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# Characterizing sleep disorders of adults with tuberous sclerosis complex: A questionnaire-based study and review

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## Abstract

An adult cohort with tuberous sclerosis complex was investigated for the prevalence of sleep disturbances and the relationship with seizure variables, medication, and psychological functioning. Information on 35 adults was gathered using four questionnaires: Epworth Sleepiness Scale (ESS), Sleep and Epilepsy Questionnaire (SEQ), Sleep Diagnosis List (SDL), and Adult Self-Report Scale (ASR). In addition, clinical, genetic and electrophysiological data were collected. Of 35 respondents, 25 had a history of epilepsy. A subjective sleep disorder was found in 31% of the cohort. Insomnia scores showed a significant positive correlation with obstructive sleep apnea syndrome and restless legs syndrome scores. Significant correlations were found between daytime sleepiness and scores on depression, antisocial behavior, and use of mental health medication. A subgroup using antiepileptic medication showed high correlations between daytime sleepiness, attention deficits, and anxiety scores.

### Keywords

Epilepsy; Sleep; Tuberous sclerosis complex; Behavior

## 1. Introduction

Tuberous sclerosis complex (TSC) is a genetic disorder affecting 1 in 6000 live births, and is caused by mutations in the tumor suppressor gene TSC1 or TSC2. These genes encode a protein complex that inhibits mTOR kinase signaling by inactivating the Rheb GTPase [1,2], a regulator of cell growth. In TSC, mutations in these genes lead to benign tumors affecting multiple organs, including the skin, kidneys, and heart. In more than 90% of patients with TSC, the brain is involved [3], often resulting in significant neuropsychiatric morbidity including seizures, mental retardation, autism, attention deficit/hyperactivity disorder (ADHD), depression, and anxiety [4,5].

Seizure disorders occur in 70–90% of patients with TSC, most often presenting in the first year of life [6,7]. Most seizures are of the “partial onset” subtype, but generalized tonic–clonic, myoclonic, and infantile spasms are also frequent. In TSC, reported EEG findings during sleep are increased epileptiform activity during non-rapid eye movement (REM) sleep and, contrastingly, less epileptiform activity during REM sleep [8], as has been described in epilepsies with other causes [9]. Similar to frontal lobe seizures resulting from



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other etiologies, in TSC, nocturnal seizures are often associated with complex motor phenomena (tonic posturing, clonic movement of one limb).

Research on sleep in TSC has been very limited, and has involved children only. Hence, little information is available on the sleep architecture of patients with TSC, how sleep states are altered by the underlying neurological condition and epilepsy, and how sleep disorders affect the individual's wake life [10–12]. The sleep disturbances in TSC are likely more complex than simply being secondary to epilepsy. In addition to the obvious neuroanatomical abnormalities, there are more possible contributing factors including mental retardation and psychiatric comorbidities such as autism and hyperactivity, which, in turn, could affect the development of circadian rhythms and bedtime routines [13]. In addition, anticonvulsant medications, often prescribed in patients with TSC, can also affect sleep [9].

In children with TSC, severe sleep problems are frequent after the onset of epileptic spasms and are often due to sleep-related epileptic events. Sleep disorders, including night waking, early waking, seizure-related sleep problems, and excessive daytime sleepiness, have previously been recognized as a frequent cause and result of stress in the more severely affected patients with TSC and their families [11]. In a postal survey of 300 children with TSC, a high prevalence of sleep disorders was reported, with problems with settling (60%) and night waking (62%) being the most common [12,14]. A follow-up questionnaire-based study looking at sleep disorders and the relationship with epilepsy in TSC found that the degree of sleep disruption was significantly higher in the group with seizures than in the siblings and matched controls and, also, was associated with a high level of behavioral disturbance [11]. There is only one controlled polysomnographic study, comparing 10 children with TSC and partial epilepsy with healthy controls [10]. Sleep architecture abnormalities, including shorter total sleep time, fragmentation by frequent awakenings, and a decrease in REM sleep, were found in nine cases of TSC [10]. Although the sample was small, there was a tendency for children with TSC and seizures to show a more disturbed sleep architecture. Although sleep disturbances were seen with and without the occurrence of nocturnal seizures and/or the presence of EEG abnormalities, sleep disorders seemed to be due mainly to sleep-related epileptic events and improved after a seizure-free period. Shorter awakenings not related to epileptic seizures were identified that were not detected by the caregivers, suggesting that the prevalence of sleep disorders in patients with TSC is underestimated [10]. To our knowledge, there have been no studies evaluating sleep disorders in adults with TSC.

The present study explores the relationship between TSC and sleep disorders in an attempt to describe the prevalence and severity of sleeping problems in this patient group and the relationship with seizure features, medication, and psychological functioning.

## 2. Methods

The study is a questionnaire-based exploration of sleep in adult patients with TSC. To be included, patients had to be adults (≥18 years of age), have a clinical diagnosis of definite TSC, and be followed at the TSC clinic at Massachusetts General Hospital in Boston; the presence of epilepsy was not a criterion for enrollment. No control patients were recruited. There was no selection on the basis of cognitive abilities or psychiatric comorbidity. Information on epilepsy intractability was obtained from our clinical database, using the definition: (1) having used three or more medications for the treatment of epilepsy, or (2) having undergone epilepsy surgery, or (3) having one or more seizures per day despite therapy.

