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SCIENTIFIC INVESTIGATIONS

Randomized Controlled Trial of Melatonin for Sleep Disturbance in Dravet Syndrome: The DREAMS Study

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Study Objectives: Dravet syndrome is a severe developmental and epileptic encephalopathy, in which 75% of patients have sleep disturbance. Melatonin is often used for sleep problems in childhood; however, there is no quality evidence supporting its use in Dravet syndrome. We hypothesized that melatonin would increase total sleep and quality of life for patients with Dravet syndrome.

Methods: A double-blind crossover randomized placebo-controlled trial was conducted, comparing 6 mg regular-release melatonin to placebo for patients with Dravet syndrome and sleep disturbance. The primary outcome measure was total sleep measured by actigraphy, with secondary outcomes including wakefulness after sleep onset (WASO), Sleep Disturbance Scale in Children and Quality of Life in Children with Epilepsy 55 questionnaires, caregiver reports of clinical change, seizure diary and serum antiepileptic drug levels. We also compared actigraphy data of patients with Dravet syndrome to an age-matched healthy control group.

Results: A total of 13 patients completed the study. There was no difference in total sleep or WASO between melatonin and placebo. However, of the 11 patients for whom caregivers reported a clear clinical difference between treatments (blinded), 8 reported improvement on melatonin ($P < .05$). Interestingly, when compared to patients in the control group, patients with Dravet syndrome had significantly increased total sleep ($P = .002$).

Conclusions: Melatonin did not increase total sleep; however, blinded caregiver reports indicate treatment with melatonin provided considerable clinical benefit for some patients with Dravet syndrome and sleep disturbance.

Clinical Trial Registration: Registry: Australian Government Department of Health, Therapeutic Goods Administration under the Clinical Trials Notification Scheme (protocol number 2241)

Keywords: actigraphy, Dravet syndrome, melatonin, scn1a, sleep

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Sleep disturbance is common in Dravet syndrome and frequently affects quality of life for patients and their families. There are no established therapies for sleep disturbance in Dravet syndrome, and the nature of the sleep disturbance itself remains poorly characterized.

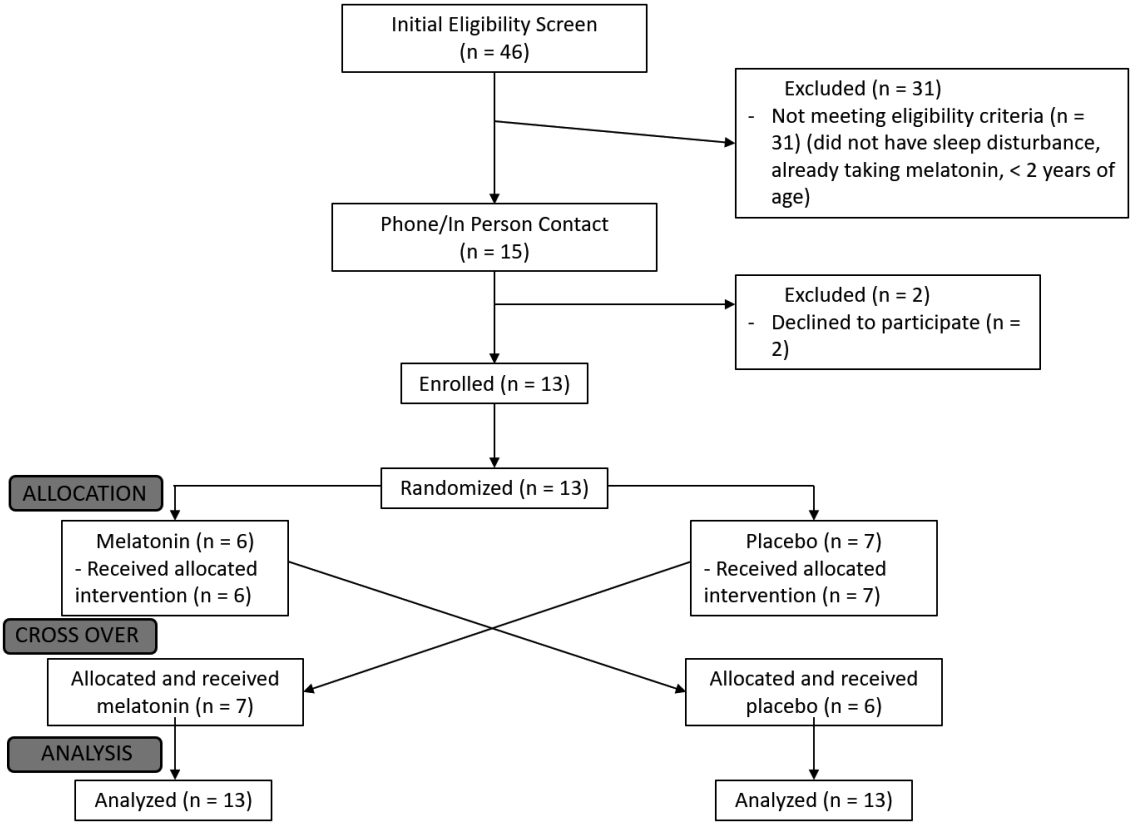
Study Impact: A subset of patients with Dravet syndrome reported dramatic clinical improvement in sleep initiation, maintenance, and quality of life when receiving melatonin. However, melatonin did not result in measurable overall improvements in total sleep or wakefulness after sleep onset. Although definitive evidence of clinical benefit for patients with Dravet syndrome and sleep disturbance was not shown, such individuals should nevertheless consider a trial of melatonin, as some individuals appear to derive dramatic benefits.

