanism: increased potassium conductance. Blockade of potassium channels has been shown in mice to be capable of reactivating the pharyngeal musculature throughout sleep (22).

However, due to the only recent identification of this process, there has not yet been an attempt to stimulate the pharyngeal muscles with noradrenergic drugs in sleeping humans. Now, more than ever, the stage has been set for stimulating the pharyngeal muscles across both NREM and REM sleep.

II. SPECIFIC AIMS

To determine the effect of noradrenergic, antimuscarinic and potassium channel blocker drugs on pharyngeal muscle activity during sleep. We hypothesize that existing drugs with these neurotransmitter profiles could (partially) restore pharyngeal muscle activity in humans during sleep.

Specifically, we will test this hypothesis by assessing;

The effect of the combination of atomoxetine (a norepinephrine reuptake inhibitor) plus fesoterodine (a newer, extended-release antimuscarinic drug) on OSA severity (DAW1033B2). Fesoterodine is an extended-release antimuscarinic with less reported side effects compared to oxybutynin. Fesoterodine could be a good candidate for a long-term therapy in subjects with OSA and the data collected in this pilot study will help to design a long-term clinical trial to test the efficacy of this association for the treatment of OSA.

1.

III. SUBJECT SELECTION

We will recruit a group of subjects with OSA. These subjects will be recruited from the community and be between 21-65 years old. The purpose of studying patients with OSA is to determine what effect this drugs will have on improving the patient's OSA severity.

- a) **Obstructive Sleep Apnea Patients (n= 15):** Patients with OSA will be recruited from our clinical sleep laboratory at Brigham and Women's Hospital, as well as from our existing database of OSA patients. These individuals will be otherwise healthy (except for well-controlled hypertension; defined as systolic blood pressure <140 mmHg and diastolic <90 mmHg) with no active medical problems and on no medication that could affect respiration or muscle control. All will be 21-65 years of age. Both men and women will have an apnea-hypopnea index (AHI) >15 events/hr during supine NREM sleep. These individuals will be recruited to encompass a large range of AHI's (from 10 to >60/hour).

Exclusion criteria:

- Any medical condition other than well controlled hypertension, GERD, hyperlipidemia.
- Any medication known to influence breathing, sleep/arousal or muscle physiology.
- Claustrophobia.
- Inability to sleep supine.
- Allergy to lidocaine, Oxymetazoline HCl, desipramine, atomoxetine/oxybutynin, dalfampridine, pseudoephedrine HCl, diphenhydramine.

PARTNERS HUMAN RESEARCH COMMITTEE DETAILED PROTOCOL

Version: March 8, 2017

- Benign prostatic hyperplasia or urinary retention, which can be exacerbated by antimuscarinics.
- Individuals with underlying cardiac disease, such as arrhythmias.
- Individuals taking psychiatric medications, such as Tricyclic antidepressants, or any of the studied medications for medical care.
- History of seizures
- History of moderate or severe renal impairment
- For women: Pregnancy.

Equal number of males and females will be recruited, recognizing that OSA is a more prevalent condition in men. We will consider all applicants regardless of sex, race, color, creed, or national origin.

IV. SUBJECT ENROLLMENT

Subjects will be recruited through email, telephone, newspaper, and or bulletin advertisements. Men and women with OSA will be recruited from a pool of patients being newly diagnosed with OSA and currently followed in our outpatient clinic or by advertisement in the sleep disorders clinic. Only patients who have stated in the initial clinical questionnaire that they are interested in hearing about research studies will be contacted by phone. Should the subject be interested in the study, they can call the study physician or coordinator to inquire about study participation. We will also recruit from our existing database of research participants.

Subjects who respond will be given a thorough review of the risks, discomforts, potential benefits to the study and their expected involvement using a prepared script approved by our Institutional Review Board. Subjects will be given a copy of the informed consent and allowed a minimum of 24 hours to review the information and make a decision on study participation. During this time, the subject will have the opportunity to discuss the research with his/her primary care physician or clinician. The study investigators will be available to answer any questions should any arise. Informed consent will be obtained by the Principal Investigator or an experienced co-investigator prior to participation in the study. The opportunity to talk to a licensed MD (who is readily available at the time of consent, and available overnight at the hospital) will be offered in each case. Subjects will have more than 24 hours to consider participating in the study. Any consent issues / problems will be reported to the PHRC in real time rather than waiting to report at the time of Continuing Review

Inclusion and exclusion criteria will be carefully assessed prior to enrollment. Assuming subjects meet the inclusion criteria, they will begin the protocol by scheduling their overnight studies in the clinical/physiology laboratories. Subjects will be informed that they may withdraw from the study at any point, with no impact on their ongoing care. We have not previously had difficulty enrolling participants into similar studies performed in our laboratory.