### 2.1. Questionnaires

Participants were sent the following questionnaires, to be completed by the patient and with the assistance of a caregiver as needed: Sleep Diagnosis List (SDL) [15], which is derived from the Sleep Diagnosis Questionnaire [16]; Epworth Sleepiness Scale (ESS) [17]; Adult Self Report Scale [18], which is derived from the Child Behavior Checklist (CBCL) [19]; and Sleep and Epilepsy Questionnaire (SEQ).

The SEQ is an eight-page questionnaire with 24 questions based on the patient intake of the Department of Sleep Medicine at our hospital and used to assess aspects of epilepsy severity and sleep. It includes questions on seizure presence, type, frequency, and severity, including treatment of these seizures in the past and present. It also contains questions on the subjective presence of sleeping problems and relationship with AEDs and psychiatric drugs, as well as experiences with treatment of sleep disorders. The ESS poses eight questions regarding the chance of a person dozing off during day-today activities, answered on a 4-point scale from 0=never doze to 3=high chance of dozing. A total score ≥10 is generally interpreted as daytime sleepiness. The SDL has been validated in epilepsy populations and consists of 30 randomly distributed questions covering five common sleep disturbances (e.g., insomnia, sleep apnea, narcolepsy, periodic leg movements, and parasomnia) in the past 6 months, rated on a 5-point scale from 1=never to 5=very often or always. A total mean score ≥3 in a category indicates the presence of a sleep disturbance. The ASR has been validated in adults with chronic conditions, has been identified as highly consistent with DSM-IV criteria, and is used to assess people's perceptions of their own psychological functioning over the last 6 months. It consists of about 140 questions, including demographic information and rating behaviors and functioning, thus gathering information on psychological syndromes (Anxious/Depressed, Withdrawn, Somatic Complaints, Thought Problems, Attention Problems, Aggressive Behavior, Rule-Breaking Behavior, Intrusive) and DSM-oriented scales (Depressive Problems, Anxiety Problems, Somatic Problems, Avoidant Personality Problems, Attention Deficit/Hyperactivity Problems, Antisocial Personality Problems).

### 2.2. Tuberous sclerosis complex mutational analysis

Genetic testing was performed at Athena Diagnostics (Worcester, MA, USA) or the MGH Neurogenetic Diagnostic Laboratory (Boston, MA, USA). Patients in whom genetic testing was negative are classified herein as NMI (no mutation identified). Patients with disease-associated mutations of the TSC1 and TSC2 genes were recorded. Mutations were not further classified.

### 2.3. Electroencephalography

Electroencephalography records were investigated for patients who had undergone surface EEG monitoring with a standard international 10–20 system of electrode placement, consisting of at least 25 minutes of recording. Only EEGs performed in the last 5 years were included in our analysis. When more than one EEG record was available, the EEG closest in date to completion of the questionnaires was used. Only information on the presence of regional epileptiform features consisting of spikes, sharp waves, and spikes and waves was gathered. Distinct localizations were not distinguished.

### 2.4. Statistical analysis

Statistical analyses were performed using SPSS Version 11.5 (SPSS, Inc., Chicago, IL). Complete (sections of) questionnaires were used for analysis. For analysis of the SEQ and ARS, 90% completion of a section was considered sufficient for analysis. ESS and SDL scores were excluded if one item was missing.

Initially, a Pearson correlation between the outcomes of the ESS and SDL subscales Insomnia and Restless Legs Syndrome was performed to investigate their relationship. A multivariate linear regression established the influence of gender, age, seizure history, and TSC mutation on the outcome of the ESS and SDL subscales.

To explore the influence of epilepsy on sleep in patients with TSC, we selected the group with a positive history for seizures and investigated the effect of a history of intractable epilepsy, seizure frequency, number of AEDs, and presence of interictal spikes on the ESS and SDL outcomes.

For secondary analysis, continuous variables were analyzed with a two-sample $T$ test and limited Pearson correlations were performed. All reported $P$ values used two-tailed tests of significance with $\alpha$ set at 0.05. Data points unknown because of unavailable answers or histories were excluded from all statistical tests. Because of our small sample and the abundance of variables, we had to restrict our statistical analysis.

### 2.5. Ethics

This study was approved by the institutional review board of our hospital.

## 3. Results

### 3.1. Characteristics of participants

Of the 146 questionnaires mailed to adult patients with TSC, 36 were returned, resulting in a relatively low response rate of 25%. The scores of two SEQs and one ASR were not included because of insufficient information. Of note is that, in the remainder, questions on education and mental health were most often not answered. The ESS and SDL were completed in full by all participants.

Demographic characteristics of patients included in the analyses are summarized in Table 1.

Of the 25 patients with a seizure history, 13 (52%) had a history of intractable epilepsy, and 7 (28%) had a history of status epilepticus. Seizure frequency ranged from daily to less than one a month. Of these 25 patients, about half (49%) had had their last seizure more than 6 months ago, and 4 (11%) had had their last seizure within the last month. None of the respondents experienced multiple seizures per day. Six patients (17%) were on AED monotherapy, and 14 (40%) were on AED polytherapy. The most common AEDs currently used were: carbamazepine (49%), lamotrigine (40%), valproate (34%), phenytoin (34%), lorazepam (31%), phenobarbital (31%), levetiracetam (26%), gabapentin (26%), topiramate (23%), oxcarbazepine (20%), benzodiazepines (20%), zonisamide (14%), and clonazepam (14%).

With respect to mental health, 17 of 31 (55%) patients indicated on the SEQ that they had visited a mental health professional over the preceding year, and 15 (50%) were taking medication for mental health concerns, with 9 on more than one psychiatric drug.

