Study Protocol

Title: Informing Treatment Decisions in the Central Disorders of Hypersomnolence: A Pragmatic Clinical Trial of Modafinil Versus Amphetamines

NCT Number: NCT03772314

Protocol date: September 25, 2020

TITLE: Informing Treatment Decisions in the Central Disorders of Hypersomnolence: A Clinical Trial of Modafinil Versus Amphetamines

Short Title: A Clinical Trial of Modafinil Versus Amphetamines

PI: Lynn Marie Trotti, MD, MSc, Associate Professor of Neurology

Funder: American Association of Sleep Medicine Foundation

Protocol Version: 8.0

Protocol Date: 9/25/2020

Abstract

Currently, there are insufficient data to guide clinical practice regarding the use of amphetamines for the treatment of narcolepsy. This may be particularly important in the case of narcolepsy type 2, for which randomized, controlled trial data show that other treatments are less beneficial than they are for participants with narcolepsy type 1. For the closely related disorder of idiopathic hypersomnia, clinical trial data to guide treatment decision-making are even more limited, with only three published controlled trials ever performed.

To address these evidence gaps, we propose a randomized, active-treatment controlled trial comparing modafinil and amphetamine salts for the treatment of narcolepsy type 2 and idiopathic hypersomnia. The primary outcome will be reduction in excessive daytime sleepiness, as measured by change in Epworth Sleepiness Scale scores from baseline to week 12 on treatment. Other important patient-reported outcomes will be considered as secondary outcomes, including Patient Global Impression of Change for sleep inertia, cognitive dysfunction, and sleepiness.

In addition to directly comparing the efficacy of these two medications for hypersomnolent patients, this study will also evaluate for relatively safety in this population. Further, we will assess for clinical predictors of treatment response. All three of these aims will be complementary in informing shared decision-making about whether to treat with modafinil or amphetamine salts.

Background

Current evidence-based treatment guidelines for narcolepsy from the American Academy of Sleep Medicine (AASM) give the highest level of recommendation to modafinil and sodium oxybate, with a lower level of evidence supporting use of methylphenidate and amphetamine-based stimulants (1). Despite this lower level of evidence in support of their benefit, central nervous stimulants are widely used in clinical practice. Very few data are available to guide clinical decision-making regarding which medication should be prescribed for which patient with narcolepsy.

Most clinical trials for narcolepsy have combined participants with types 1 and 2, despite the known difference in underlying pathophysiology of these disorders (2). Post-hoc analyses have suggested that there are important differences in treatment response between participants with these two distinct disorders, with patients with narcolepsy type 2 significantly less likely to achieve “much improved” or “very much improved” status on the Clinical Global Impression of Change scale in modafinil and sodium oxybate trials (3). In contrast to narcolepsy type 1, which has a distinct phenotype and well-characterized pathophysiology of hypocretin neuronal loss, idiopathic hypersomnia is much more closely related to narcolepsy type 2. The clinical features of narcolepsy type 2 and idiopathic hypersomnia are so similar that diagnosis-independent cluster analysis sorts patients with these two disorders into the same cluster, which is distinct from those patients with narcolepsy type 1 (4). The multiple sleep latency test is the only tool that can distinguish these disorders, but patients with narcolepsy type 2 and idiopathic hypersomnia frequently change diagnostic categories on repeat testing (5-7). Finally, although the causes of both narcolepsy type 2 and idiopathic hypersomnia are currently unknown, emerging data suggest a possible shared pathophysiology (8).

Data to guide clinical practice for patients with idiopathic hypersomnia are even more sparse than for patients with narcolepsy type 2. To date, only three randomized controlled trials of any medication for idiopathic hypersomnia have been published (9-11). None of these trials investigated amphetamine-based stimulants, whose use in idiopathic hypersomnia is supported only by very small patient series (12). Further, no treatments are currently recognized by the US FDA for the treatment of idiopathic hypersomnia. This lack of data complicates shared decision-making and frequently results in the denial of medication coverage, severely limiting treatment options.

