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

The Effect of Melatonin on Sleep and Ventilatory Control in Obstructive Sleep Apnea – Aims 2 and 3

Who is conducting the study, why you have been asked to participate, how you were selected, and what is the approximate number of participants in the study?
Naomi Deacon, PhD and her associates, are conducting a research study funded by the National Institutes of Health (NIH) to find out whether melatonin treatment can reduce oxidative stress, help stabilize breathing and improve the quality of sleep in people with sleep apnea. We believe that melatonin may prevent damage and health consequences of sleep apnea, and also reduce the number of apneic events. You have been asked to participate in this study because you were identified as someone who would be appropriate for our study. There will be approximately 40 participants in this study.

Why is this study being done?
The purpose of this study is to find out whether melatonin can help stabilize breathing, reduce the number of apneic events and help prevent some of the negative health consequences of sleep apnea. In obstructive sleep apnea, the upper airway closes over and over again during sleep. This leads to disrupted sleep and daytime sleepiness. Because the airway closes oxygen in the blood drops and this forms highly reactive molecules of oxygen which can damage cells and tissues in the body. This causes what is called oxidative stress, which can increase risk for several health problems such as high blood pressure and heart disease. The repeated low oxygen levels also change how the brain controls breathing, making breathing unstable, which then makes sleep apnea worse.

Currently, the best treatment for obstructive sleep apnea is sleeping with a mask that continuously blows air into the nose (continuous positive airway pressure or CPAP treatment). While this treatment stops the upper airway from closing in most individuals, many individuals have difficulty sleeping with the mask in place and therefore do not use the CPAP treatment. These people are at risk of being tired during the day and suffering from car or work place accidents. We are conducting research we hope may lead to development of new treatments for obstructive sleep apnea for individuals that have difficulty sleeping with the mask.

Melatonin is a hormone produced in the brain which helps the body know night from day, and controls when you feel tired and want to sleep. Melatonin is also a powerful antioxidant which can reduce oxidative stress and has been found to be effective in treating several diseases in humans which are caused by oxidative stress. People with sleep apnea have lower levels of melatonin than people without sleep apnea. Therefore

this study aims to investigate whether taking melatonin supplements can reduce oxidative stress, which may stabilize breathing and reduce the number of apneic events.

Melatonin is not considered a drug in the USA, but a food substance which is sold over the counter. Melatonin is a mildly hypnotic agent commonly used to treat insomnia, jet lag and sleep dysregulation, with the main potential side effect being sleepiness or grogginess the following day. However these affects are rare and not considered a high risk.

We are asking you to take part in this study because you may or may not have sleep apnea and we have identified you as someone who may be suitable for this study. This research study will investigate the effect of melatonin on blood oxidative markers and the control of breathing both while awake and during sleep. You will be randomly assigned to one of two groups; one will be given melatonin and the other will be given a placebo (non-drug tablet that looks the same) and you will not be told which you are receiving. You will complete two day experiments followed by an overnight experiment while you sleep in the laboratory. You will complete the first day and night before taking either melatonin or the placebo at home for 30 days, then you will return to complete the second day and overnight study.

What will happen to you in this study and which procedures are standard of care and which are experimental?

If you agree to be in this study, we will ask you to sign this consent form before we do any study procedures. You will then be required to complete an afternoon and overnight study which are explained in detail below. You will then go home and take the pill (either melatonin or placebo) for 30 days at the time instructed, after which you will be asked to return to repeat the afternoon and overnight study. If you have not previously been diagnosed with sleep apnea and we determine during the study that you do have sleep apnea, following completion of the study you will be referred for standard of care treatment for sleep apnea.

Day experiment

We will ask you to come to the UCSD Clinical Teaching Facility (CTF) Sleep Laboratory at 4pm. You should not eat any food for at least three hours before you come to the laboratory. Also, please avoid alcohol the night before, and avoid caffeine and strenuous exercise on the morning of the experiment.

First we will give you a medical exam, including taking height, weight and physical measurments to ensure you are fit and healthy to take part in the study.

You will then be asked to complete three questionnaires which assess your sleep quality (Pittsburgh sleep quality), general health (SF-36) and sleepiness (Epworth Sleepiness Scale).

You will then complete four tests.
1. To assess your lung function you will be asked to blow as hard as you can into a machine through a mouthpiece. This test may be repeated several times to ensure we record your very best effort.
2. To assess your concentration and reaction time you will also complete a quick (5 minute) psychomotor vigilance test (PVT) through a computer program.
3. To assess the health of your blood vessels you will perform a non-invasive test called EndoPat. Prior to this test you will be asked to remove any watches or jewellery from your hands and wrists. You will lay on your back and a probe will be placed on a finger on both hands. A blood pressure cuff will be inflated on one arm to occlude blood flow for 5 minutes, after which the cuff will be rapidly deflated and the response of the blood vessels in your fingers will be evaluated.4. You will then undergo two tests to measure how your body responds to oxygen and carbon dioxide. To do this we will stick electrodes on your chest to monitor your heart rate and a probe will be placed on your finger to measure your blood oxygen levels. You will be asked to lie on your back and place a clip on your nose. While breathing on a mouth piece you will be instructed to take deep breaths for about 5 minutes, then you will breathe from a bag containing either high or low oxygen. The carbon dioxide you breathe out will build up in the bag, so we can measure how your body responds to gradual changes in both oxygen and carbon dioxide. Each test will take about 20 minutes and will be separated by about 10 minutes break. The breathing tests will take approximately 1 hour to complete.