### 3.2. Sleep parameters

On the SDL, Insomnia subscale scores were significantly positively correlated with Obstructive Sleep Apnea Syndrome (OSAS) scores (corr. 0.512, $P$<002) and Restless Legs Syndrome (RLS) scores (corr. 0.372, $P < 0.028$). The raw Narcolepsy score was positively correlated with the RLS score (corr. 0.480, $P$<0.004). There was only one responder with a Narcolepsy score ≥3. This patient also had RLS and Insomnia scores above the threshold. As this person was on AED polytherapy and mental health medication and, on the SEQ, reported to “be a zombie” because of sleep medication, we do not suspect this person to be a

true narcoleptic. RLS and OSAS scores also correlated significantly with each other (corr. 0.411, $P<0.014$). Some correlations between the sleep subscales are outlined in Table 2.

Multivariate linear regression analysis did not show a significant effect of age, gender, TSC mutation, or positive seizure history on the ESS score. On the SDL subscales, female gender did have a significant effect on Insomnia ($P<0.05$). SDL Parasomnia, OSAS, and Narcolepsy subscale scores were not included in the regression analysis because few patients scored high for these disorders.

Regression analysis within the group with a positive seizure history did not show a significant association of seizure frequency, number of AEDs, and presence of interictal spikes with RLS or Daytime Sleepiness scores.

### 3.3. Prevalence of subjective sleep disturbance

According to the SDL, there were subjective indications of a sleep disturbance in the preceding 6 months for 11 patients (31%), with 8 patients (23%) scoring above the threshold for Insomnia, 5 (14%) for RLS, 2 (6%) for OSAS, and 1 (3%) for Narcolepsy. No patients had significant parasomnias. All of the patients with insomnia had a positive seizure history. Of the patients with insomnia, 2 were on one AED, 2 were on two AEDs, and 1 was on five AEDs; 1 patient was not on any AEDs. Of the 11 patients scoring ≥3 on the Insomnia subscale, 8 patients had relatively frequent seizures, with 1 patient having more than daily seizures, 2 patients daily seizures, and 5 patients weekly seizures; no patients had less than weekly seizures. Among these patients, 3 had ever suffered a status epilepticus, of the total of 7 patients who reported having status epilepticus. Of note is that the two patients with the highest insomnia scores were women with epilepsy, one using three and the other five AEDs and aged respectively 24 and 23 years.

On the ESS, 15 patients (43%) scored ≥10, which reflects daytime sleepiness indicating a sleep disorder, and 1 patient (3%) scored 18, suggesting a severe sleep disorder. When the EES scores above and below 10 were compared, no significant differences were found in the number of current AEDs, the presence of interictal spikes on the EEG, or SDL subscale scores. Three patients had a high score on the ESS as well as the SDL. Looking at patients with a positive history of epilepsy, half of the patients with a history of intractable epilepsy scored over the ESS threshold, compared with 25% of the patients without this history. These numbers were too low for statistical comparison.

### 3.4. Association with mental health

Fifteen patients (43%) were currently on psychiatric medication, with 9 patients using one and 6 patients using more than one psychiatric drug. Psychiatric medications noted were selective serotonin reuptake inhibitors (8), tricyclic antidepressants or other antidepressants (6), benzodiazepines (4), lamotrigine (4), valproic acid (2), risperidone (1), and olanzapine (1). Of the 17 respondents who answered “yes” to the SEQ question asking if they had visited a mental health professional this year, 10 (59%) indicated that sleeping problems had an effect on their daily routines, and 10 (59%) scored≥10 on the ESS. On the SDL, 3 of these 17 (18%) had scored ≥3 on the Insomnia subscale and 2 (12%) scored ≥3 on the RLS subscale.

Of the 15 people who scored high on the ESS, 7 were on psychiatric medication. There was a significant positive correlation between the ESS and depressive symptoms, as well as antisocial symptoms, and a trend toward increased anxiety with higher ESS scores (see Table 3). When focusing on the subgroup using AEDs, depression and anxiety scores were significantly elevated, as were problems with attention. Notably, the antisocial scores were

not significant in the group using AEDs, and the Insomnia subscale scores on the SDL showed extremely low correlations with all of the psychological outcomes.

### 3.5. Association with medication

Thirteen respondents (40%) had tried medical intervention for sleeping problems, most often lorazepam (5), zolpidem (4), melatonin (2), and flu medication containing paracetamol and antihistamines (2). Most were considered helpful, although about half of the zolpidem and lorazepam users reported grogginess the next day. Eleven patients (33%) had tried nonmedicinal interventions to improve sleep, most often relaxation techniques, which were reported to be helpful.

Of the patients with a positive seizure history, 15 (60%) reported an effect of AEDs on their sleep. Specific medications that were causing longer sleep periods, sleepiness, or grogginess were valproic acid (4 patients), carbamazepine (4 patients), phenytoin (2 patients), and diazepam, levetiracetam, lamotrigine, phenobarbital, and clonazepam. AEDs or devices causing disrupted sleep and/or sleeplessness were lamotrigine, lorazepam, and the vagus nerve stimulator.

When the groups using and not using benzodiazepines were compared with respect to their ESS and Narcolepsy scores to investigate a sedative effect, there was a significant effect on Narcolepsy ($P<0.007$) scores and a trend toward higher ESS scores. There was a significant positive correlation between number of mental health medications used and level of anxiety ($P < 0.0095$).