Although explanatory, randomized, placebo-controlled trials (RCTs) are the gold-standard for assessing efficacy, they are frequently insufficient to guide clinical practice because of narrow inclusion/exclusion criteria and comparison to a placebo rather than to a real-world clinical alternative (13, 14). Patients with comorbid conditions are frequently excluded from clinical trials [e.g., (10, 15)], despite a high rate of comorbidity in patients with narcolepsy (16), limiting generalizability of results. Furthermore, enrollment in a traditional explanatory RCT is limited to those patients whose symptom severity is such that they can commit to a placebo treatment for the duration of the study, should they be randomized to that arm. This excludes many patients who are seen in clinical practice, whose disease severity is such that use of a placebo is untenable, because of the impacts of untreated excessive daytime sleepiness on ability to work, drive, and maintain family obligations (17, 18). This further limits the generalizability of explanatory RCTs to those patients with relatively mild disease manifestations. Finally, use of a placebo comparator does not guide decision-making between two different active treatments, which is the type of information needed in clinical practice.

In contrast, trials that incorporate degrees of pragmatism (19, 20) can help overcome some of these obstacles to increase generalizability and more clearly guide clinical practice. Inclusion criteria are intentionally broad, allowing inclusion of patients with clinically-important comorbidities (e.g., mood disorders among narcolepsy patients), to better mimic the range of patients encountered in clinical practice (13, 20). Two active treatments may be directly compared, rather than employing a placebo (13), so that patients considering enrollment can be assured that they will receive an active treatment for the duration of the study. The majority of measures collected are those that can be embedded into clinical practice (20).

Pragmatic trials also emphasize the use of outcomes that are important to patients (20). To date, RCTs for the central disorders of hypersomnolence have predominantly focused on excessive daytime sleepiness. While this is undeniably the core symptom of these disorders, other symptoms may be equally or more problematic for patients. Among people with narcolepsy in the Nexus Narcolepsy Registry, 57.1% cited difficulty concentrating, focusing, or thinking as a reason they initially sought medical evaluation for narcolepsy (21). In an FDA-convened patient panel of patients with narcolepsy, chronic cognitive dysfunction was the aspect of excessive sleepiness that received the most attention, with participants endorsing “brain fog”, impaired alertness, decreased mental agility, and difficulty thinking (22). We have been collaborating with the Hypersomnia Foundation, a national organization for people with hypersomnia disorders, to delineate the most important symptoms identified by these patients. As of May 2018, 1077 participants with hypersomnia disorders had completed our questionnaire. Limiting data to those 570 respondents with idiopathic hypersomnia or narcolepsy without cataplexy/type 2, it is clear that many respondents have persistent symptoms that are not being well-addressed by their current treatments. Eighty percent experience daily or near-daily difficulty with morning sleep inertia, without a significant difference between those taking and not taking wake-promoting medications ($p = 0.65$). Fifty-two percent experience daily “brain fog”, again not different between those treated and not treated ($p = 0.11$). Even among treated patients, 60% still experience daytime sleepiness (Trotti, unpublished data). Taken together, these patient reported data highlight the need to evaluate all these symptoms when assessing for differential responses by treatment type.

Objectives:

To address the limitations in current evidence for the treatment of central disorders of hypersomnolence and better guide shared clinical decision-making, we propose a pragmatic clinical trial comparing modafinil and amphetamine salts in patients with narcolepsy type 2 or idiopathic hypersomnia.

Aim 1: To compare the effectiveness of modafinil and amphetamine salts in patients with narcolepsy type 2 or idiopathic hypersomnia. The primary outcome will be the change in Epworth Sleepiness Scale score from pre-treatment baseline. Secondary outcomes will include Patient Global Impression of Change from baseline for sleepiness, sleep inertia, and cognitive dysfunction.

Aim 2: To compare the safety of modafinil and amphetamine salts in the treatment of narcolepsy type 2 or idiopathic hypersomnia.

Aim 3: To evaluate for clinical predictors of response to modafinil and amphetamine salts in these patients.

Study Design & Methods

Treatment-naïve adult patients (n = 44), or adult patients free of wake-promoting medication or willing to discontinue current wake-promoting medication seeking evaluation at the Emory Sleep Center for narcolepsy type 2 or idiopathic hypersomnia will be invited to participate and randomized to one of the treatment arms upon consent. Although pragmatic trials often do not involve blinding to condition, those trials where outcomes of interest are primarily subjective often require blinding to minimize bias (20), which will be necessary in this case. Randomization, allocation concealment, blinding, and medication dispensing will be managed by Emory's Investigational Drug Service (IDS). The IDS will use 1:1 computer generated randomization (23), with a block design to ensure equal number of participants receiving each study medication. Block size will not be disclosed to the study investigators or staff. Identity of medications will be concealed by the pharmacy using matched pills and pill containers. The IDS is located in a separate building from the study team and will have no interaction with participants. Medications will be transferred from the pharmacy via courier. This protocol will be approved by the Emory University Institutional Review Board and registered at clinicaltrials.gov prior to enrollment of the first participant.