At 6pm you will have a 2 hour break to have dinner.

Overnight sleep study

At 8pm you will be set up for the overnight sleep study, which will measure your breathing during sleep.

This will involve the following procedures:

- We will apply paste-on electrodes (pads with wires attached) to your scalp, chin, chest and face. This is done so that we can monitor (check) your wakefulness, sleep, and heart rhythm throughout the study.
- Small electrodes will be placed on the legs to monitor leg movement while you are asleep.
- A breathing mask which allows us to measure your breathing rate and volume and to measure gases you breathe out. You will wear either a full-face mask or a nasal mask, depending on how well the mask fits and which you are more comfortable with. If you wear a nasal mask you will be asked to breathe solely through your nose and a small piece of tape will be applied over your mouth. The tape will have a large tab for quick and easy removal and you will be shown how to remove it. If at any stage you wake up, you will be able to remove the tape should you need to breathe through your mouth or talk. The level of carbon dioxide that you exhale will be measured through the mask.

- One band will be placed around your chest another around your abdomen to measure breathing movements, a probe will be placed on your finger to measure your oxygen levels.
- A small (~2mm) tube inserted through one nostril to the back of the throat after the nostril has been decongested with a spray (Oxymetazoline Hydrochloride 0.05% w/v) and anaesthetised with a local anaesthetic spray and gel (Lignocaine). The tube will not affect swallowing or breathing and usually causes minimal discomfort once in place.
- 2 fine wire (<0.1 mm thick) electrodes will be placed into the muscles under your tongue to measure the activity of the muscles in your upper airway. These are inserted via needles into the floor of the mouth after local anaesthetic (lignocaine 4%) has been applied with a cotton swab placed underneath your tongue. Once in place, the needles are removed leaving the fine wires in the muscle. This may cause some minor discomfort during and immediately (a few seconds) after insertion of the electrodes. However, once in place the wires usually cause very little or no discomfort and additional anaesthetic is not required.

Once all of this equipment is placed on you and you are comfortable, you will be asked to look in several directions, blink, wriggle your feet and make chewing movements so that we can check that all of our equipment is working.

On the second visit you will take the treatment (melatonin or placebo) at the same time you have been instructed to during the 30 days prior. After that we will turn off the light and let you go to sleep. We will ask that you try and sleep on your back for as much of the night as possible. However, if you need a break from sleeping on your back, you will be allowed to sleep on your side for a while and then you will be asked to return to your back.

We will record your breathing and sleep until approximately 6am when you will be woken and the study equipment will be disconnected and removed.

We will then sterilize the skin of your inner elbow with alcohol and insert a needle to take a blood sample to measure markers for oxidative stress.

The investigator will ask you whether you experienced any side effects or discomfort. You will then be able to sleep longer if you wish. We will ask you to stay until you feel rested enough to return home. You should not drive your car, especially if you are feeling sleepy. We can help you with public transportation or a taxi (we will give you a taxi voucher) if you cannot be taken home by a responsible adult.

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 an extra overnight visit if needed?

☐ Yes ☐ No Initials _____

You will be assigned by chance to a study group. Your chance of being assigned to each group is 1 in 2. You will be assigned to a group in a random manner, with someone matching your age, height and weight assigned to the opposite group to you. Neither you nor the researcher can choose the group to which you will be assigned. Assignment to groups will be done by an independent researcher. Both groups will undergo the same procedures. The only difference between the groups will be whether you are given melatonin or placebo.

How much time will each study procedure take, what is your total time commitment, and how long will the study last?

It will take you 31 days to complete the aim of this study. During this time, we will ask you to come in for 2 afternoon and overnight stays at the UCSD Clinical Teaching Facility (CTF) Sleep Laboratory. The total amount of time this aim will require is 28 hours to complete both afternoon and overnight studies. The duration of the study overall will be approximately 3 years.

What risks are associated with this study?