## 4. Discussion

To our knowledge, this is the only study of sleep in adults with TSC. Various limitations are inherent to our questionnaire-based approach. The response rate to the questionnaires was 25%, which is relatively low for this study type and resulted in a small sample size. The unequal male to female ratio of responders could be explained by the relatively higher prevalence of daytime sleepiness scores in our female cohort, perhaps resulting in more affinity for this study in women. Of the respondents, 25 (76%) had a positive seizure history, which is relatively lower than the reported prevalence of epilepsy in 90% of patients with TSC. This could indicate that the respondents are mildly affected with respect to neurological involvement, which is supported by their relatively high level of education. Apart from this gender and IQ bias, our study group does seem to be representative; many of our results [e.g., female gender did have a significant effect on insomnia ($P<0.05$) and age approached significant effect on symptoms of restless legs syndrome ($P<0.08$)] are consistent with occurrences in the general population and thus validate our study group. As this was an exploratory study, no power calculations were performed to determine the sample size. Additionally, we have shown many statistical comparisons to generate hypotheses for future research. Hence, the power and $P$ values should be interpreted cautiously.

A specific limitation is the lack of objective data such as information from polysomnographic (PSG) studies to confirm results of the subjective patient reports. Because of the disparity in timing, the EEG data may not accurately reflect the electrographic nature of the patient's brains at the time the questionnaires were completed. However, there is evidence demonstrating consistent localization of focal interictal epileptiform features in patients with TSC over a 10-year period [20]. We did not have matched controls for our study group.

Excessive daytime sleepiness (EDS) is a common sleep/wake complaint among people with epilepsy, typically attributed to the effects of AEDs and seizures. A major finding in our cohort was that 15 of 35 (43%) had a high score on the ESS, indicating EDS. Notably, 12 (80%) were female, which cannot solely be explained by the female responder bias. Although the number of patients was too small to perform statistical analysis, there was a trend toward more daytime sleepiness in patients with a history of intractable epilepsy. Of the eight patients who used a benzodiazepine, four (50%) had a score above the cutoff on the ESS, which confirms the sedative effect of benzodiazepines, although we cannot rule out other influences such as sleep disturbances and medication. Of the 15 patients taking mental health medication, 7 (47%) had an ESS score 10, indicating these patients are at greater risk for daytime sleepiness.

### 4.1. Relationship between epilepsy features and sleep

Epilepsy has been implicated in the disturbance of sleep physiology in a variety of ways, especially in the epilepsies associated with structural brain lesions. Sleep is widely recognized as an activator of interictal epileptiform discharges during EEG recordings and, additionally, has a pronounced effect on secondary generalization of partial seizures [21]. The prevalence of a subjective sleep disorder in 31% of the total study group, and in 40% of patients with TSC with a positive seizure history, is similar to the significantly high prevalence of 39% previously reported in an adult cohort with partial epilepsy [22], where the presence of a sleep disturbance adversely affected quality of life. In another controlled study of adult patients with epilepsy, higher rates of the sleep complaints insomnia and daytime sleepiness were also reported by patients with epilepsy, although symptoms of RLS were decreased [23].

Although not all patients with a positive seizure history had insomnia, all patients with insomnia did have a positive seizure history, confirming that in patients with TSC with epilepsy, health care providers should be alert for the presence of a sleep disorder as well as nocturnal seizures. Frequent awakenings have also been observed in patients with learning disabilities [24] and in autistic patients without TSC [25], and both groups have a higher prevalence of epilepsy, confirming the association between neurodevelopmental disorders, epilepsy, and sleeping problems.

### 4.2. Restless legs syndrome

In our study group, five patients (14%) had indications for RLS as measured by the SDL. Additionally, the RLS score on the SDL correlated positively and significantly with Insomnia, Narcolepsy, and OSAS scores. RLS is a clinical diagnosis with an estimated 9 to 20% prevalence in the elderly [26]. Half of the patients report a positive family history, and it has been associated with age, iron metabolism abnormalities, and chronic and end-stage renal disease [27]. In renal disease, no biochemical test value is associated with the presence of RLS. The pathophysiology of RLS has been related to the dopaminergic system, and several studies have shown significant improvement with treatment with dopaminergic agents. All five patients with TSC with a high RLS score had renal involvement. However, as most patients with TSC have renal involvement and this is often symptomatic, we cannot make any conclusions about renal pathology and RLS in patients with TSC.

In adults with ADHD, significantly increased nocturnal motor activity and enhanced frequency of arousals associated with periodic leg movements have been documented. Vice versa, there is a high comorbidity of ADHD in adult patients with RLS [28] as well as in patients with TSC [5]. In clinical practice, adults with ADHD often complain about sleep disorders [28]. Thus, clinicians should be aware that ADHD and RLS need to be considered either as differential diagnoses or as comorbidities in TSC.

### 4.3. Psychological functioning

Solely high scores on these self-report scales cannot be used for diagnosis of a psychiatric disorder. However, these questionnaires can assist in detection of problems in a specific area. In a recent questionnaire study [29], the presence of a subjective sleep disturbance, depression, or anxiety had a great effect on the quality of life in adults with epilepsy, even greater than short-term seizure control. High rates of depression and anxiety have been reported in TSC [5,30]. In this cohort the correlation between the ESS and Depression scores was highly significant ($P<0.014$), irrespective of AED use. This phenomenon has previously been observed in adult patients with epilepsy [31] and could indicate that daytime sleepiness represents a vital sign of depression, of which clinicians should be aware. The correlation between daytime sleepiness and increased symptoms of anxiety and depression indicates that treatment of the cause of this sleepiness may decrease psychological problems in patients with TSC, or vice versa, whether it be adjusting medication, screening for nocturnal seizures or depression, or other considerations. Remarkably, increased scores on the SDL Insomnia subscale were not associated with anxiety, suggesting there is no indication that the observed EDS was caused by insomnia in these anxious patients. Although Antisocial scores correlated with higher ESS scores, they were not associated with use of AEDs, suggesting they are not related to epilepsy features in patients with TSC. Possibly, the Antisocial scores reflect features of aggression and/or autism, which are known be highly prevalent in TSC and often result in the use of mental health medication.