Inclusion criteria will be a diagnosis of narcolepsy type 2 or idiopathic hypersomnia. These diagnoses will be made in accordance with the International Classification of Sleep Disorders, third edition (ICSD-3) criteria (24). All participants will have daily sleepiness for at least three months and an absence of cataplexy. For patients in whom hypocretin has been tested, values will be above 110 pg/mL. Participants with narcolepsy type 2 will additionally demonstrate a multiple sleep latency test mean sleep latency (MSLT-SL) less than or equal to 10 minutes, with at least two sleep onset REM periods (SOREMs) between nocturnal polysomnogram and next-day MSLT. Participants with idiopathic hypersomnia will demonstrate at least one of: 1) MSLT-SL less than or equal to 10 minutes, with fewer than two sleep onset REM periods (SOREMs) between nocturnal polysomnogram and next-day MSLT; 2) total sleep time of > 660 minutes accrued over up to 24 hours of continuous polysomnographic monitoring; or 3) 24-hour total sleep time of > 660 minutes, as estimated by wrist actigraphy averaged over at least 7 days.

Participants suspected of having a diagnosis of narcolepsy type 2 or idiopathic hypersomnia who have never had a nocturnal polysomnogram and next-day MSLT, will be scheduled for an additional study visit to complete an overnight and day study prior to visit 2.

Participants already diagnosed with narcolepsy type 2 or idiopathic hypersomnia must be free of wake-promoting medication or willing to discontinue current wake-promoting medication. Medicines will be discontinued for up to two weeks; length of discontinuation will be dependent on the half-life of the medication(s).

During the research slow-down created by the COVID19 pandemic, several modifications will be made to allow continued data collection while protecting the health of participants, study staff, and the population:

1) Consent and questionnaires will be completed virtually, rather than in-person. The video platform that will be used to complete virtual consents and questionnaires is Zoom. This platform is currently approved by Emory.

2) Investigational drug will be shipped directly to the participant from IDS, rather than having the participant pick up in person from IDS
3) Inclusion criteria will be changed to eliminate the need for PSG/MSLT. The Emory sleep lab is currently closed for non-urgent procedures, and so no patients suspected of having idiopathic hypersomnia or narcolepsy can currently undergo PSG/MSLT. We will use the following for the provisional diagnosis of idiopathic hypersomnia or narcolepsy type 2 during the period that the sleep lab is closed for testing:
    a. Clinical suspicion of idiopathic hypersomnia or narcolepsy type 2 by a sleep medicine provider
    b. Home sleep apnea test demonstrating absence of obstructive sleep apnea (pAHI < 15), if sleep medicine provider feels that a home sleep apnea test is clinically indicated to rule out sleep apnea
    c. Sleep diary x 1 week demonstrating average sleep time > 7 hours/night and no individual nights of < 6 hours
    d. Other inclusion/exclusion criteria will continue to apply

Exclusion criteria will include obstructive sleep apnea (AHI > 15), severe periodic limb movements of sleep with arousals (PLM arousal index > 30), allergy to either of the study drugs, and contraindication to either of the study drugs. For modafinil, these contraindications include: history of left ventricular hypertrophy, mitral valve prolapse, severe cardiovascular disease, unstable angina, myocardial infarction, severe hepatic impairment, substance abuse history, psychosis, or unstable depression or mania (25). Contraindications to amphetamine salts, in addition to those listed above, include: other cardiac structural abnormalities, cardiomyopathy, severe arrhythmias, uncontrolled hypertension, glaucoma, Tourette's syndrome, and epilepsy. Women who are pregnant, planning to become pregnant within 16 weeks, or breastfeeding will be excluded, as the safety of these medications during pregnancy and breastfeeding is not well-established. Participants who have taken either modafinil or amphetamine salts for another indication (e.g., ADHD) will be excluded if it has been < 12 months since this treatment.

