6/16/2015

Comparison of Two Techniques of Combination Therapy for Treatment of Obstructive Sleep Apnea (OSA)

NCT04029311

RESEARCH SUBJECT INFORMATION AND CONSENT FORM

TITLE:	**COMPARISON OF TWO TECHNIQUES COMBINATION THERAPY FOR OSA**
PROTOCOL NO.:	Sponsor WIRB® Protocol #
SPONSOR:	J. Michael Adame, D.D.S., PA
INVESTIGATOR:	J. Michael Adame, D.D.S. 206 W. Mahl Edinburg, Texas, 78539 United States
STUDY-RELATED PHONE NUMBER(S):	J. Michael Adame, D.D.S. Phone Number: (956) 383-4400

SUMMARY

The purpose of this consent form is to help decide if you would like to participate in the research study.

- You are being asked to be in a research study to compare two types of therapies for sleep apnea.
- You were selected as a possible participant because you meet the requirements for this study which are:
  a. eighteen (18) years old or older
  b. Baseline Apnea-Hypopnea Index (AHI) of greater or equal to 5
  c. Intolerance to Continuous Positive Airway Pressure (CPAP)
  d. Partial response to Oral Appliance Therapy (OAT)
  e. AHI greater or equal to 5

We ask that you read this form and ask any questions that you may have before agreeing to be in the study. You should not join this research study until all of your questions are answered.

Things to know before deciding to take part in a research study:

- The main goal of a research study is to learn things to help patients in the future.
- The decision to join or not join the research study will not cause you to lose any medical benefits. If you decide not to take part in this study, your doctor will continue to treat you.
- Your medical records may become part of the research record. If that happens, your medical records may be looked at and/or copied by the sponsor of this study and government agencies or other groups associated with the study.

PURPOSE OF THE STUDY

The frequency of Sleep-Disordered Breathing (SDB) in adults has been increasing. It is a common disorder, which usually requires lifelong care. SDB is associated as a secondary disease to many others including cardiovascular diseases, strokes, metabolic disorders and impaired memory function. Due to the wide range and serious implications of untreated SDB, there is high motivation to treat it. Unfortunately, the gold standard of treating Obstructive Sleep Apnea (OSA) Continuous Positive Airway Pressure (CPAP) therapy results in around a 50% observance rate and a popular alternative (oral appliance therapy) results in around a 50% sub-therapeutic rate, which leaves many patients untreated or not treated well enough. An advantage of combination therapy is that it can reduce the frequently high CPAP pressures, which lead to intolerance and also improve the effectiveness of oral appliance therapy thus providing an adherent and effective option. To date however, there is only one cited study using a single type of combination therapy option in a very limited number of patients (10) over a very short period (3 days). As a result, this study may provide health care practitioners with valuable information, which may increase the opportunity for patients to improve their health outcomes and overall wellness.

PROCEDURES

- You will be randomly assigned to one therapy or the other and you are to use the therapy for one month.
- After one month, you are switched to the other therapy and you are to use it for one month. You will use the therapy only while sleeping.
- You will be expected to fill out forms before you start therapy which ask if you had prior difficulty or side effects with CPAP or oral appliance therapy.
- During the study, you will also be expected to fill out forms which ask if you used the therapy each night.
- You will be expected to return to the office for a follow up after one week of using each therapy or unless you feel a need to return sooner to the office to ask questions or have something checked or fixed.
- At the end of each month you will be asked to fill out the same form asking about difficulty or side effects with CPAP or oral appliance therapy. Also at the end of each month, you will be expected to take home a pulse oximeter for an overnight study.
- You will also be asked to bring in your CPAP at the end of each month.
- Your height will be measured and you will also be weighed before, after one month, and at the end of the study.
- You remain anonymous - Your identity will not be disclosed.

RISKS AND DISCOMFORTS

Discomforts may be experienced and are those usually associated with the use of CPAP and/or oral appliance therapy.