The high score on Problems with Attention in the group of patients with TSC using AEDs reflects previous observations of a high prevalence of ADHD in patients with epilepsy [32,33]. The reasons for this association are not fully understood, but include effects of seizures, antiepileptic medications, underlying neurodevelopmental vulnerability, and subclinical epileptiform activity [32,34].

Because people with intellectual disabilities have been found to have high rates of sleep disturbances which are related to mental health problems and the use of antiepileptic medication [35,36], we expect the prevalence of the aforementioned mental health complaints to be even higher in the TSC population with lower IQs.

### 4.4. Genetic effect

Previous studies have demonstrated a more severe neurological phenotype in patients with TSC2 mutations [33,37]. The outcomes of this study did not show a significant difference between mutations in TSC1 and TSC2, suggesting that a genetic basis for the sleep disorder in TSC is unlikely.

### 4.5. Therapy

Presumably, improvements of sleep duration and quality will positively affect the daytime behavior of the child [38], as well as the psychological functioning of adults with TSC. However, in patients with epilepsy, sleep is often fragmented in the absence of seizures or medication, suggesting that sleep instability may be an inherent component of certain forms of epilepsy [9].

Antiepileptic drugs seem to have variable effects on nocturnal sleep and daytime vigilance [39] and have different short-term and long-term effects. Carbamazepine, the AED most often used by our participants, seems to have a positive effect on sleep with long-term use, as do newer drugs like lamotrigine, gabapentin, and levetiracetam [40,41]. Valproate and topiramate do not seem to have that effect. Further studies are needed to determine the long-term effects of AED therapy on sleep and wakefulness and psychological function and

whether the antiepileptic effects vary in patients with different types of epilepsy and TSC. Alterations in the timing or type of AEDs may be helpful.

Carbamazepine, oxcarbazepine and topiramate have specific therapeutic efficacy in nocturnal epileptic seizures, possibly through action on the same mutated acetylcholine receptors [42], and might be effective in nocturnal seizures in TSC. Contrary to a beneficial effect in a healthy population without epilepsy [41], a study investigating the effects of levetiracetam in patients with TSC reported poor sleep, especially in nonresponders [43].

In our study, the use of benzodiazepines was significantly related to a high Narcolepsy score and also was clearly correlated with daytime sleepiness, confirming the sedating effect of this medication, although there are other explanations such as seizure severity. Traditional sedatives have been found to be less effective in patients with TSC, and they often worsen the situation by increasing hyperactivity [44]. Perhaps, patients in our cohort had had sleepiness and RLS before treatment, resulting in benzodiazepine treatment. General considerations are that sedating AEDs should be minimized during the day but could be useful before bed. Activating AEDs should be used as appropriate.

The sedative component of benzodiazepines, measured by the reduction of locomotor activity, has been attributed to neuronal circuits expressing specific GABA-a receptors, the most prevalent receptor subtype in the brain. The development of GABA-b receptor modulators could open up a new era of therapy for troubles like insomnia, epilepsy, and narcolepsy, with lower doses and fewer side effects [45]. GABA is the main inhibitory neurotransmitter of the central nervous system. Epileptogenesis in TSC may be related to an impairment of GABAergic transmission, which is supported by the effectiveness of drugs with affinity for these receptors in the treatment of epilepsy in TSC. Additionally, particular neuronal networks defined by respective GABA-a receptor subtypes can now be linked to the regulation of various behavioral patterns [46]. This is of relevance for the pharmacotherapy of sleep and psychological dysfunction in patients with TSC. Although one patient in our cohort reported less sleep with gabapentin, in our clinical experience, the GABA analog gabapentin may, in addition to its antiepileptic action, improve sleep complaints. Gabapentin may help deepen sleep, positively affecting stage 4 sleep and reducing arousals during the night, and could be potentially helpful for both sleep onset and sleep maintenance. Additionally, gabapentin can be effective in the treatment of RLS [47].

Individuals with TSC often take other medications, increasing the risk of drug interactions. As few significant side effects have been described, melatonin may be an effective and safe treatment option for sleep problems. Melatonin is a chronobiotic drug with hypnotic properties [48]; it increases levels of serotonin in the brain, thus raising the seizure threshold [13], and has been used as adjuvant therapy to AEDs in children with intractable seizures [49]. Children with intractable epilepsy exhibited significant improvement in various sleep variables including sleep apnea, as well as ESS Sleepiness scores under melatonin therapy [50]. There was also a significant reduction in seizure severity. In children with TSC, it has been suggested that the exogenous melatonin does not act by correcting abnormal endogenous melatonin secretion but by a simple sedative effect [44]. As melatonin excretion in children is very similar to that seen in adults, these findings could be extrapolated to the adult TSC population [44]. In another study comparing the effects of 5 mg of melatonin versus placebo in patients with TSC, total sleep time increased and there was a trend toward decreased sleep latency, but with varying responses between subjects [38]. In a follow-up study, no evidence of a dosage effect was found between 5 and 10 mg of melatonin [38]. Future studies in the specific TSC population are warranted to confirm this.