Participants who are taking a medication that has a potential interaction with modafinil to cause QTc prolongation will be eligible if either: 1) they can safely discontinue the potentially interacting medication prior to and throughout the study (in conversation with the prescribing physician), or 2) they undergo an an electrocardiogram (EKG) prior to baseline visits that shows a normal QTc interval while on the potentially interacting medication.

Patients whose hypersomnia is judged to be due to or primarily associated with a medical or psychiatric disease, e.g., Parkinson's disease, myotonic dystrophy, severe depression, will be excluded. However, patients with a diagnosis of narcolepsy type 2 or idiopathic hypersomnia who have medical or psychiatric comorbidities not thought to be causal to daytime sleepiness will not be excluded. Drs. Trotti and Rye, board-certified neurologists, will assess for the relationship between any medical comorbidities and hypersomnolence. Dr. Bliwise, a clinical psychologist, will assess for the relationship between any psychiatric comorbidities and hypersomnolence.

1) The primary outcome will be change in sleepiness from baseline, as measured by the Epworth Sleepiness Scale at baseline and week 12. Secondary outcomes will be sleep inertia and cognitive dysfunction. Current literature does not support the use of a particular, validated instrument for either of these measures, which have historically not been assessed in RCTs performed in participants with the central disorders of hypersomnolence. However, stakeholders have identified these two clinical features as particularly problematic, and therefore it is important to include measures of change of these symptoms in pragmatic clinical trials. The patient global impression of change (PGI-C) is a validated tool to assess change in symptoms (26), which has been used for the assessment of a wide variety of

sleep and non-sleep symptoms in clinical trials (27-31). We will assess three separate PGI-C features: sleepiness, sleep inertia (defined for participants as "difficulty waking up and getting out of bed in the morning because of sleepiness"), and cognitive dysfunction (defined for participants as "difficulty with thinking, problems with attention or concentration, and/or 'brain fog'"). For participants taken off meds, they will be asked to "compared to the medication (or medications) you were taking just before your started the study, which treatment did you prefer overall". Measures will be collected at baseline, week 4, week 8, and week 12. Week 4 and 8 measures will be collected remotely from patients using the electronic, HIPAA-compliant REDCap data collection system (32). Baseline and week 12 measures will be collected in a face-to-face visit, mimicking the frequency of follow up in routine clinical practice.

Medications will be provided initially as: modafinil 100 mg qam and amphetamine salts 10 mg qam. For patients reporting difficulty awakening at baseline, the first dose will be taken 1 hour before planned awakening, whenever possible. For patients without difficulty awakening at baseline, first dose will be taken upon awakening. Patients will be advised to increase dosage once a week with the following schedule: week 2, 1 pill qam and 1 qnoon; week 3: 2 pills qam and 1 qnoon; week 4 and beyond: 2 pills qam and 2 pills qnoon. Patients will be instructed not to titrate further once they feel symptoms are well-controlled and to reduce dosage one step in the case of mild to moderate side effects. In the case of severe side effects, participants will be instructed to discontinue treatment but will still continue all remaining study visits and questionnaires. This titration will allow participants to reach doses of modafinil as high as 200 mg bid, the maximum FDA approved dose of modafinil in the treatment of narcolepsy. Participants will reach a maximum dose of amphetamine salts of 20 mg bid. Although the maximum FDA approved dose of amphetamine salts for treatment of narcolepsy is higher at 60 mg/day, adverse events are dose-related and higher doses do not necessarily convey additional benefit (33); in clinical practice, finding the lowest effective amphetamine dosage and maintaining this dosage as long as it is effective is a practical component of the management of both the risk of side effects and the problem of tolerance that occurs in 1/3rd patient with narcolepsy treated with amphetamines (34).

Participants will be randomized to receive a 12-week treatment course with either modafinil or amphetamine-dextroamphetamine. Both are US FDA approved for the treatment of narcolepsy, although are considered off-label use for idiopathic hypersomnia. The main risks of participation are from the study medications (which are the standard of care). Common adverse events include: headache, nervousness, anxiety, insomnia, anorexia, xerostomia, palpitations/tachycardia, emotional lability, agitation. Less commonly reported adverse events included: nausea/vomiting, rhinitis, diarrhea, dizziness, dyspepsia, pharyngitis, HTN, chest pain, vasodilation, elevated ALT or AST, paresthesia, depression, constipation, abdominal pain, weight loss, motor/phonic tic exacerbation, dyspnea, diaphoresis, dysmenorrhea, impotence, visual disturbance, restlessness, tooth disorder, photosensitivity. Rare but serious AEs include:

