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University of California, San Diego
Consent to Act as a Research Subject

RESCUE-Drug: Rescuing OSA Patients Unable to Tolerate CPAP Using Endotype-Targeted Drug Therapy

Introduction

Christopher Schmickl, M.D, Ph.D. and associates conducting this research are asking for your consent to participate. This section provides a summary of important information. The rest of the form provides additional details.

- Research is voluntary - whether or not you join is your decision. You can discuss your decision with others (such as family and friends).
- You can say yes but change your mind later.
- If you say no, we will not hold your decision against you.
- Your decision will not affect your health care or any other benefits you may be entitled to.
- You can say no even if the person inviting you is part of your healthcare team.
- Please ask questions or mention concerns before, during or after the research.

The purpose of this study is to find out how the combination of Diamox (acetazolamide), Effexor (venlafaxine), and Lunesta (eszopiclone) may treat obstructive sleep apnea. These drugs are FDA approved. We will examine how well the combination of these drugs may improve sleep apnea traits (i.e. enhance airway openness and reduce sleep apnea severity). In order to find out the most effective combination therapy, you will try different drug regimens including 1-3 study drugs. Each drug regimen will last 3 days. On the third day, you will complete an overnight sleep study and receive a new drug regimen. Participation in the study may or may not benefit you directly, and may result in new knowledge that may help others.

Study activities will be performed at the Altman Clinical Translational Research Institute Clinic, 9452 Medical Center Dr, La Jolla, CA 92037. If you agree to be in this study, the following will happen to you:

Daytime Visit #1

If you have not had a diagnostic sleep test in the last 3 months, or we do not have access to your results, you will be required to undergo a **home sleep test (HST)** to confirm your potential eligibility for the study.

Home Sleep Test (HST)

You will be given a standard home sleep test device and instruction on how to complete the test (10 minutes for instruction). This device is strapped over the chest prior to sleep with a button to both start and stop recording. The strap measures chest movements to measure breathing effort, a tube under your nose is used to measure your breathing and a finger probe measures blood oxygen saturation. You will be asked to return the device the next morning and the data will be

downloaded and analyzed. If the results of your HST shows evidence of a sleep disorder you will be referred to seek medical treatment with your primary care physician. In some cases, the quality of your sleep may not allow us to get all the data we need. In these cases, you may be invited back to repeat the sleep test. However, you are under no obligation to conduct an HST. After you complete the Home Sleep Test, you will receive a phone call to let you know if you are eligible for the remaining study activities. We will also provide you a letter summarizing the result of your Home Sleep Test.

Are you willing to repeat your Home Sleep Test, if needed? You will be compensated $25 for the additional study visit.

☐ Yes ☐ No Initials _____

This visit will be scheduled for 45 minutes between 8AM-5PM.

Overnight Visit #1

You will be asked to come in for an overnight sleep study at 8PM. Before sleep, you will complete a basic exam to measure your height, weight, vitals, and neck/hip/waist measurements.

You will be asked to sleep supine while having sensors pasted on your scalp, face, chest and legs that will help determine when you are asleep or awake. A microphone will be placed on your neck to monitor snoring, and a probe will be placed on your finger to measure your oxygen level. An adhesive body position sensor and 2 pairs of magnets will be placed on your body to measure what position you are sleeping in, and the volume of your chest while breathing. All of this equipment is standard for a diagnostic sleep study and should not be uncomfortable.

The study will end at approximately 6AM and all the monitoring equipment will be removed.

If your sleep apnea severity is less than moderate, you will be compensated for completing this overnight visit and not scheduled for additional study visits. Otherwise, in the morning, you will complete sleep questionnaires and have your blood pressure taken. You will also complete a 10-minute computerized reaction assessment and be asked to tap the spacebar every time you see a red dot appear.

In some cases, the quality of your sleep may not allow us to get all the data we need. In these cases, you may be invited back for an additional overnight stay. However, you are under no obligation to participate in the extra overnight study.

Are you willing to be contacted for the extra overnight visits, if needed? You will be compensated for the additional study night ($100).

☐ Yes ☐ No Initials _____

Before leaving, you will be given a 2-day supply of drug regimen A, which are either acetazolamide or placebo (sugar) pills. The drug regimen you receive is based on chance. After completing drug regimen A, you will return to our study location for overnight visit #2.