It has been reported that vagus nerve stimulation treatment may affect respiration during sleep, resulting in stimulation-related apneas and hypopneas; improved daytime alertness has also been reported [51]. Additional studies with larger numbers of subjects are necessary to determine the effect of vagus nerve stimulation on daytime sleepiness and overnight sleep, comparing different stimulation intensities.

Previous studies have shown that the diagnosis and treatment of OSAS should be considered in patients with poor seizure control or worsening of the epilepsy and that treatment of OSAS can improve seizure control [52].

## 5. Conclusion

This study confirms a high prevalence of sleep disorders in adult patients with TSC and the association with epilepsy features as well as mental health complaints. Although the uncontrolled nature of our data and relatively small and skewed study group limit conclusions, careful history taking and polysomnography including EEG should be performed when sleeping problems or daytime sleepiness interfere with daily activities. Home videos and sleep diaries are an inexpensive and proven method of monitoring sleep patterns [13]. Early detection and treatment of nocturnal epileptiform features and sleep abnormalities will have a positive effect on the quality of life, including mental health, of patients with TSC. Daytime sleepiness could be an indicator of a depressive disorder or other mental health problem, and diagnosis and treatment of the causative factor could improve quality of life.

Future larger and controlled studies should provide more insight into the relationship with epilepsy and the neuroanatomic basis of sleep disorders in patients with TSC, as well as the neurophysiological features of sleep in TSC. Therapeutic trials for epilepsy as well as sleep and mental health disorders in patients with TSC can provide more direction in the development and choice of specific pharmacological agents.

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## References

1. Manning BD, Tee AR, Logsdon MN, Blenis J, Cantley LC. Identification of the tuberous sclerosis complex-2 tumor suppressor gene product tuberin as a target of the phosphoinositide 3-kinase/akt pathway. Mol Cell. 2002; 10:151–162. [PubMed: 12150915]
2. Inoki K, Li Y, Zhu T, Wu J, Guan KL. TSC2 is phosphorylated and inhibited by Akt and suppresses mTOR signalling. Nat Cell Biol. 2002; 4:648–657. [PubMed: 12172553]
3. Roach ES, Sparagana SP. Diagnosis of tuberous sclerosis complex. J Child Neurol. 2004; 19:643–649. [PubMed: 15563009]
4. Pulsifer MB, Winterkorn EB, Thiele EA. Psychological profile of adults with tuberous sclerosis complex. Epilepsy Behav. 2007; 10:402–406. [PubMed: 17392032]
5. Muzykewicz DA, Newberry P, Danforth N, Halpern EF, Thiele EA. Psychiatric comorbid conditions in a clinic population of 241 patients with tuberous sclerosis complex. Epilepsy Behav. 2007; 11:506–513. [PubMed: 17936687]
6. Holmes GL, Stafstrom CE. for Tuberous Sclerosis Study G. Tuberous sclerosis complex and epilepsy: recent developments and future challenges. Epilepsia. 2007; 48:617–630. [PubMed: 17386056]
7. Thiele EA. Managing epilepsy in tuberous sclerosis complex. J Child Neurol. 2004; 19:680–686. [PubMed: 15563014]