These can include:

- pressure and/or inflammation and/or infection of the nasal cavity,
- CPAP mask pressure and/or straps holding CPAP mask pressure,
- mask leaks causing discomfort,
- feelings of claustrophobia
- oral appliance discomfort including pressure to the teeth, gums, or jaw joint

BENEFITS

Benefits of participation:

- include a likelihood that you will be able to use your CPAP with the oral appliance which will in tum manage your sleep apnea
- Managing sleep apnea successfully or in an improved manner has been shown to lower high blood pressure, decrease the chance for stroke, reduce blood sugar levels in diabetics and lower the risk of death.
- The results of this study may help people in the future.

COSTS

You have already paid for the oral appliance therapy. No further charges are expected during the duration of this research.

AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

What information may be used and given to others?
The study doctor will get your personal and medical information. For example:

- Past and present medical records
- Research records
- Records about your study visits

Who may use and give out information about you?
The study doctor and the study staff.

Who might get this information?
The sponsor of this research. "Sponsor" means any persons or companies that are:

- working for or with J. Michael Adame, D.D.S, PA, Adame Dental Sleep Medicine, PLLC or Pulmonary & Sleep Center of the Valley

Your information may be given to:

- The U.S. Food and Drug Administration (FDA),
- Department of Health and Human Services (DHHS) agencies,
- Governmental agencies in other countries,
- Governmental agencies to whom certain diseases (reportable diseases) must be reported, and
- Western Institutional Review Board® (WIRB®).

Why will this information be used and/or given to others?

- to do the research,
- to study the results, and
- to see if the research was done right.

If the results of this study are made public, information that identifies you will not be used.

What if I decide not to give permission to use and give out my health information?
Then you will not be able to be in this research study.

May I review or copy my information?
Yes, but only after the research is over.

May I withdraw or revoke (cancel) my permission?
Yes, but this permission will not stop automatically.

You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the study doctor. If you withdraw your permission, you will not be able to stay in this study.

When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others.

Is my health information protected after it has been given to others?
There is a risk that your information will be given to others without your permission.

Confidentiality

Information from this study will be given to the sponsor. "Sponsor" includes any persons or companies that are contracted by the sponsor to have access to the research information during and after the study.

The information will also be given to the U.S. Food and Drug Administration (FDA). It may be given to governmental agencies in other countries where the study device may be considered for approval. Medical records which identify you and the consent form signed by you will be looked at and/or copied for research or regulatory purposes by:

- the sponsor

and may be looked at and/or copied for research or regulatory purposes by:

- the FDA,
- Department of Health and Human Services (DHHS) agencies,
- governmental agencies in other countries, and
- Western Institutional Review Board® (WIRB®).

Absolute confidentiality cannot be guaranteed because of the need to give information to these parties. The results of this research study may be presented at meetings or in publications. Your identity will not be disclosed in those presentations.

VOLUNTARY PARTICIPATION AND WITHDRAWAL

Your participation in this study is voluntary. You may decide not to participate or you may leave the study at any time.

Your participation in this study may be stopped at any time by the study doctor or the sponsor without your consent for any reason, including:

- if it is in your best interest
- if you do not consent to continue in the study after being told of changes in the research that may affect you

QUESTIONS

Contact J. Michael Adame, D.D.S. at (956) 383-4400 for any of the following reasons:

- if you have any questions about your participation in this study,
- if you have questions, concerns or complaints about the research.

If you have questions about your rights as a research subject or if you have questions, concerns or complaints about the research, you may contact:

Western Institutional Review Board® (WIRB®)
1019 39th Avenue SE Suite 120
Puyallup, Washington 98374-2115
Telephone: 1-800-562-4789 or 360-252-2500
E-mail: Help@wirb.com

WIRB is a group of people who independently review research.

WIRB will not be able to answer some study-specific questions, such as questions about appointment times. However, you may contact WIRB if the research staff cannot be reached or if you wish to talk to someone other than the research staff.

Do not sign this consent form unless you have had a chance to ask questions and have gotten satisfactory answers.

If you agree to be in this study, you will receive a signed and dated copy of this consent form for your records.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

CONSENT

I have read this consent form (or it has been read to me). All my questions about the study and my part in it have been answered. I freely consent to be in this research study.

