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Official Title: Effects of Clobazam on sleep and daytime function in patients with epilepsy

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Effects of Clobazam on sleep and daytime function in patients with epilepsy

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Background/Rationale

Many studies indicate that patients with epilepsy frequently have fragmented sleep, as well as excessive daytime somnolence (Holoway et al 2011, Meyer et al 2011, Manni et al 2010, Krishnan et al 2012). Causes include primary sleep fragmenting disorders (sleep apnea, movement disorders), nocturnal seizures that contribute to sleep fragmentation, and other abnormalities. Sleep complaints are widely reported among patients with various epilepsy syndromes (Lopez et al 2013). Insomnia is a particularly frequent complaint, seen in 40-51% of epilepsy patients (Vendrame 2013, Lopez et al 2013). Furthermore, epilepsy patients who have insomnia also have a higher frequency of depressive symptoms, as well as poorer quality of life (Vendrame 2013). Insufficient or poor quality sleep increases the risk of a variety of disorders, leading to abnormalities of endocrine (Buxton, Pavlova et al 2010) and immune function (Lange et al 2011). Insomnia probably has the some of the same consequences as insufficient sleep from other causes. For example, in a recent study in our group (Buxton, Pavlova et al, 2011), we found that sleep fragmentation, as measured by wake after sleep onset (WASO), predicts diabetes risk in insomnia patients.

Antiepileptic treatment may affect sleep (Bazil et al 2008). Effects vary by type of medication and comorbidities. Generally, with improvement of seizure control, the regularity of the sleep cycle improves and sleep becomes more consolidated. However, some antiepileptic medications have been associated with insomnia (Bazil et al 2008). Although sleep has been studied in relation to some antiepileptic medications (Bazil et al 2008, 2012, Zou et al 2012), there are no currently available published systematic reports on the effect of Clobazam on sleep. We propose to study the effect of Clobazam on sleep and daytime alertness.

Hypothesis

Primary hypothesis: **Patients with epilepsy have longer, more consolidated sleep after treatment with clobazam is started.** This hypothesis will be tested in a prospective study, using within subject comparisons, where by sleep measures before treatment are compared to those after treatment.

Secondary hypothesis: **Sleep improvement will lead to a lesser subjective daytime sleepiness and improved quality of life**. This hypothesis will be tested by comparing subjective measures of sleepiness and quality of life, measured by standard instruments (Epworth sleepiness scale score, ESS, Karolinska sleepiness scale KSS, and quality of life in epilepsy, QOLIE) relative to total sleep time and wake after sleep onset.

Methods

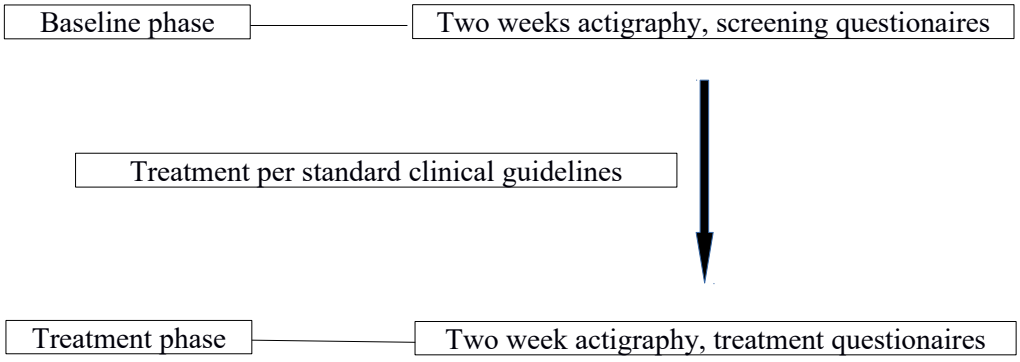
Research methods

Subject Population. We propose to prospectively include patients from our epilepsy clinics and inpatient who are starting treatment with Clobazam. All patients who are considered for treatment with clobazam will be approached for participation. We will exclude patients with known untreated moderate or severe sleep apnea, or with major circadian rhythm disorders, as these may confound our analyses.