8. Curatolo, editor. Tuberous sclerosis complex: from basic science to clinical phenotypes. High Holborn, London: MacKeith Press for the International Child Neurology Assoc.; 2003.
9. Foldvary-Schaefer N, Grigg-Damberger M. Sleep and epilepsy. Semin Neurol. 2009; 29:419–428. [PubMed: 19742416]
10. Bruni O, Cortesi F, Giannotti F, Curatolo P. Sleep disorders in tuberous sclerosis: a polysomnographic study. Brain Dev. 1995; 17:52–56. [PubMed: 7762764]
11. Hunt A, Stores G. Sleep disorder and epilepsy in children with tuberous sclerosis: a questionnaire-based study. Dev Med Child Neurol. 1994; 36:108–115. [PubMed: 7510655]
12. Hunt A, Shepherd C. A prevalence study of autism in tuberous sclerosis. J Autism Dev Disord. 1993; 23:323–339. [PubMed: 8331050]
13. Hancock E, O'Callaghan F, Osborne JP. Effect of melatonin dosage on sleep disorder in tuberous sclerosis complex. J Child Neurol. 2005; 20:78–80. [PubMed: 15791928]
14. Hunt A. Development, behaviour and seizures in 300 cases of tuberous sclerosis. J Intellect Disabil Res. 1993; 37(Pt 1):41–51. [PubMed: 7681710]
15. Sweere Y, Kerkhof GA, De Weerd AW, et al. The Sleep Diagnosis List [SDL]: a questionnaire for screening general sleep disorders. Sleep–Wake Res Netherlands. 1998; 9:117–121.
16. Sweere Y, Kerkhof GA, De Weerd AW, Kamphuisen HA, Kemp B, Schimsheimer RJ. The validity of the Dutch Sleep Disorders Questionnaire [SDQ]. J Psychosom Res. 1998; 45:549–555. [PubMed: 9859856]
17. Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. Sleep. 1991; 14:540–545. [PubMed: 1798888]
18. Achenbach, TM.; Rescorla, LA. Manual for the ASEBA Adult Forms & Profiles. Burlington: Univ of Vermont, Research Center for Children, Youth, & Families; 2003.
19. Achenbach TM, Dumenci L. Advances in empirically based assessment: revised cross-informant syndromes and new DSM-oriented scales for the CBCL, YSR, and TRF: comment on Lengua, Sadowksi, Friedrich, and Fischer [2001]. J Consult Clin Psychol. 2001; 69:699–702. [PubMed: 11550735]
20. Jansen FE, van Huffelen AC, Bourez-Swart M, van Nieuwenhuizen O. Consistent localization of interictal epileptiform activity on EEGs of patients with tuberous sclerosis complex. Epilepsia. 2005; 46:415–419. [PubMed: 15730539]
21. Bazil CW, Walczak TS. Effects of sleep and sleep stage on epileptic and nonepileptic seizures. Epilepsia. 1997; 38:56–62. [PubMed: 9024184]
22. De Weerd A, de Haas S, Otte A, et al. Subjective sleep disturbance in patients with partial epilepsy: a questionnaire-based study on prevalence and impact on quality of life. Epilepsia. 2004; 45:1397–1404. [PubMed: 15509241]
23. Khatami R, Zutter D, Siegel A, Mathis J, Donati F, Bassetti CL. Sleep–wake habits and disorders in a series of 100 adult epilepsy patients: a prospective study. Seizure. 2006; 15:299–306. [PubMed: 16546407]
24. Petre-Quadens O, Jouvet M. Sleep in the mentally retarded. J Neurol Sci. 1967; 4:354–357. [PubMed: 4227012]
25. Johnson KP, Malow BA. Assessment and pharmacologic treatment of sleep disturbance in autism. Child Adolesc Psychiatr Clin North Am. 2008; 17:773–785.
26. Spiegelhalder K, Hornyak M. Restless legs syndrome in older adults. Clin Geriatr Med. 2008; 24:167–180. [PubMed: 18035239]
27. Ekbom K, Ulfberg J. Restless legs syndrome. J Intern Med. 2009; 266:419–431. [PubMed: 19817966]
28. Philipsen A, Hornyak M, Riemann D. Sleep and sleep disorders in adults with attention deficit/hyperactivity disorder. Sleep Med Rev. 2006; 10:399–405. [PubMed: 17084648]
29. Kwan P, Yu E, Leung H, Leon T, Mychaskiw MA. Association of subjective anxiety, depression, and sleep disturbance with quality-of-life ratings in adults with epilepsy. Epilepsia. 2009; 50:1059–1066. [PubMed: 19170734]
30. Pulsifer MB, Winterkorn EB, Thiele EA. Psychological profile of adults with tuberous sclerosis complex. Epilepsy Behav. 2007; 10:402–406. [PubMed: 17392032]

31. Jenssen S, Gracely E, Mahmood T, Tracy JI, Sperling MR. Subjective somnolence relates mainly to depression among patients in a tertiary care epilepsy center. Epilepsy Behav. 2006; 9:632–635. [PubMed: 16996802]
32. Kaufmann R, Goldberg-Stern H, Shuper A. Attention-deficit disorders and epilepsy in childhood: incidence, causative relations and treatment possibilities. J Child Neurol. 2009; 24:727–733. [PubMed: 19491115]
33. Lewis JC, Thomas HV, Murphy KC, Sampson JR. Genotype and psychological phenotype in tuberous sclerosis. J Med Genet. 2004; 41:203–207. [PubMed: 14985384]
34. Hamoda HM, Guild DJ, Gumlak S, Travers BH, Gonzalez-Heydrich J. Association between attention-deficit/hyperactivity disorder and epilepsy in pediatric populations. Expert Rev Neurother. 2009; 9:1747–1754. [PubMed: 19951134]
35. Boyle A, Melville CA, Morrison J, et al. A cohort study of the prevalence of sleep problems in adults with intellectual disabilities. J Sleep Res. 2010; 19(1, Pt 1):42–53. [PubMed: 19912512]
36. Hylkema T, Vlaskamp C. Significant improvement in sleep in people with intellectual disabilities living in residential settings by non-pharmaceutical interventions. J Intellect Disabil Res. 2009; 53:695–703. [PubMed: 19460068]
37. Dabora SL, Jozwiak S, Franz DN, et al. Mutational analysis in a cohort of 224 tuberous sclerosis patients indicates increased severity of TSC2, compared with TSC1, disease in multiple organs. Am J Hum Genet. 2001; 68:64–80. [PubMed: 11112665]
38. O'Callaghan FJ, Clarke AA, Hancock E, Hunt A, Osborne JP. Use of melatonin to treat sleep disorders in tuberous sclerosis. Dev Med Child Neurol. 1999; 41:123–126. [PubMed: 10075098]
39. Foldvary-Schaefer N, Grigg-Damberger M. Sleep and epilepsy: what we know, don't know, and need to know. J Clin Neurophysiol. 2006; 23:4–20. [PubMed: 16514348]
40. Cicolin A, Magliola U, Giordano A, Terreni A, Bucca C, Mutani R. Effects of levetiracetam on nocturnal sleep and daytime vigilance in healthy volunteers. Epilepsia. 2006; 47:82–85. [PubMed: 16417535]
41. Foldvary N, Perry M, Lee J, Dinner D, Morris HH. The effects of lamotrigine on sleep in patients with epilepsy. Epilepsia. 2001; 42:1569–1573. [PubMed: 11879368]
42. Romigi A, Marciani MG, Placidi F, et al. Oxcarbazepine in nocturnal frontal-lobe epilepsy: a further interesting report [letter]. Pediatr Neurol. 2008; 39:298. [PubMed: 18805375]
43. Collins JJ, Tudor C, Leonard JM, Chuck G, Franz DN. Levetiracetam as adjunctive antiepileptic therapy for patients with tuberous sclerosis complex: a retrospective open-label trial. J Child Neurol. 2006; 21:53–57. [PubMed: 16551454]
44. Hancock E, O'Callaghan F, English J, Osborne JP. Melatonin excretion in normal children and in tuberous sclerosis complex with sleep disorder responsive to melatonin. J Child Neurol. 2005; 20:21–25. [PubMed: 15791917]
45. Gottesmann C. GABA mechanisms and sleep. Neuroscience. 2002; 111:231–239. [PubMed: 11983310]
46. Mohler H. GABA[A] receptor diversity and pharmacology. Cell Tissue Res. 2006; 326:505–516. [PubMed: 16937111]
47. Walters AS, Ondo WG, Kushida CA, et al. Gabapentin enacarbil in restless legs syndrome: a phase 2b, 2-week, randomized, double-blind, placebo-controlled trial. Clin Neuropharmacol. 2009; 32:311–320. [PubMed: 19667976]
48. Braam W, Smits MG, Didden R, Korzilius H, Van Geijlswijk IM, Curfs LM. Exogenous melatonin for sleep problems in individuals with intellectual disability: a meta-analysis. Dev Med Child Neurol. 2009; 51:340–349. [PubMed: 19379289]
49. Peled N, Shorer Z, Peled E, Pillar G. Melatonin effect on seizures in children with severe neurologic deficit disorders. Epilepsia. 2001; 42:1208–1210. [PubMed: 11580772]
50. Elkhayat HA, Hassanein SM, Tomoum HY, Abd-Elhamid IA, Asaad T, Elwakkad AS. Melatonin and sleep-related problems in children with intractable epilepsy. Pediatr Neurol. 2010; 42:249–254. [PubMed: 20304327]
51. Malow BA, Edwards J, Marzec M, Sagher O, Fromes G. Effects of vagus nerve stimulation on respiration during sleep: a pilot study. Neurology. 2000; 55:1450–1454. [PubMed: 11094096]