INTRODUCTION

Dravet syndrome is a severe infantile-onset developmental and epileptic encephalopathy associated with mutations in *SCN1A* (OMIM 182389) in more than 80% of cases.[1] Usually patients first present with convulsive febrile seizures near 6 months of age, classically prolonged and often hemiclonic.[2] Early development is normal, but developmental regression or plateau typically becomes apparent by 2 years.[2] Although refractory epilepsy is a major management challenge, people with Dravet syndrome also frequently experience comorbidities including a progressively worsening crouch gait, speech problems, behavioral difficulties, and disturbed sleep.[3–7] We recently found that sleep disturbance occurred in 75% of patients with Dravet syndrome;[3] however, currently there are no evidence-based therapies whose use is supported in this patient population who have such a challenging and complex range of problems.

One appealing therapeutic candidate is melatonin, a hormone produced endogenously by the pineal gland and involved in sleep-wake cycles.[8,9] Synthetically produced melatonin may be given exogenously and there are both immediate and sustained-release formulations available.[10] Melatonin is approved by the Food and

Figure 1—CONSORT flow diagram.



Drug Administration for treatment of sleep disturbance in older adults but the existing data supporting or refuting use in children with intellectual disability are limited, with no blinded trials in people with Dravet syndrome.[10,11] Currently, the best evidence in childhood epilepsy comes from a randomized, double-blind, crossover trial in normally developing children with insomnia and epilepsy, which found that melatonin decreased sleep latency and wakefulness after sleep onset (WASO).[12]

We conducted a study in people with Dravet syndrome, using a randomized, double-blind, placebo-controlled trial design, to investigate the efficacy and safety of melatonin in treatment of sleep disturbance within this population (the DREAMS study). A secondary aim of the study was to better characterize the nature of sleep disturbance in people with Dravet syndrome by asking caregivers to complete sleep disturbance scale questionnaires, and by comparing 2-week actigraphy results while receiving placebo to an age-matched control group of healthy children with normal sleep.