Weekly Phone Calls

You will receive a weekly call to remind you to start your drug regimen after the wash out periods.

Overnight Visit #2

You will return to the UCSD sleep laboratory at 8PM for your second overnight sleep study.

The evening of your overnight, the following activities will happen:

- Vitals
- Before bed, you will be given two pills (acetazolamide + eszopiclone or two placebo pills). Prior to this visit, if you received a 2-day supply of acetazolamide (drug regimen A), you will be given acetazolamide and eszopiclone. If you received a 2-day supply of placebo, you will be given two placebo pills.
- Sleep Study – The same equipment will be used for the setup of your initial sleep study.

The morning after your overnight, the following activities will be completed:

- Sleep Questionnaires
- Vitals
- Computerized Reaction Assessment
- Blood Draw

If you allow, we will take 3-4 teaspoons of blood. Please note that this blood will be separated into white blood cells, serum (a clear liquid that contains proteins, hormones, and electrolytes but no clotting factors and no blood cells) and plasma (a clear liquid that contains proteins, hormones, electrolytes, and clotting factors but no blood cells) for analyses regarding your genetics and protein levels. Information from your blood will be used to see if there are markers predicting response to the study drugs, assess the effects of study drugs on your body's function (e.g. immune system), and to assess links between other diseases. Your DNA (the genetic material inside your cells) will be studied to find out about variation in the genetic code that may be associated with outcomes related to the study. Genetic markers may be used to evaluate your genetic ancestry (i.e., determine which population your ancestors may have come from based on genetic material; this information may be used to determine if an individual's ancestry is associated with particular responses and, if so, whether this information could be useful in future personalized medicine efforts). You will not be provided with any results or information regarding your genes or protein levels.

If you consent to giving blood or tissue specimens as part of this study, these specimens will become the property of the University of California. The blood samples will not be shared with other researchers/institutions outside of University of California, San Diego.

Before leaving, you will be given a 2-day supply of drug regimen B, which are either acetazolamide or placebo (sugar) pills. If you had received a 2-day supply of acetazolamide (at the end of overnight visit #1), you will now be given placebo pills. If you had received a 2-day supply of placebo (at the end of overnight visit #1), you will now be given acetazolamide pills.

You will complete a 4-10 day wash out period—where no study drugs are taken—before starting drug regimen B. You will take drug regimen B every night before bed for 2 days.

Overnight Visit #3

You will return to the UCSD sleep laboratory at 8PM. You will perform a repeat of the activities that occurred during overnight visit #2. You will be given either a combination of two pills (acetazolamide + eszopiclone) or two placebo pills. If your drug regimen B was acetazolamide, you will receive acetazolamide and eszopiclone pills before bed. If your drug regimen B was placebo, you will receive placebo pills before your sleep study.

Your final drug regimen is based on your response to drug regimens A and B. Before leaving, you will be given a 2-day supply of drug regimen C. All participants will be given a 2-day supply of acetazolamide. If drug regimen A or B resolved your sleep apnea then you will be given another dose of acetazolamide alone during the overnight visit #4, else you will be given three pills (acetazolamide + eszopiclone + venlafaxine) during overnight visit #4.

Before taking drug regimen C (acetazolamide), you will complete a 4-10 day wash out period—where no study drugs are taken. You will then take drug regimen C (acetazolamide) every night before bed for 2 days.

Overnight Visit #4

You will return to the UCSD sleep laboratory at 8PM. You will perform a repeat of the activities that occurred during overnight visit #2. If your sleep apnea did not resolve with drug regimen A or B, you will be given a combination of three pills (acetazolamide + eszopiclone + venlafaxine). Otherwise, you will be given acetazolamide alone before sleep. Your participation in the study will be completed in the morning, after questionnaires, the computerized reaction assessment, vitals, and blood sample are collected.

To summarize you will complete the following visits:

1. Daytime Visit #1—If you have not had a diagnostic sleep test in the last 3 months, or if we do not have access to your results, you will be given a Home Sleep Test. Based on your result, we will schedule you for the sleep studies.

2. Overnight Visit # 1—to confirm your sleep apnea severity. At the end of this visit you will receive drug regimen A to be started after 0-7days.

3. Overnight Visit #2—to see how drug regimen A affects your sleep apnea. At the end of this visit you will receive drug regimen B to be started after a 4-10 day wash out period.