If the data collected will be considered insufficient by the PI or by the co-investigators, the subject will be asked to repeat the whole study or a part of it without signing a new informed consent form.

V. STUDY PROCEDURES

Protocol:

PARTNERS HUMAN RESEARCH COMMITTEE

DETAILED PROTOCOL

Version: March 8, 2017

Two overnight sleep studies will be performed approximately 1 week apart: a placebo night and a atomoxetine-plus-fesoterodine (DAW1033B2) night, in double-blinded randomized control design. For each night, the subjects will arrive at the sleep laboratory at approximately 7:00pm. A physician will perform a comprehensive physical and medical history. The placebo or atomoxetine-plus-fesoterodine (80+4mg) will be administered 30 minutes before lights out.

Measurements and equipment:

Subjects will be instrumented with standard polysomnography (PSG) recording sensors. Sleep stage and arousals will be measured with electrodes pasted on to the scalp, face, chin and chest (EEG, EOG, EKG, chin EMG). Paste-on EMG electrodes will be placed over the anterior tibialis muscle to detect leg movements. Respiratory effort belts will be placed around the chest and abdomen to measure breathing movements. Oxygen saturation will be measured continuously with a pulse oximetry probe placed on either the fingertip or earlobe. Snoring will be detected with a small microphone positioned over the suprasternal notch. Body position will be recorded with a sensor taped to the thoracic belt. Each of these devices is standard for diagnostic PSG and should not be uncomfortable.

Data analysis:

Apnea, hypopneas, sleep stages and arousals from sleep will be scored by a registered technician blinded to the treatment allocation. Hypopneas will be defined as a 30% reduction of the amplitude of the nasal pressure signal associated with an arousal from sleep or a 3% desaturation.

Reimbursement

Subjects will receive \$100/night for participation in each overnight study (TOTAL = \$200 for each PART of the study). Reimbursement for parking expenses will be provided.

If the subjects will repeat a part or the entire protocol because of insufficient data collection, they will be reimbursed \$100 for any extra night.

VI. BIostatistical ANALYSIS

Subjects will be prospectively enrolled until 12 had completed both study nights. Sample size was chosen to facilitate detection of a clinically-important 50±55% reduction in AHI. Calculations were based on previous studies conducted in our laboratory. To account for a ~20% failure rate approximately 15 patients will be enrolled in the study.

In order to reduce the influence of potential outlier, data will be expressed as median [interquartile range] and data on placebo vs DAW1033B2 will be compared using Wilcoxon test. A p value < 0.05 will be considered as statistically significant.

VII. RISKS AND DISCOMFORTS

We believe that the risks associated with participation in this study are minimal. All study procedures have been conducted in our laboratory without serious incident. Anticipated risks and discomforts are listed below:

1. The equipment used for assessing sleep (paste on electrodes) is standard and poses no risk. The electrodes may be mildly uncomfortable and could cause some sleep interruption. Thus subjects may feel somewhat tired the day following this study.

**PARTNERS HUMAN RESEARCH COMMITTEE
DETAILED PROTOCOL**

Version: March 8, 2017

2. Atomoxetine: Side effects include alopecia, dry mouth, tiredness, irritability, nausea, decreased appetite, constipation, dizziness, sweating, dysuria, sexual problems, decreased libido, urinary retention or hesitancy, increased obsessive behavior, weight changes, slowed growth in children, palpitations, increases in heart rate and blood pressure.
3. Fesoterodine: the most common side effects of fesoterodine 4 mg extended release in previous clinical trials were dry mouth and constipation. Less frequent side effects were abdominal pain, dry eyes, dyspepsia and urinary retention.

VIII. POTENTIAL BENEFITS

Although it is unlikely that there will be any direct physical benefit to the subjects from participating in this study, we will make known to each subject, if requested, some of the information we have gathered from this physiologic testing. This study provides a unique opportunity to gain insight into the specific mechanisms by which these novel drugs may improve upper airway muscle function. The results may, in the future, lead to improved strategies for the treatment of sleep apnea. However, if previously unknown abnormalities of sleep and breathing are encountered, this information will be passed onto the subject. Results can be forwarded to the primary care physician or clinician at the request of the subject.