Pre-treatment sleep symptoms will be evaluated using validated instruments including, Pittsburgh Sleep Quality Inventory (PSQI), depression symptoms - Beck Depression Inventory (BDI), and severity of insomnia - Insomnia Severity Index (ISI). We will also record the subject's Body Mass Index (BMI). Subjects will then be asked to complete a one week sleep and seizure log, simultaneous wrist actigraphy monitoring, and daytime sleepiness Epworth Sleepiness Scale (ESS), and daily visual analog scale (Karolinska sleepiness scale, KSS), as well as quality of life (QOLIE), prior to starting treatment – **baseline phase.**

Treatment with Clobazam, as well as clinical follow-up will be performed as per standard of care. After the effective dose is reached and the treating physician confirms that the medication is well tolerated, subjects will repeat the same log, actigraphy and questionnaire measurements over a one week period– **treatment phase.** We will then compare total sleep time (TST), wake after sleep onset (WASO), subjective sleep (from sleep log), and sleepiness prior to treatment to the same measures after treatment with Clobazam (Fig. 1).

Fig 1: Study schema



Statistical analyses

Primary analyses will include within subject comparison of total sleep time (TST) and wake after sleep onset (WASO), as measured by actigraphy, before versus after treatment. Preliminary analysis indicate that 20 subjects will give us 98% power to demonstrate efficacy of Clobazam to improve the above sleep measures with effect size of 3, assuming the standard deviation is 3 with a two-sided one group t-test at alpha=0.05 level.

Our secondary hypothesis is that in epilepsy patients, quality of life and subjective sleepiness improve with improved sleep. To test this hypothesis, we will correlate the rate of sleepiness with the sleep variable. The dependant variables will be ESS, KSS (subjective

sleepiness measures), and the independent variables will be WASO and TST. Bonferoni correction will be performed to adjust for multiple comparisons.

The Neuroscience Institute at the Brigham and Women's Hospital provides statistical analyses at a reduced rate to neurologists within our department.

Timeline

Within three months of the start of the funding period, we plan to have recruited study staff, purchased equipment and obtained Human Subject's Committee approval. At this time, recruitment of eligible patients will start. Testing of each subject requires approximately two month of monitoring: one week of actigraphy sensor monitoring before treatment (baseline phase), subject's titration period as dictated by their treating physician, and another 1 week after the prescribed dose has been reached - treatment phase. These two testing phases will be approximately a month apart to ensure that the enrolled patients have reached effective dose and have not reported serious side effects. We will aim to have two subjects enrolled and actigraphy data collection done simultaneously. Thus, with efficient recruitment and minimal attrition rate, 20 participants can complete the study within 18 months of the start of the funding period. Proposed timeline would be as follows:

Study start: September 2014

First subject enrolled: December 2014

Completion of enrollment: May 2016

Final study report: June 2016

Challenges and plans to address them

1) **Adverse events to Clobazam**. It is possible that the patients enrolled in the study experience adverse effects of Clobazam or for other reasons need to change the medication. In these cases, we may need to exclude these participants. In this case, the overall number of enrolled participants will need to be adjusted to allow adequate analyses.
2) **Interactions with other medications and medication changes.** The patients who are eligible for the study may be on other medications. Some may need medication change during the data acquisition. In these cases, treatment will follow standard clinical care guidelines (to avoid any adverse medical outcomes). Any medication changes will be recorded for post-hoc analyses.
3) **Recruitment.** We aim to approach all eligible patients from our clinic and inpatient for participation. However, it is possible that too few will volunteer to participate. In this case, advertisement will be broadened and neurologists and epileptologists from around the Greater Boston approached for recruitment of eligible patients. As more than 1000 patients are seen by epileptologists within our division, and we have successfully recruited patients for other studies on sleep and epilepsy (Pavlova et al, 2013), we anticipate little difficulties.

Alternate analyses if challenges cannot be addressed

In case our study is under-powered to detect a statistically significant difference in the primary outcome measures, more detailed analyses will be performed on the secondary outcome measures – the subjective improvement of sleepiness or of depressive symptoms, as well as overall quality of life.

Publication plans

Meetings/Congresses

We will aim to submit an abstract to the major annual academy meetings – American Epilepsy Society and American Academy of Neurology. A more detailed sleep analysis may additionally be presented to the American academy of sleep medicine.

Scientific/Medical Journals

We will prepare a manuscript from the acquired results and submit for publication to the journal *Epilepsia* (a major journal for research on epilepsy). An alternative journal may be *Epilepsy Research* or *Epilepsy and Behavior*.

Study impact

The **strengths** of our study include the importance and the physiological plausibility of the hypotheses to be tested, the compelling background studies that have lead to the hypotheses, the prospective study design and within subject comparisons, which will provide a strong and efficient test of the hypotheses. The issue of quality of life, resulting from healthy sleep is of crucial clinical importance when treating patients with epilepsy. Therefore, we anticipate that the findings of our study will have a **major impact** the field of epilepsy.

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