METHODS

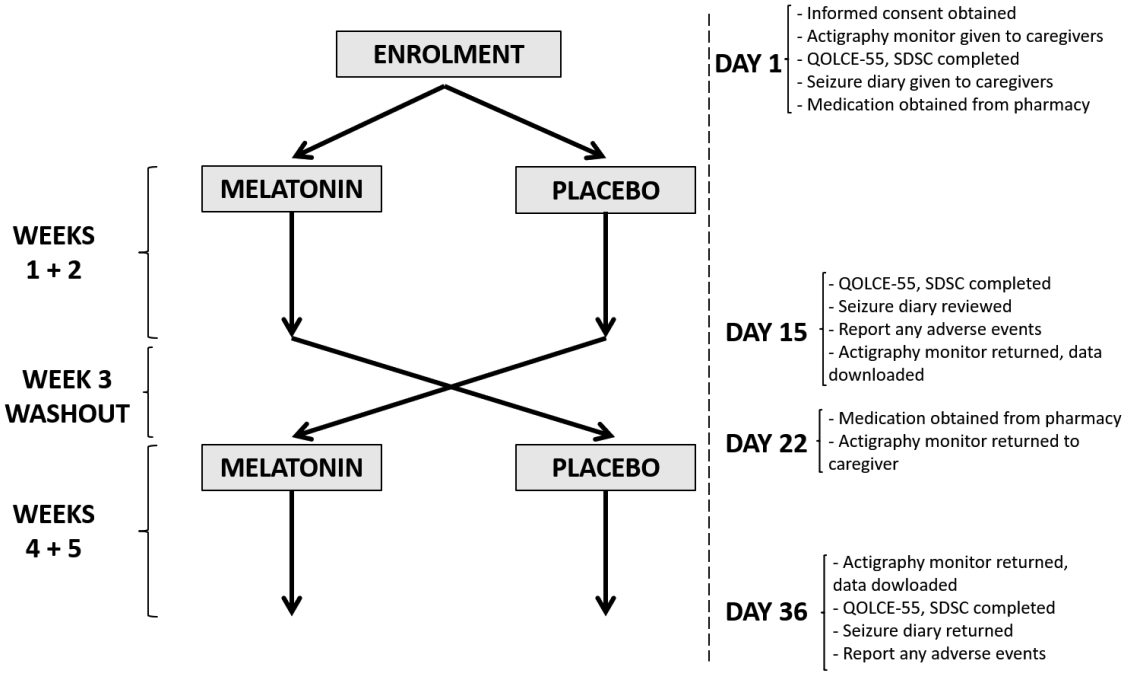
Recruitment, Inclusion/Exclusion Criteria and Trial Design

We recruited patients aged 2 to 50 years from the Dravet syndrome clinic at Austin Health (Heidelberg, VIC, Australia). All individuals had Dravet syndrome associated with an *SCN1A* mutation, diagnosed by a pediatric epileptologist (KAM, IES). Patients were selected if they, or their family, reported disturbed sleep of any kind. Patients were excluded if they had taken melatonin in the past 4 weeks, had a diagnosis of obstructive sleep apnea, had known hypersensitivity to melatonin, had a musculoskeletal abnormality that prevented them from being able to wear the actigraphy wristband, or were pregnant. The study participant flowsheet is shown in **Figure 1**, and the trial design is summarized in **Figure 2**.

A randomized, double-blind, crossover placebo-controlled trial design was used in which patients received either placebo or 6 mg regular-release melatonin capsules prepared by Melbourne Compounding Centre (Seddon, VIC, Australia). The 6-mg dose was chosen because it is in the range used in prior studies of children with epilepsy.[12,13] Caregivers were instructed to give the medication 30 minutes before bedtime for a 2-week period because we were interested in studying melatonin's hypnotic effects. Participants were given an actigraphy bracelet (Actiwatch 2; BMedical Pty Ltd, Milton, Queensland, Australia) to wear for each 2-week treatment period. In a number of cases, the wristband had to be secured with duct tape, and/or under clothing, in order to prevent the participants from spontaneously removing them.