- dependency, abuse
- psychosis
- mania
- aggressive behavior
- sudden death
- myocardial infarction
- stroke
- HTN
- cardiomyopathy (long-term use)
- seizures
- hypersensitive reaction, multi organ
- anaphylaxis
- Stevens-Johnson syndrome

- toxic epidermal necrolysis
- priapism
- peripheral vasculopathy
- Raynaud phenomenon
- Growth suppression (long-term use, peds pts)
- rhabdomyolysis
- withdrawal signs and symptoms if abrupt discontinuation (prolonged with high dose use)
- angioedema
- drug reaction with eosinophilia and systematic signs and symptoms
- hallucinations
- suicidal ideation

However, the medications being used in this study are currently standard of care for narcolepsy, being tested in this study for equivalency. Therefore, although there are risks to participation in this research, they are of the same magnitude of the risks patients take when seeking treatment for these disorders outside of this research. The benefit to be gained is a clearer understanding of the relative risks and benefits of these medications and the clinical features that can help predict response to treatment.

Community Participation

Dr. Trotti consulted with leadership from the Hypersomnia Foundation and Narcolepsy Network in the initial submission of this work and will present results from the study at at least one meeting of one or both of these patient organizations following its completion.

Participant Selection

This study will recruit up to 55 participants, with a sample size target of 44 participants who complete participation in the 12 week medication trial. Participants will be newly diagnosed, medication-naïve individuals, or formerly diagnosed, free of wake-promoting medication or willing to discontinue current wake-promoting medication with diagnoses of: narcolepsy type 2 or idiopathic hypersomnia.

Inclusion criteria will be: 1) narcolepsy type 2 or idiopathic hypersomnia; 2) age 18-65; 3) informed consent.

Exclusion criteria will be: 1) contraindication to modafinil or amphetamine salts (history of left ventricular hypertrophy, mitral valve prolapse, other cardiac structural abnormalities, severe cardiovascular disease, unstable angina, myocardial infarction, cardiomyopathy, severe arrhythmias, uncontrolled hypertension, severe hepatic impairment, substance abuse history, psychosis, glaucoma, Tourette's syndrome, and epilepsy); 2) obstructive sleep apnea (AHI > 15); 3) severe periodic limb movements of sleep with arousals (PLM arousal index > 30); 4) allergy to either of the study drugs; and 4) pregnancy or breastfeeding.

Participants who withdraw from study medication will be invited to complete remaining questionnaires/study visits.

Visit Schedule

Visit 1: Enrollment: After reviewing information about the study and confirming participation, subjects will answer questions about their sleep disorder and the symptoms experienced. This visit is expected to last about one hour. If participants are suspected of having a diagnosis of narcolepsy type 2 or idiopathic hypersomnia and have never had an overnight polysomnogram (PSG) and next-day MSLT, they will be scheduled for an

additional study visit to complete a PSG and MSLT before visit 3. If participants already have a confirmed diagnosis of narcolepsy type 2 or idiopathic hypersomnia and are taking certain stimulant medications they will be asked to wean off of this medication before and during the study. After weaning off of medicines, the participant will be given a four-week supply of one of the two study medications. The medication will be provided will be assigned randomly, the participant and the doctor will not be told which of the two study medications are given.

Visit 2: Participants will only participate in this visit if they haven't had a sleep study prior to enrollment. Sleep testing: During this visit, participants will come to the Sleep Center for an overnight sleep study, during which they will be monitored with multiple wires on their body to measure sleep, breathing, and activity at night. The next day, they will remain at the Sleep Center until approximately 5 pm, taking naps five times during the day.

After these results are received and if the results are positive for a diagnosis of narcolepsy type 2 or idiopathic hypersomnia, participants will be given a four-week supply of one of the two study medications and will proceed with the remaining study visits. If the results are negative for narcolepsy type 2 or idiopathic hypersomnia, participants will be withdrawn from the study.

Visit 3 (four weeks medication dispensed at either Visit 1 or Visit 2): Complete questionnaires and pick up medication for the next four weeks (the same medication they have been taking already) at the Emory Sleep Center.

Visit 4 (four weeks after Visit 3): Complete questionnaires and pick up medication for the next four weeks (the same medication they have been taking already) at the Emory Sleep Center.