I authorize the release of my medical and research records for the purpose of this study.
By signing this consent form, I have not given up any of my legal rights.

_____
Subject Name (printed)

_____ _____
Signature of Subject Date

_____
Witness Name (printed)

_____ _____
Signature of Witness Date

Ver. 06/15/2015

"Comparison of Two Techniques of Combination Therapy for Treatment of OSA [11]

Purpose of the study and background

- **Purpose of the study**

To compare two techniques of combination therapy for obstructive sleep apnea (OSA) and determine if clinical data obtained before, during and after suggests that either or both techniques improve tolerance to CPAP and/or are statistically more efficacious than CPAP or oral appliance therapy alone.

- **Background**

The prevalence of sleep-disordered breathing {SOB) in adults has been increasing. It is a common disorder, which usually requires lifelong care. A recent study has shown that in the last 2 decades, substantial increases have been seen in 30-70 year olds for both genders (1).

One of the likely leading causative factors for the increase in SOB is obesity. The ongoing obesity epidemic has given rise to other epidemics (off-spring epidemics) and the increase in SOB is one of them. (1) The increase in body mass index (BMI) can cause an increase in fat deposition and decrease in neuromuscular control of the airway, which can increase the collapsibility of the airway. (2)

SOB is associated with much co-morbidity including cardiovascular diseases, strokes, metabolic disorders and impaired neurocognitive function. {3-5) Due to the wide range and serious implications of untreated SOB, there is high motivation to treat it. The American Academy of Sleep Medicine (AASM) recommendations for treatment of OSA include: weight loss, behavioral therapy, oral appliance therapy, positive airway pressure (PAP) therapy and surgical intervention. (6) There also continues to be emerging and investigational therapies which may contribute to managing or improving SOB in the future.

PAP may be delivered in continuous positive airway pressure {CPAP), bi-level positive airway pressure (BPAP) or auto titrating positive airway pressure (APAP) modes. The gold standard for treatment of OSA is CPAP; however, it has been shown that APAP can be better tolerated and used a greater number of hours than CPAP in long term randomized study (7, 8). CPAP improves systemic hypertension, and it has been demonstrated that successful CPAP treatment prolongs survival (9). In addition, improvements in glucose metabolism have also been shown with CPAP therapy {22). While PAP therapy continues to be the first line therapy offered (10), adherence issues are well established. (11) A recent study following patients from 2-6 years, showed an adherence rate of 54.8% with an average use of 4.02 hours/night. (12). Adherence issues therefore may result in less favorable effectiveness than required. (13)

An alternative option for the treatment of SOB is oral appliance therapy (OAT). The AASM and the American Academy of Dental Sleep Medicine (AADSM) have provided management guidelines for the utilization of oral appliance therapy (14, 15). Although not as efficacious as CPAP, OAT is indicated for use in patients with mild to moderate OSA who prefer OAT to CPAP, or who do not respond to CPAP, are not candidates for CPAP, or who fail CPAP or behavioral measures such as weight loss or sleep position change. (15) OAT has also demonstrated cardiovascular benefits by lowering blood pressure and reducing mortality (16, 19). OAT has also been shown to have a good adherence rates as determined by mean hours of usage. One example of this is a study by Lowe and others showed an 'index of agreement' of 0.99 between the monitor clock time and the subject's log sheets. In the study, the mean hours of wear was 6.8 hours. (17)

While the benefits and good adherence of OAT are recognized, the efficacy of OAT remains less than optimal (partial response). Using a definition of decreasing Apnea-Hypopnea Index (AHi) to less than or equal to 10, it has been shown that the percent success rates for OAT was: Mild OSA-81%, Moderate OSA-60% and Severe OSA-25%. The mean success rate of OAT was 52% (18).

It would seem prudent that the simultaneous use of both CPAP and OAT (combination therapy) may be beneficial to consider. One pilot study has shown that combination therapy can reduce CPAP pressure (as compared to original PAP titration study) and improve effectiveness of OAT (20). Another study was able to show that OAT could be a short-term alternative to CPAP (21). The study demonstrated that an oral appliance could be as successful, or near successful as CPAP, and as being a convenient option for travel purposes.