4. Overnight Visit # 3—to see how drug regimen B affects your sleep apnea. At the end of this visit you will receive drug regimen C to be started after a 4-10 day wash out period.

5. Overnight Visit #4—to see how drug regimen C affects your sleep apnea.

6. Weekly Phone Calls—to remind you to start each drug regimen.

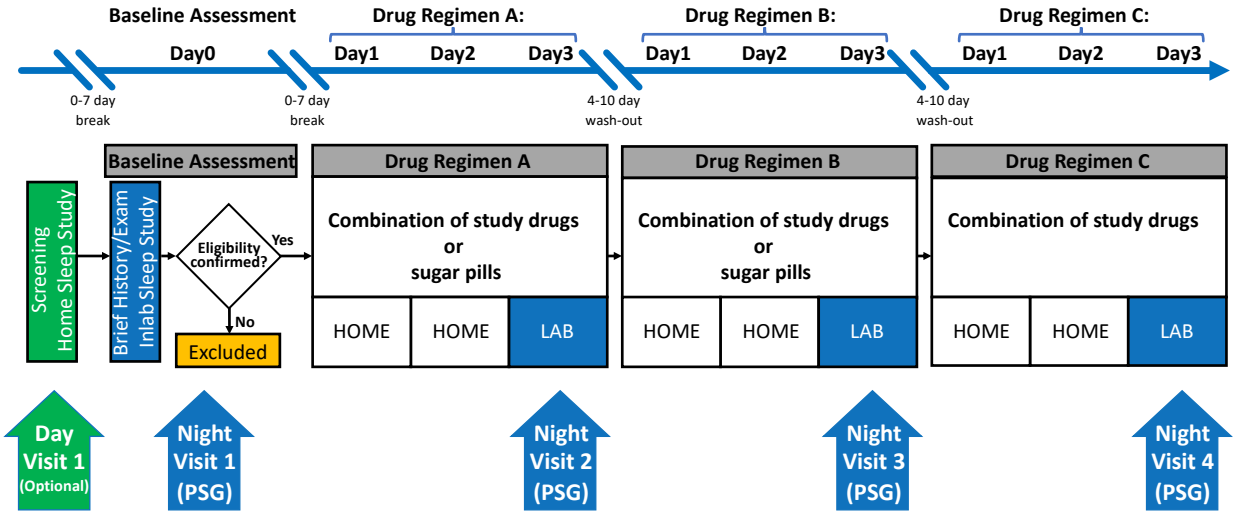

Figure of the Study Timeline and Visits. You will be given a 2-day supply of acetazolamide or placebo (sugar pill) to take at **home**. On the third day, you will return to the **sleep laboratory** to complete an overnight sleep study and receive 1-3 study drugs or placebo before sleep.

The most commonly expected risks of the study are feeling sleepy the next morning after your overnight sleep studies and having temporary discomfort after your blood draw.

The most serious risks of the study may include infection from venipuncture (blood draw) and tingling in limbs/nausea/suicidal thoughts/rapid heartbeat from the drug regimens.

Additional detailed information about this research is provided below. Please feel free to ask questions before signing this consent.

Why have you been asked to participate, how you were selected, and what is the approximate number of participants in the study?

You have been asked to participate in this study because you are an obstructive sleep apnea patient that was unable to use positive airway pressure therapy (PAP) to resolve your OSA and are interested in alternative therapies. There will be approximately 40 participants enrolled in this study at UCSD.

What will happen to you in this study and which procedures are standard of care and which are experimental?
The overnight sleep studies and drug regimens are voluntary study activities and separate from your standard of care. No activities in this study are standard of care.

After overnight sleep study 1, you will be assigned by chance to one of two study groups (which only differ in the order in which the acetazolamide + eszopiclone regimen vs placebo regimen are administered). Your chance of being assigned to each group is 1 in 2. Neither you nor the researcher(s) can choose the group to which you will be assigned.

How much time will each study procedure take and how long will the study last?

1. Daytime Visit #1 will last 45 minutes
2. Overnight Visit #1 will last 10-12 hours (mostly sleeping)
3. Overnight Visit #2 will last 10-12 hours (mostly sleeping)
4. Overnight Visit #3 will last 10-12 hours (mostly sleeping)
5. Overnight Visit #4 will last 10-12 hours (mostly sleeping)
6. Weekly phone calls will last 5 minutes.