Visit 5 (four weeks after Visit 4): Meet with a study team member to discuss experience with the medication. Complete questionnaires and return any unused study drug.

APPENDIX 1. SCHEDULE OF STUDY VISITS

	VISIT 1	VISIT 2 – SLEEP STUDY	VISIT 3	VISIT 4	VISIT 5
Informed Consent	X				
Medical History	X				
Study Inclusion/Exclusion	X				
Concomitant Medication Review	X	X	X	X	X
Wean off current wake-promoting medicines	X				
Adverse Experiences		X	X	X	X
Participant Payment	X				X
PSG/MSLT sleep study		X			
Sleepy Packet	X				
Sleep Inertia Questionnaire	X	X	X	X	X
Epworth Severity Scale	X	X	X	X	X
CGI- Baseline Questionnaire	X	X	X	X	X
CGI- Sleep Inertia Questionnaire	X	X	X	X	X
CGI- Sleepiness Questionnaire	X	X	X	X	X
CGI- Cognitive Dysfunction Questionnaire	X	X	X	X	X
Treatment Questionnaire	X	-	X	X	X
Treatment Comparison Questionnaire	X	-	X	X	X
Study Drug Titration Reviewed	X				
Randomization	X	OR X			
Dispensing or Administration of Study Drug	X	OR X	X	X	
Counting of Returned Study Drug			X	X	X

Informed Consent Process

Consent will be obtained in-person from a study PI, co-I, or coordinator. Comprehension will be ensured by allowing ample time for questions and discussion and verbally reviewing the information with the subject in addition to reviewing the written consent form. The discussion will take place at the Emory Sleep Center.

Compensation

Participants will be compensated $25 for visit 1 (enrollment) and $25.00 for the week 12 study visit (visit 5), for a total of $50.

Statistical Analysis

Sample size will be 22 in each group. This sample size is sufficient to demonstrate a reduction in ESS of 4 points with amphetamine salts, assuming a standard deviation of change from baseline of 6.2 (35). This is

a conservative, but clinically significant, change in Epworth, compared to the observed change from baseline of 5.3 points in clinical trials of modafinil [weighted average from (15, 35, 36)]. This sample size provides 82.8% power to find a moderately large effect size for amphetamine salts. For non-inferiority, we will use a responder definition of those achieving a 25% reduction in ESS, a data-driven minimal clinically significant change in patients with narcolepsy (29). Assuming 80% of participants meet this threshold, 22 participants per group will provide 80% power to a non-inferiority limit of 30% (37, 38).

Intention-to-treat analyses will be performed, using last observation carried forward in the event of participant drop-out. The change in ESS at week 12 from baseline will be compared between the two treatment groups via t-test (compared for unequal variances if necessary) and will be evaluated on a hypothesis of non-inferiority. Similar analyses will be performed on secondary outcomes, considering the proportion of responders in each treatment arm who rate themselves "much improved" or "very much improved". Categorical outcomes, including these PGI-C proportions and adverse events, will be compared using Chi-square or Fisher exact test. Exploratory analyses will evaluate response at week 4 and week 8 between the two medications groups, to determine if there is a difference in time to symptom control.

Considering each medication separately, predictors of response will be assessed using logistic regression. The main predictor of interest will be hypersomnia diagnosis, i.e., narcolepsy type 2 or idiopathic hypersomnia. Other predictors, to be considered in separate, exploratory regression models, include: MSLT mean sleep latency, MSLT number of SOREMs, sex/gender, baseline ESS, age, and comorbidities. Significant predictors in univariate models will be combined in a multivariate model. Although the investigative team has extensive clinical trial and statistical experience, additional statistical consultation will be provided as needed through Emory's CTSA consultation program.

Data Safety Monitoring and Reporting

Participants will be screened for medication contraindications (detailed above) prior to participation, to minimize risk of serious drug adverse reactions. During the study, participants will be encouraged to report any adverse events and will be provided with 24-hour contact information with which to do so. Participants will be systematically assessed for expected and idiosyncratic adverse reactions every four weeks during participation. Dr. Trotti will review routine adverse event logs at least once a week. For adverse events reported between routine assessments, Dr. Trotti or Dr. Rye will review immediately and provide guidance to the participant on if and how to adjust study mediation (e.g., discontinue in the case of a severe adverse reaction) and any additional care that should be sought (e.g., urgent or emergency care). Dr. Trotti will convey any reportable events to the Emory IRB using the standard reporting timeline, based on event severity. Dr. Trotti will also oversee protocol compliance and data accuracy. She will perform reviews of case report forms every four weeks, to ensure consistency with protocol and data entry accuracy. Dr. Trotti and the study coordinator will work together to complete the Emory IRB's "EU Self-Monitoring Tool" (available at http://www.ctac.emory.edu/clinical_trial_guidebook/data_and_safety_monitoring_plans.html) every six months.