There are two primary ways to use combination therapy. One way uses the oral appliance as an anchor for a customizable nasal mask interface (CNMI) while another way uses the patient's preferred CPAP mask separate from the oral appliance. This study will prospectively and randomly assign patients to one of the two combination therapy options and they will use each one for two months. Clinical data obtained during the study will be at one month and at the end of two months and will include: AHi, CPAP pressure, and mask leakage, Nadir, T90, hours of usage and ESS.

Sources:

1) Peppard, Paul E., Am J Epdemiol, 2013 May 1, 177 (9), 1006-1014

2) Schwarz AR, Patil SP, Proc Am Thoracic Soc, 2008 Feb 15; 5(2):185-92

3) Marshall, NS, Sleep Apnea as an independent risk factor for all-cause mortality: The Busselton Health Study, Sleep 2008 Aug; 31 (8):179-85.

4) Drager LF; OSA: A cardio metabolic risk in obesity and the metabolic syndrome, J Am Coll Cardiol. 2013 Aug 13; 62(3): 569-76.

5) Yount T, Sleep Disordered Breathing and mortality: eighteen year follow up of the Wisconsin Sleep Cohort. Sleep, 2008; 31: 1071-78.

6) Epstein, U, Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults, J Clin Sleep Medicine, 2009 Jun 15; 5(3): 263-76

7) Sullivan CE, Reversal of obstructive sleep apnea by continuous positive pressure applied through the nares. Lancet 1981;1:862-5

8) Hudgel DW, A long-term randomized, cross-over comparison of auto-titrating and standard nasal continuous airway pressure. Sleep.2000 Aug 1; 23(5):645-8.

9) Robinson GV, Obstructive Sleep Apnea/hypopnea syndrome and hypertension. Thorax 2004;59:1089-94

10) Gay, P, Evaluation of positive airway pressure treatment for sleep related breathing disorders in adults; Sleep, 2006 Mar, 29 (3), 381-401.

11) Reeves-Hoche MK, Nasal CPAP: An objective evaluation of patient compliance. American Journal of Respiratory & Critical Care Medicine. 1994;149:149-54

12) Wang Q, Analysis of long-term compliance to CPAP patients with OSA, and 2016 Aug 9; 96(30):2380-4.

13) Grote L, Therapy with CPAP: incomplete elimination of sleep related breathing disorder. Eur Respir J 2000; 16:921-7.

14) Kannan Ramar, MBBS, MD, Clinical Practice Guidelines for the Treatment of Obstructive Sleep Apnea and Snoring with Oral Appliance Therapy: An Update for 2015

15) Kushida CA, Practice parameters for the treatment of snoring and Obstructive Sleep Apnea with oral appliances: an update for 2005. Sleep. 2006; 29: 240-3.

16) Gotsopoulos H, Oral Appliance therapy reduces blood pressure in OSA: a randomized, controlled trial. Sleep 2004;27:934-41

17) Lowe AA, Treatment, airway and compliance effects of a titratable oral appliance. Sleep. 2000 Jun 15; 23 Suppl 4:S172-8.

18) Ferguson et al (2006) Sleep 29:244-62.

19) Anandam A, Cardiovascular mortality in OSA treated with CPAP or OAT: an observational study. Respirology 2013 Nov;18(8):1184-90

20) El-Solh AA, Combined oral appliance and PAP therapy for OSA: a pilot study. Sleep Breath. 2011 May; 15(2):203-8.

21) Almeida FR, Mandibular advancement spline as a short-term alternative treatment in patients with OSA already effectively treated with CPAP. J Clin Sleep Med.2013 Apr 15; 9(4):319-24.

22) Rasche, K, Obstructive sleep apnea and type 2 diabetes, Eur J Med Res. 2010; lS(Suppl 2): 152-156.