Your participation in the study will last 6-8 weeks.

What risks are associated with this study?
Participation in this study may involve some added risks or discomforts. In addition to the risks described at the beginning of this form, please see the following:

Risks Associated with the Study Drugs:

Drug administered at home and in the sleep laboratory:
-*Acetazolamide* has the following common side effects: tingling sensation in limbs, altered taste when drinking carbonated beverages, moderate need to urinate, and fatigue.

Drugs administered in the sleep laboratory only:
-*Eszopiclone* has the following common side effects: metallic taste in the mouth, nausea and sleepiness.

-*Venlafaxine* has the following common side effects: nausea, dry mouth, headache, sweating. Additionally, individuals with major depression disorder and other psychiatric disorders may experience suicidal thoughts while taking venlafaxine; this is an uncommon side effect. As a preventive measure, individuals who have a diagnosed psychiatric disorder (other than well-controlled depression or anxiety) will not be able to participate in the study. Furthermore, if we become aware of any suicidal thoughts, then an urgent evaluation by a physician involved in the research study will be performed, who will provide information about resources and recommend close follow up with the subject's primary care physician or arrange for evaluation by emergency care providers as indicated.

After taking study drugs in the sleep laboratory, you will be required to stay at least 8 hours and be assessed for alertness before being allowed to drive home.

Study drugs may not be safe for pregnant women and breastfeeding. You must use birth control, while you participate in the study over the 6-8 week period. If you enroll in the study and later become pregnant, you will be withdrawn. During the 6-8 weeks of participating in this study, you must not drive until 8 hours after any drug administration, and only if you feel alert enough to do so. All of the above listed side effects are reversible upon discontinuation of study drugs.

Risks of Sleep Studies: During the sleep studies, there may be discomfort at the electrodes or monitors sites that can develop; a localized skin irritation/allergy can occur due to application of the skin surface electrodes for recordings of your brain waves, heart activity, and muscle activity. You might be sleepy the next morning after participating in the study.

Risks of a blood draw/blood pressure test: You may have temporary pain or discomfort during the blood draw.

Risks of Loss of Confidentiality: Even with all of the study procedure precautions that will be taken to protect confidentiality, there is still a risk of loss of confidentiality associated with this study. Research records will be kept confidential to the extent allowed by law. The study personnel are well trained in securing and safely storing all your data.

Study Assignment: You will be assigned to a study group at random (by chance). Your assignment is based on chance rather than a medical decision made by the researchers. The study group you are assigned to might not be the group you would prefer to be in. Your assigned study group might also prove to be less effective or have more side effects than the other study groups(s), or other treatments available for your condition.

Unknown Risks: Because this is a research study, there may be some unknown risks that are currently unforeseeable. You will be informed of any significant new findings.

Are there risks to the reproductive system or a developing fetus?

The drug regimens of the treatment procedures may pose some unforeseeable risks on the reproductive system (sperm, eggs) or to the developing fetus. For this reason, participants in this investigational study should not become pregnant or father a child. We require that all participants agree to either abstain from sexual intercourse or use a reliable, effective birth control for this period, such as hormonal contraceptive, intrauterine device (IUD), diaphragm with spermicide, contraceptive sponge or use of condom (by the partner).

After you have been enrolled in this study and during the research, pregnancy testing will be performed. If you have a positive pregnancy test, we may withdraw you from the study. If you (or your partner) become pregnant or if there is any chance of pregnancy (e.g., late menstrual period), please contact the study personnel immediately so that we may provide medical assistance and counseling.

What are the alternatives to participating in this study?
The alternatives to participation in this study are not to participate in the study.

What benefits can be reasonably expected?
There is no direct benefit to you for participating in this study. Benefits of this study are principally to science and future patients, in that we may be able to identify effective drug therapies as alternatives to treating obstructive sleep apnea. This information may be useful to clinicians and patients.

What happens if you change your mind about participating?
If you decide that you no longer wish to continue in this study, you will be requested to reach out to a member of our research team. We will terminate any of your remaining study activities.

Can you be withdrawn from the study without your consent?
You may be withdrawn from the study for the following reasons:

- You become ill,
- Are required to use medications that are known to disrupt sleep or interfere with the study drugs.