IX. MONITORING AND QUALITY ASSURANCE

We will follow the Data and Safety Monitoring Plan included as an attachment. As this study is a physiological investigation and not clinical trial, a formal Data and Safety Monitoring Board will not be implemented. The PI will be responsible for monitoring safety and quality assurance. Additionally, the ongoing results, problems, and limitations of the study will be presented on a regular basis to the investigators in the Division of Sleep Medicine. Any adverse events will be promptly reported to the Human Research Committee for review according to HRC guidelines.

Adequacy of Protection Against Risks

All of our laboratory personnel involved in the research of human subjects have completed the required institutional program for education in the protection of human research participants and their confidentiality. The institutional educational program consists of the review of regulatory and informational documents pertaining to human-subject research, passing a test demonstrating knowledge of the ethical principles and regulations governing human-subject research and signing a statement of commitment to the protection of human subjects.

All electronic data will be stored on secure computers under password protection with no access allowed to individuals outside of our research team. All paper data will be stored under lock and key with access only given to the study staff.

Protection Against Risks

PARTNERS HUMAN RESEARCH COMMITTEE DETAILED PROTOCOL

Version: March 8, 2017

We believe that all possible safeguards are in place to minimize the risk. However, several steps will be taken to insure patient comfort and safety. We will work with our IRB to come up with a safety monitoring plan to minimize risk and discomfort. This will include:

- Reporting any complications of our studies immediately to the IRB.
- Appoint a safety officer (David Andrew Wellman, MD) who will work with our physicians and technicians to maximize safety and comfort.
- Our study coordinator will call each subject 2-3 weeks after the study to determine if any problems resulted from the study.

The study coordinator will meet with the safety officer and PI monthly (and as needed) to go over any complaints or problems. The safety officer will call the patients with problems directly to verify important issues. If problems are identified, the protocol will be adjusted as needed. Based on conversations with the NIH and the NHLBI policy (<http://www.nhlbi.nih.gov/funding/ethics.htm>), we will not require a formal data safety monitoring board. However, we do have a thorough data safety monitoring plan whereby our safety officer will review all adverse events in order to classify them as serious adverse events, minor adverse events, and whether they are anticipated or unanticipated, and study related or unrelated as per our IRB rules and the NHLBI policy. The medical monitor will be an academic physician with considerable experience in clinical research but not involved in our research program or a co-investigator in any of our studies (Dr. David White). The medical monitor will strictly adhere to the following definitions:

Definitions

Definitions are per January 2007 OHRP *Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events*, OHRP Guidance, <http://www.hhs.gov/ohrp/policy/AdvEvtGuid.htm>

Adverse Event (AE): any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

Serious adverse event (SAE): any adverse event that:

- Results in death
- Is life threatening, or places the subject at immediate risk of death from the event as it occurred
- Requires or prolongs hospitalization
- Causes persistent or significant disability or incapacity
- Results in congenital anomalies or birth defects
- Is another condition which investigators judge to represent significant hazards

Unanticipated Problem (UP): any incident, experience, or outcome that meets all of the following criteria:

- unexpected, in terms of nature, severity, or frequency, given the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and the characteristics of the subject population being studied;
- related or possibly related to participation in the research, in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research;

**PARTNERS HUMAN RESEARCH COMMITTEE
DETAILED PROTOCOL**

Version: March 8, 2017

- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Adverse Events (FDA) versus Unanticipated Problems (OHRP)

- All adverse events are not necessarily unanticipated problems
- All unanticipated problems are not necessarily adverse events
- Some events may be both