Criteria for Subject Selection

- Number of subjects: 50-100
- Gender of Subjects: Male and female with attempt of equal participation
- Age of Subjects: 18 and older
- Racial and Ethnic Origin: Distribution will mirror that of normal patient base of the clinics which is primarily Hispanic.
- Inclusion Criteria: Diagnosis of OSA with AHi greater than or equal to 5, CPAP intolerance due to CPAP pressure too high, mask fit/leak, Oral Appliance Therapy partial responders of AHi at or above 5, patients demonstrated successful adherence to oral appliance therapy.
- Exclusion Criteria: Daily use of alcohol, CNS depressants and narcotics, pregnancy and prisoners

• Vulnerable Subjects: Ethnic minorities and economically disadvantaged

Methods and Procedures

At least fifty patients who were intolerant to CPAP and had a partial response to OAT (AHi greater than or equal to 5 will be recruited randomly and prospectively into one of two groups (at least 25 each in each group). The group options were: 1} Combination therapy with CNMI and 2) Combination therapy with patient's preferred CPAP mask.

These CPAP intolerant patients underwent a PAP titration during an overnight PSG or were assigned an autoPAP and had accumulated at least one month of data. Intolerance to CPAP was defined as patients who reported to their sleep physician that they were intolerant due to CPAP pressure, mask fit/leak issues. They were also asked to fill out a CPAP intolerance questionnaire to document the reason for the intolerance.

Patients who were determined to be partial responders to OAT were determined to have met an adherence and titration protocol. Adherence was defined as using the oral appliance for at least 4 hours per night for 70% of the nights in the 30-day period leading up to the study. The titration protocol includes a minimum of one month of titration along with using patient testimony, bed partner testimony and overnight oximetry to aid in the titration and when tested with an HST or in-lab PSG, the AHi was greater than or equal to 5 (verification sleep test).

Patients who were assigned the option of using their previously preferred CPAP mask, they underwent one CPAP care session and then the two month time period would begin.

If patients were assigned the CNMI option, they were allowed one week for follow up/adjustments of the customized mask, they also underwent one CPAP care session and then the two month time period would begin.

- Data Analysis and Data Monitoring - Data will be analyzed quantitatively using, but not limited to, the Kolmogorov-Smirnov test, Student's t test or the Wilcoxon rank- sum test, and SPSS 12.0 for Windows {Chicago, IL, USA).

  Demographic: Ask patients for age and gender
  Physiologic: Weight Scale - Weight+ Ruler - Height= Body mass index (BMI)
  Pulse Oximeter: Nadir (low 02 saturation), Time percent below 90 {T90)
  Polysomnography {PSG): Apnea-Hypopnea Index (AHi), CPAP pressure, leakage
  CPAP Airview or Data Card: AHi, CPAP pressure, leakage
  Home Sleep Study (HST): AHi, Nadir, and T90

- Data Monitoring - At time of start of study at Adame Dental Sleep Medicine, PLLC or at J. Michael Adame, DDS, P.A. Obtain from patient:

  1) CPAP intolerance questionnaire
  2) Compliance questionnaire with oral appliance
  3) Obtain CPAP data from PAP titration or autoPAP: CPAP pressure, Leakage, Apnea-Hypopnea Index (AHi), Nadir, Time percent below 90 (T90), hours of usage
  4) Home Sleep Test (HST): AHi, Nadir, T90
  5) AutoPAP: AHi, mask leakage
  6) Gather patient demographics: age, gender, BMI

  At one (1) Month
  1) CPAP intolerance questionnaire
  2) Compliance questionnaire with Oral Appliance
  3) Gather CPAP data from "Airview" or Data card: CPAP pressure, leakage, AHi,
  4) Gather oxygen saturation data from Pulse Oximeter: Nadir and T90
  5) Optional verification (PSG or HST)

  After 2nd Month
  1) CPAP intolerance questionnaire
  2) Compliance questionnaire with Oral Appliance
  3) Gather CPAP data from "Airview" or Data card: CPAP pressure, leakage, AHi,
  4) Gather oxygen saturation data from Pulse Oximeter: Nadir and T90
  5) Optional verification (PSG or HST)

• Data Storage and Confidentiality- Data will be safeguarded by assigning study participants anonymous identification numbers. Depending on relevant data, it will be stored in a password protected computer with encrypted files in the sleep lab at the Pulmonary & Sleep Center of the Valley to which sub-investigator, Tony Abreu may access. At J. Michael Adame, D.D.S., PA and Adame Dental Sleep Medicine, PLLC facilities data will be on a password protected computer with encrypted files to which Dr. J. Michael Adame and research coordinator Amy Carrizales may access.