Confidentiality

Data collection will be performed using the REDCap research tool, including online assessments. REDcap provides secure, web-based applications that offer easy data manipulation with audit trails for reporting, monitoring, and querying patient records and an export mechanism to statistical programs (e.g., SAS). REDcap servers are housed in a local data center at Emory University and all web-based information transmission is encrypted. REDcap was developed specifically to be compliant with HIPAA-security guidelines. Paper records (e.g., consent forms) will be stored in a locked office. When subsets of data are

housed on individual computers for data analysis and manuscript preparation, the minimum amount of identifiers will be included and computers will be encrypted.

Citations

1. Morgenthaler TI, Kapur VK, Brown T, Swick TJ, Alessi C, Aurora RN, et al. Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin. Sleep. 2007;30(12):1705-11.
2. Khan Z, Trotti LM. Central Disorders of Hypersomnolence: Focus on the Narcolepsies and Idiopathic Hypersomnia. Chest. 2015;148(1):262-73.
3. Black J, Swick T, Bogan R, Lai C, Carter LP. Impact of sodium oxybate, modafinil, and combination treatment on excessive daytime sleepiness in patients who have narcolepsy with or without cataplexy. Sleep Med. 2016;24:57-62.
4. Sonka K, Susta M, M. B. Narcolepsy with and without cataplexy, idiopathc hypersomnia with and without long sleep time: a cluster analysis. Sleep Medicine. 2015;epub ahead of print.
5. Trotti LM, Staab BA, Rye DB. Test-retest reliability of the multiple sleep latency test in narcolepsy without cataplexy and idiopathic hypersomnia. J Clin Sleep Med. 2013;9(8):789-95.
6. Ruoff C, Pizza F, Trotti LM, Sonka K, Vandi S, Cheung J, et al. The MSLT is Repeatable in Narcolepsy Type 1 But Not Narcolepsy Type 2: A Retrospective Patient Study. J Clin Sleep Med. 2017.
7. Lopez R, Doukkali A, Barateau L, Evangelista E, Chenini S, Jaussent I, et al. Test-Retest Reliability of the Multiple Sleep Latency Test in Central Disorders of Hypersomnolence. Sleep. 2017;40(12).
8. Rye DB, Bliwise DL, Parker K, Trotti LM, Saini P, Fairley J, et al. Modulation of Vigilance in the Primary Hypersomnias by Endogenous Enhancement of GABAA Receptors. Sci Transl Med. 2012;4(161):161ra51.
9. Mayer G, Benes H, Young P, Bitterlich M, Rodenbeck A. Modafinil in the treatment of idiopathic hypersomnia without long sleep time-a randomized, double-blind, placebo-controlled study. J Sleep Res. 2015;24(1):74-81.
10. Philip P, Chaufton C, Taillard J, Capelli A, Coste O, Leger D, et al. Modafinil improves real driving performance in patients with hypersomnia: a randomized double-blind placebo-controlled crossover clinical trial. Sleep. 2014;37(3):483-7.
11. Trotti LM, Saini P, Bliwise DL, Freeman AA, Jenkins A, Rye DB. Clarithromycin in gamma-aminobutyric acid-Related hypersomnolence: A randomized, crossover trial. Ann Neurol. 2015;78(3):454-65.
12. Trotti LM. Idiopathic Hypersomnia. Sleep Med Clin. 2017;12(3):331-44.
13. de Boer IH, Kovesdy CP, Navaneethan SD, Peralta CA, Tuot DS, Vazquez MA, et al. Pragmatic Clinical Trials in CKD: Opportunities and Challenges. J Am Soc Nephrol. 2016;27(10):2948-54.
14. Borgerson K. Are explanatory trials ethical? Shifting the burden of justification in clinical trial design. Theor Med Bioeth. 2013;34(4):293-308.
15. Randomized trial of modafinil for the treatment of pathological somnolence in narcolepsy. US Modafinil in Narcolepsy Multicenter Study Group. Ann Neurol. 1998;43(1):88-97.
16. Ohayon M. Narcolepsy is complicated by high medical and psychiatric comorbidities: a comparison with the general population. Sleep Med. 2013;14(6):488-92.
17. Pizza F, Jaussent I, Lopez R, Pesenti C, Plazzi G, Drouot X, et al. Car Crashes and Central Disorders of Hypersomnolence: A French Study. PLoS One. 2015;10(6):e0129386.
18. Ozaki A, Inoue Y, Nakajima T, Hayashida K, Honda M, Komada Y, et al. Health-related quality of life among drug-naive patients with narcolepsy with cataplexy, narcolepsy without cataplexy, and idiopathic hypersomnia without long sleep time. J Clin Sleep Med. 2008;4(6):572-8.
19. Loudon K, Treweek S, Sullivan F, Donnan P, Thorpe KE, Zwarenstein M. The PRECIS-2 tool: designing trials that are fit for purpose. BMJ. 2015;350:h2147.
20. Ford I, Norrie J. Pragmatic Trials. N Engl J Med. 2016;375(5):454-63.