You may also be withdrawn from the study if you do not follow the instructions given you by the study personnel. You may refuse to participate or withdraw at any time without penalty or loss of benefits to which you are entitled. If you decide that you no longer wish to continue in this study, you will be requested to:

- Return any equipment and/or unused study drugs to our research staff
- Provide a reason for discontinuation (if possible)

Will you be compensated for participating in this study?
In compensation for your time and travel, you will receive total $585.00 for participating in this research and all blood draws.

- Daytime Visit #1: $25
- Overnight Visit #1: $100
- Weekly call: $20
- Overnight Visit #2: $100
- Weekly Call: $20
- Overnight Visit # 3: $100
- Weekly Call: $20
- Overnight Visit #4: $100
- Completion of entire study: $100
- If data is inconclusive and an additional day time visit is needed, you will be paid $25. If data is inconclusive and an additional overnight sleep study visit is needed, you will be paid $100.

Personal information about you, including your name, address, and social security number, will be released to the UCSD Accounting Office for the purpose of payment and for tax

reporting to the Internal Revenue Service (IRS), if the total amount you receive is $600+ in a calendar year.

Parking will be available free of charge and you will also be reimbursed for public transportation or taxi vouchers. If you terminate the study early, then you will receive an amount based on the visits that have been completed. If any of the visits are missed, then you will not be compensated for those visits.

Are there any costs associated with participating in this study?
There will be no cost to you for participating in this study. Parking expenses at UCSD study sites will be covered.

What if you are injured as a direct result of being in this study?
If you are injured as a direct result of participation in this research, the University of California will provide any medical care you need to treat those injuries. The University will not provide any other form of compensation to you if you are injured. You may call the Human Research Protections Program Office at (858) 246-4777 for more information about this, to inquire about your rights as a research subject or to report research-related problems.

What about your confidentiality?
Research records will be kept confidential to the extent allowed by law. To guard your confidentiality, you will be assigned a unique identifying number to label all your data collection sheets. All personal information will be kept strictly confidential by the investigators. All study forms, and data collected will be kept locked in a secure location. All your data forms will only list your unique study ID number. All research staffs are trained in the protection of subject privacy and confidentiality. Research records may be reviewed by the UCSD Institutional Review Board, or the study Sponsor, the ATS Foundation.

Because of the need to release information to these parties, absolute confidentiality cannot be guaranteed. The results of this research study may be presented at meetings or in publications; however, your identity will not be disclosed in those presentations.

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.

Your DNA will be examined based on analysis of specific genetic variants and/or whole genome sequence information. Your DNA is your inherited genetic material that contains instructions for the cells that make up your body. Whole genome sequence analysis provides information about the entire order, or sequence, of the DNA in your genome.

Personal identifiers might be removed from the information or biospecimens collected as part of the research. After such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without your additional informed consent.

Biospecimens (such as blood) collected from you for this study and/or information obtained from your biospecimens may be used in this research or other research, and shared with other organizations. You will not share in any commercial value or profit derived from the use of your biospecimens and/or information obtained from them.

Federal and State laws generally make it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways: a) Health insurance companies and group health plans may not request your genetic information that we get from this research. b) Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums. c) Employers with 5 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Be aware that these laws **do not** protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

Will you receive any results from participating in this study?
If any clinically relevant research results are found in the data collected during your overnight sleep studies, a written report of the abnormality will be shared with you and you may be recommended to seek appropriate evaluation with your primary care doctor. These abnormalities may include but are not limited to irregular heart rhythms and high blood pressure. As stated previously, we will not provide results of the genetic testing that you complete. We will use an approach to examine your genome that does not immediately offer clinically relevant results that can be used for your healthcare.

Who can you call if you have questions?
This study has been explained to you and your questions have been answered. If you have other questions or research-related problems, you may reach Dr. Christopher Schmickl and his research study coordinators at (858) 246-2154.

You may call the Human Research Protections Program Office at 858-246-HRPP (858-246-4777) to inquire about your rights as a research subject or to report research-related problems.

Your Signature and Consent
You have received a copy of this consent document and a copy of the “Experimental Subject's Bill of Rights” to keep.

You agree to participate.

_____ _____
Subject's signature Date

_____ _____
Signature of the person conducting the informed consent discussion Date