• Transition from Research Participation - subjects are patients of record of the clinics.

Risk/Benefit Assessment

• Risk Category- Low, minimal risk

• Potential Risk - pressure and/or inflammation and/or infection of the nasal cavity, CPAP mask pressure and/or straps holding CPAP mask pressure, mask leaks causing discomfort, tubing restriction of movement and feelings of claustrophobia. Oral appliance discomfort including pressure to the teeth, gums, or jaw joint.

• Protection against Risks - patients will be thoroughly educated on proper CPAP and Oral Appliance use and maintenance. Patients will be given follow-up appointments within one week of initial delivery to troubleshoot and issues and/or side effects. Patients will be told to call or come into the clinic if they have any concerns before their scheduled visit. Scheduled follow-up visits will include attention to side effects or issues to ensure they are addressed. Any side effect and/or issue is expected to be temporary and if intervention is necessary, a full resolution is expected.

• Potential Benefits to the Subjects - The use of the CPAP with the oral appliance has the possibility of assisting subjects with managing their sleep apnea. Successfully managing or improving issues with sleep apnea has been shown to lower high blood pressure, decrease the chance for stroke, reduce blood sugar levels in diabetics, and lower the risk of death. Additionally, results from this study may assist other individuals with sleep apnea in the future.

Subject Identification, Recruitment and Consent/Assent

• Method of Subject Identification and Recruitment - Patients of record of Pulmonary and Sleep Center of the Valley, J. Michael Adame, D.D.S, PA and Adame Dental Sleep Medicine, PLLC who meet inclusion/exclusion criteria will be asked to participate in the study. Research coordinator will read WIRB approved script to recruit patient.

• Process of Consent - Dr. J. Michael Adame and/or Amy Carrizales will personally read the consent form in the potential subjects' language of choice (i.e. Spanish or English).

- Give the person providing informed consent as much time as they need to make a decision.
- If the person providing informed consent needs more time than is allowed by the research design, not enroll the prospective subject.
- Evaluate whether the person providing informed consent is experiencing time pressure to make a decision, and if so, do not enroll the prospective subject, even if the person providing informed consent agrees to be in the research.
- Ensure there is no threat of harm or adverse consequences to the prospective subject for a decision to not take part in the research.
- Stop the informed consent process once the person providing consent indicates that he or she does not want to take part in the research.

- Evaluate whether the person providing informed consent is being coerced or unduly influenced by others to take part in the research, and if so, not enroll the prospective subject, even if the person providing informed consent agrees to be in the research.
- Communicate in the preferred language of the person providing informed consent.
- Adapt the presentation of the information to the subject's capacities in terms of intelligence, rationality, maturity and language.
- Invite and answer questions from the person providing informed consent. Evaluate whether the person providing informed consent understands the information provided, and not enroll a prospective subject who does not understand, even if that person providing informed consent agrees to be in the research.
- Ensure that no information is provided to the prospective subject or the person providing informed consent that is made to waive or appear to waive any of the prospective subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.
- Communicate to the person providing informed consent all the information in the consent document or script approved by the IRB.
- Invite and answer questions from the person providing informed consent

• Consent Forms - WIRB approved consent form.

• Documentation of Consent - Dr. J. Michael Adame will ensure a valid consent is obtained and documented for all participants. Signed consents will be obtained on hard copy (paper) and kept at J. Michael Adame, D.D.S., PA and/or Adame Dental Sleep Medicine, PLLC facilities on a password protected computer with encrypted files to which Dr. J. Michael Adame and Amy Carrizales may access. A copy of signed consents will be given to each participant.

• Costs to the Subject: Routine costs associated with CPAP therapy. Financial assistance can be granted on a case-by-case basis as normal to daily operations of the clinics.

• Payment for Participation: none