52. Hollinger P, Khatami R, Gugger M, Hess CW, Bassetti CL. Epilepsy and obstructive sleep apnea. Eur Neurol. 2006; 55:74–79. [PubMed: 16567944]

## Table 1

Characteristics of patients.

| | No AED (*N* = 15) | AED use (*N* = 20) | ESS ≥ 10 (*N* = 15) | SDL ≥ 3 (*N* = 11) |
|---|---|---|---|---|
| Men (*N* = 10) | 2 | 8 | 3 | 3 |
| Women (*N* =2 5) | 13 | 12 | 12 | 8 |
| Single (*N* = 19) | 9 | 10 | 8 | 5 |
| Employed (*N* = 24) | 13 | 11 | 10 | 8 |
| Mean age | 33 | 33 | 34 | 34 |
| Lower secondary education or less (*N* = 11) | 5 | 6 | 3 | 3 |
| Pre-university education or higher (*N* = 29) | 9 | 10 | 10 | 6 |
| Positive seizure history (*N* = 25) | 5 | 20 | 9 | 10 |
| AED polytherapy (*N* = 14) | — | 14 | 6 | 5 |
| TSC2 mutation (*N* = 12) | 3 | 9 | 3 | 2 |

*Note.* The entire responder group consisted of 35 patients, of whom 20 were currently using AEDs. Fifteen and eleven responders scored high on the Epworth Sleepiness Scale (ESS) and Sleep Diagnosis List (SDL), respectively.

## Table 2

Correlations between outcomes on the Sleep Diagnosis List scale (excluding parasomnia scores)

| | Insomnia | Narcolepsy | Obstructive sleep apnea syndrome | Restless legs syndrome |
|---|---|---|---|---|
| Insomnia | — | 0.279 ($P$<0.104 | 0.512 ($P$<0.002)[a] | 0.372 ($P$<0.028) |
| Narcolepsy | 0.279 ($P$<0.104) | — | 0.286 ($P$<0.095) | 0.480 ($P$<0.004)[a] |
| Obstructive sleep apnea syndrome | 0.512 ($P$<0.002)[a] | 0.286 ($P$<0.095) | — | 0.411 ($P$<0.014)[a] |
| Restless legs syndrome | 0.372 ($P$<0.028)[a] | 0.480 ($P$<0.004)[a] | 0.411 ($P$<0.014)[a] | — |

[a]Significant.

## Table 3

Correlation between psychological complaint scores and scores on sleep scales, for the total responder group and the subgroup of patients currently using AEDs.

| Adult Self-Report Scale | Epworth Sleepiness Scale score | | Sleep Diagnosis List Insomnia score | |
|---|---|---|---|---|
| | Entire group ($N$ = 35) | AED users ($N$ = 20) | Entire group ($N$ = 35) | AED users ($N$ = 20) |
| Depressed | 0.41 ($P$<0.014)[a] | 0.37 ($P$<0.11) | −0.07 | 0.005 |
| Anxious | 0.32 ($P$<0.061) | 0.47 ($P$<0.04)[a] | −0.03 | 0.03 |
| Avoidant | 0.193 | 0.16 | −0.149 | 0.35 ($P$<0.13) |
| Somatic Complaints | 0.10 | 0.02 | −0.29 ($P$<0.091) | −0.18 |
| Attention Deficits | 0.27 | 0.46 ($P$<0.04)[a] | −0.12 | −0.13 |
| Hyperactivity | 0.06 | 0.24 | −0.02 | 0.11 |
| Antisocial | 0.37 ($P$<0.03)[a] | −0.11 | 0.01 | 0.05 |

[a]Significant.