Participation in this study may involve some added risks or discomforts. Should you agree to participate in this study, there is a chance that you could experience an allergic reaction to melatonin. However this is very rare and we expect the risk to be small. In an effort to minimize those risks, we will inquire about any sensitivity and known allergies to melatonin that you may have or experienced. Other risks include the following:

We believe the risks to be small, but present and include:

1. Melatonin is a well-known supplement that has been used for many years as a sedative and sleep agent. The common side effects of melatonin are:

   - Drowsiness
   - Headache
   - dizziness

   Very rare but potentially serious side effects include:

   - allergic reaction, including skin rash, hives, difficult breathing, swelling of your face, lips, tongue, or throat.
   - low blood pressure
   - abdominal discomfort
   - mild anxiety
   - irritability

- confusion
- short-lasting feelings of depression

Although these are possible side effects, these are rarely reported and melatonin is sold without prescription as a supplement in the U.S., therefore it is unlikely you will experience any of these side effects.

2. Both low oxygen and high carbon dioxide will make you want to breath harder and can induce feelings of dizziness or discomfort. If at any time you feel uncomfortable and wish to end the test early you will be advised to simply remove your mouth from the mouth piece. Any discomfort should dissipate immediately. Although these are potential risks, due the preliminary medical exam and continual monitoring of your heart rate and blood oxygen levels, the risks associated with these tests are very low.
3. There is a slight risk of hematoma (swelling due to rupture of blood vessel) and infection from insertion of the tongue electrodes and the needle for blood draws. There is a slight risk of lightheadedness due to IV start. However this will be conducted by a trained technician and carries the same risk of routine dental procedures or blood tests most people are familiar with. We consider this risk to be very small.
4. There is a risk of gagging and discomfort from the insertion of the tube into your throat, however any discomfort usually dissipates quickly and the catheter is tolerated well.
5. Due to the extent of the equipment, you are unlikely to sleep well and may be fatigued (tired) the next day. However, once the study is over, you will be allowed to sleep without any equipment.
6. You should not drive or take part in other potentially dangerous activities while you are feeling sleepy. If you plan to drive, you will have to stay in laboratory until you have rested enough to drive safely. Moreover we will ask you to stay in our laboratory at least 8 hours after you have taken the melatonin pill.
7. The electrodes, bands around your chest, sensors on your top lip, nose mask, microphone, and probe on your finger may be uncomfortable. They may also disturb your sleep slightly. Rarely, the tape and electrodes used may cause a mild skin rash.
8. There is a risk of loss of confidentiality.

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.

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.

What are the alternatives to participating in this study?
The alternative to participation in this study is to not participate and if you have sleep apnea, to receive standard of care treatment for sleep apnea, which may include CPAP, as per your treating physicians' decision.

What benefits can be reasonably expected?
There will not be any direct benefit to you from these procedures. However, information gained from this study may assist with improving treatment for people with obstructive sleep apnea and ultimately improve the quality of life for those who suffer from it.

Can you choose to not participate or withdraw from the study without penalty or loss of benefits?
Participation in research is entirely voluntary. 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 should tell us. We will make sure that you stop the study safely. We will also talk to you about follow-up care, if needed.

You will be told if any important new information is found during the course of this study that may affect your wanting to continue.

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

- Dr. Malhotra believes that it is in your best medical interests.
- You may also be withdrawn from the study if you do not follow the instructions given you by the study personnel.

Will you be compensated for participating in this study?
In compensation for your time and travel, you will receive $150 for each overnight sleep study. If you enroll in the study but are subsequently found to be ineligible, you will be paid $50. If for any reason we ask you to come back for another overnight study, you will receive an additional $150. You will also receive $50 for the daytime chemoreflex tests. Therefore you will receive a maximum of $350 for completion of both day and overnight studies. You will also receive parking vouchers (coupons) for each visit to our laboratory or taxi vouchers if you take a taxi.

Are there any costs associated with participating in this study?
There will be no cost to you for participating in this study. All of the tests and procedures that will be done for this research will be paid for by study funds. We will pay for any sleep studies done for research purposes.

Costs for any ongoing or routine medical care you would receive apart from this study will be billed to you or to your insurance company in the usual way. You will be responsible for any deductibles or co-payments required by your insurer.

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. We will make every effort to maintain your privacy and confidentiality, both during and following the information with your study, by use of a code in place of your name and identifying information. The list linking your information with your study code will be kept separate from other study data stored on a secure disk for access by the study investigator and research staff. A hard copy will be stored in a locked cabinet. Study data will be stored securely at UCSD. All research staff are trained in the protection of subject privacy and confidentiality. Research records may be reviewed by the UCSD Institutional Review board and the study funding agency, the National Institutes of Health (NIH).

Federal law requires UCSD (UCSD and its hospitals, health care providers and researchers) to protect the privacy of health information that identifies you.
If you decide to take part in this research study, your health information may be used within UCSD and may be shared with others outside of UCSD, as explained in the separate HIPPA authorization form you will sign in order to participate in this study.

Who can you call if you have questions?
Atul Malhotra, MD and/or _____ has explained this study to you and answered your questions. If you have other questions or research-related problems, you may reach Atul Malhotra, MD at 858-657-6159.

You may call the Human Research Protections Program Office at (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