**PARTNERS HUMAN RESEARCH COMMITTEE
DETAILED PROTOCOL**

Version: March 8, 2017

X. REFERENCES

1. Eckert DJ, White DP, Jordan AS, Malhotra A, Wellman A. Defining phenotypic causes of obstructive sleep apnea. Identification of novel therapeutic targets. *Am J Respir Crit Care Med* 2013;188:996-1004.
2. Wellman A, Eckert DJ, Jordan AS, Edwards BA, Passaglia CL, Jackson AC, Gautam S, Owens RL, Malhotra A, White DP. A method for measuring and modeling the physiological traits causing obstructive sleep apnea. *J Appl Physiol* 2011;110:1627-1637.
3. Wellman A, Edwards BA, Sands SA, Owens RL, Nemati S, Butler JP, Passaglia CL, Jackson AC, Malhotra A, White DP. A simplified method for determining phenotypic traits in patients with obstructive sleep apnea. *J Appl Physiol* 2013.
4. Younes M. Contributions of upper airway mechanics and control mechanisms to severity of obstructive apnea. *Am J Respir Crit Care Med* 2003;168:645-658.
5. Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. *J Clin Invest* 1995;96:1897-1904.
6. Nieto FJ, Young TB, Lind BK, Shahar E, Samet JM, Redline S, D'Agostino RB, Newman AB, Lebowitz MD, Pickering TG. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep heart health study. *Jama* 2000;283:1829-1836.
7. Brooks D, Horner RL, Kozar LF, Render-Teixeira CL, Phillipson EA. Obstructive sleep apnea as a cause of systemic hypertension. Evidence from a canine model. *J Clin Invest* 1997;99:106-109.
8. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *The New England journal of medicine* 2000;342:1378-1384.
9. Hung J, Whitford EG, Parsons RW, Hillman DR. Association of sleep apnoea with myocardial infarction in men. *Lancet* 1990;336:261-264.
10. Wessendorf TE, Teschler H, Wang YM, Konietzko N, Thilmann AF. Sleep-disordered breathing among patients with first-ever stroke. *J Neurol* 2000;247:41-47.
11. Hoffstein V. Blood pressure, snoring, obesity, and nocturnal hypoxaemia. *Lancet* 1994;344:643-645.
12. Shahar E, Whitney CW, Redline S, Lee ET, Newman AB, Nieto FJ, O'Connor GT, Boland LL, Schwartz JE, Samet JM. Sleep-disordered breathing and cardiovascular disease: Cross-sectional results of the sleep heart health study. *Am J Respir Crit Care Med* 2001;163:19-25.
13. Redline S, Strauss ME, Adams N, Winters M, Roebuck T, Spry K, Rosenberg C, Adams K. Neuropsychological function in mild sleep-disordered breathing. *Sleep* 1997;20:160-167.
14. Findley LJ, Unverzagt ME, Suratt PM. Automobile accidents involving patients with obstructive sleep apnea. *Am Rev Respir Dis* 1988;138:337-340.
15. Edwards BA, Sands SA, Eckert DJ, White DP, Butler JP, Owens RL, Malhotra A, Wellman A. Acetazolamide improves loop gain but not the other physiological traits causing obstructive sleep apnoea. *J Physiol* 2012;590:1199-1211.
16. Wellman A, Malhotra A, Jordan AS, Stevenson KE, Gautam S, White DP. Effect of oxygen in obstructive sleep apnea: Role of loop gain. *Respir Physiol Neurobiol* 2008;162:144-151.
17. Chan E, Steenland HW, Liu H, Horner RL. Endogenous excitatory drive modulating respiratory muscle activity across sleep-wake states. *Am J Respir Crit Care Med* 2006;174:1264-1273.
18. Lai YY, Kodama T, Siegel JM. Changes in monoamine release in the ventral horn and hypoglossal nucleus linked to pontine inhibition of muscle tone: An in vivo microdialysis study. *J Neurosci* 2001;21:7384-7391.
19. Fenik VB, Davies RO, Kubin L. Rem sleep-like atonia of hypoglossal (xii) motoneurons is caused by loss of noradrenergic and serotonergic inputs. *Am J Respir Crit Care Med* 2005;172:1322-1330.

**PARTNERS HUMAN RESEARCH COMMITTEE
DETAILED PROTOCOL**

Version: March 8, 2017

20. Grace KP, Hughes SW, Shahabi S, Horner RL. K⁺ channel modulation causes genioglossus inhibition in rem sleep and is a strategy for reactivation. *Respir Physiol Neurobiol* 2013;188:277-288.
21. Grace KP, Hughes SW, Horner RL. Identification of the mechanism mediating genioglossus muscle suppression in rem sleep. *Am J Respir Crit Care Med* 2013;187:311-319.
22. Grace KP, Hughes SW, Horner RL. Identification of a pharmacological target for genioglossus reactivation throughout sleep. *Sleep* 2014;37(1):41-50.
23. Jordan AS, White DP, Lo YL, Wellman A, Eckert DJ, Yim-Yeh S, Eikermann M, Smith SA, Stevenson KE, Malhotra A. Airway dilator muscle activity and lung volume during stable breathing in obstructive sleep apnea. *Sleep* 2009;32:361-368.
24. Jordan AS, White DP, Owens RL, Eckert DJ, Rahangdale S, Yim-Yeh S, Malhotra A. The effect of increased genioglossus activity and end-expiratory lung volume on pharyngeal collapse. *J Appl Physiol (1985)* 2010;109:469-475.
25. Stanchina ML, Malhotra A, Fogel RB, Ayas N, Edwards JK, Schory K, White DP. Genioglossus muscle responsiveness to chemical and mechanical stimuli during non-rapid eye movement sleep. *Am J Respir Crit Care Med* 2002;165:945-949.