21. Thorpy M, Black J, Gow M, Ohayon M, Pasta D, Patterson M, et al. Demographics and diagnosis experience of people with narcolepsy: results from the first eight months of the Nexus narcolepsy registry. 23rd Congress of the European Sleep Research Society; Bologna, Italy2016. p. P314.
22. The Voice of the Patient: Narcolepsy. 2014.
23. Urbaniak GC, Plous S. Research Randomizer (Version 4.0) [Computer software].
24. International classification of sleep disorders. 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014.
25. Modafinil FDA approved labeling 2007 [Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/020717s020s013s018lbl.pdf.
26. Guy W. ECDEU assessment manual for psychopharmacology (DHEW Publication No. ADM 76-338). Washington, D.C.: U.S. Governmenta Printing Office; 1976 1976.
27. Rosenberg RP, Bogan RK, Tiller JM, Yang R, Youakim JM, Earl CQ, et al. A phase 3, double-blind, randomized, placebo-controlled study of armodafinil for excessive sleepiness associated with jet lag disorder. Mayo Clin Proc. 2010;85(7):630-8.
28. Liu GJ, Wu L, Lin Wang S, Xu LL, Ying Chang L, Fu Wang Y. Efficacy of Pramipexole for the Treatment of Primary Restless Leg Syndrome: A Systematic Review and Meta-analysis of Randomized Clinical Trials. Clinical therapeutics. 2016;38(1):162-79 e6.
29. Scrima L, Emsellem HA, Becker PM, Ruoff C, Lankford A, Bream G, et al. Identifying Clinically Important Difference on the Epworth Sleepiness Scale: Results from a Narcolepsy Clinical Trial of JZP-110. Sleep Medicine. 2017;epub ahead of print.
30. Maund E, Guski LS, Gotzsche PC. Considering benefits and harms of duloxetine for treatment of stress urinary incontinence: a meta-analysis of clinical study reports. CMAJ. 2017;189(5):E194-E203.
31. Wiffen PJ, Derry S, Bell RF, Rice AS, Tolle TR, Phillips T, et al. Gabapentin for chronic neuropathic pain in adults. Cochrane Database Syst Rev. 2017;6:CD007938.
32. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377-81.
33. Guilleminault C. Amphetamines and narcolepsy: use of the Stanford database. Sleep. 1993;16(3):199-201.
34. Parkes JD, Dahlitz M. Amphetamine prescription. Sleep. 1993;16(3):201-3.
35. Dauvilliers Y, Bassetti C, Lammers GJ, Arnulf I, Mayer G, Rodenbeck A, et al. Pitolisant versus placebo or modafinil in patients with narcolepsy: a double-blind, randomised trial. The Lancet Neurology. 2013;12(11):1068-75.
36. Randomized trial of modafinil as a treatment for the excessive daytime somnolence of narcolepsy: US Modafinil in Narcolepsy Multicenter Study Group. Neurology. 2000;54(5):1166-75.
37. Power calculator for binary outcome non-inferiority trial.: Sealed Envelope Ltd; 2012 [Available from: https://www.sealedenvelope.com/power/binary-noninferior/
38. Blackwelder WC. "Proving the null hypothesis" in clinical trials. Control Clin Trials. 1982;3(4):345-53.