At baseline, caregivers completed two validated surveys: Sleep Disturbance Scale For Children (SDSC) and Quality of Life in Children with Epilepsy 55 (QOLCE-55).[14,15] These questionnaires were chosen because we expected the patient population to be overwhelmingly pediatric, given that our recruitment was from a pediatric neurology clinic. As well, any adult participants would have developmental impairment, so we thought

Figure 2—Trial design.



QOLCE-55 = Quality of Life in Children with Epilepsy 55, SDSC = Sleep Disturbance Scale For Children.

the data from these questionnaires would still be useful, even though they are not designed for this patient population. The same questionnaires were completed at the conclusion of each 2-week period, at which time caregivers were also asked for the number of convulsive seizures that had occurred over the 2 weeks and if any adverse events were noted, and the actigraphy wristbands were returned. There was a washout period of 1 week between the two treatment periods. At the conclusion of the second 2-week treatment period, caregivers were asked if they had noticed any clinical changes during either 2-week period which they suspected were the result of receiving melatonin.

As an optional aspect of the study, participants were invited to provide blood samples for serum antiepileptic drug levels at the conclusion of each treatment period. This was done to study the potential effect of melatonin on hepatic drug metabolism.[16]

Randomization and Blinding

Randomization was performed by a pharmacist at the Austin Health Clinical Trials Pharmacy. After all patients had completed the study, initial unblinding was partial, so that investigators learned whether individual patients had received "Treatment A" first or second but did not know if "Treatment A" was melatonin or placebo. This allowed statistical analysis to be performed while investigators were still blinded to treatment received. After statistical analysis was complete, final unblinding was performed.

Sample Size Calculation

Based on our initial calculations and estimates, a target sample size of 20 patients was chosen. A rigorous power calculation was not possible because of the lack of knowledge regarding variability of sleep parameters in the Dravet syndrome population. Jain et al.[12] found statistically significant differences in a study with a similar design in 10 normally developing children with epilepsy; based on this, 20 was considered a more than adequate sample size, even allowing for increased variability in children and adults with Dravet syndrome.

Comparing Sleep Patterns in Patients With Dravet Syndrome and Patients in the Control Group

As a secondary aim of the study, an age-matched cohort of healthy children and adults without disturbed sleep was recruited. Individuals in the control group were recruited through a call for volunteers to clinic/research staff and their families. These individuals wore the actigraphy monitors for a 2-week period during which time they were asked not to alter their normal routines. Total sleep and WASO were compared between the individuals in the control group and patients with Dravet syndrome when receiving placebo.

Statistical Analysis

The primary outcome measure was average total sleep time over the 2-week period estimated on the basis of actigraphy data. Secondary outcome measures included mean WASO, mean sleep latency, mean sleep efficiency, change in SDSC and QOLCE-55 scores, convulsive seizure frequency, caregiver impression of clinical change, and adverse events.

All continuous data were compared using one-tailed Wilcoxon signed-rank tests, with the exception of Dravet/control comparisons where two-tailed tests were used. Fisher exact test was used to compare the proportion for whom caregivers reported definite improvement for melatonin versus placebo.

Ethics

This study was approved by the Human Research Ethics Committee of Austin Health, Project No. DT16/78. The trial was registered with the Australian Government Department of Health, Therapeutic Goods Administration under the Clinical Trials Notification Scheme (protocol number 2241).

Table 1—Characteristics of patients with Dravet syndrome and individuals in the control group.

Variable	Dravet Syndrome	Control Group
n	13	13*
Mean age in years (range)	12.2 (4.9 – 38)	11.3 (4.5 – 44)
Male:Female	4:9	6:7
SCN1A mutation	13/13	N/A

* = one of the individuals in the control group withdrew from the study and was replaced; her demographic data are not included in this table. N/A = not applicable.

RESULTS

Patient Demographics

Patient demographics are given in **Table 1**. Thirteen patients with Dravet syndrome and sleep disturbance were recruited (**Table 2**), as well as 14 healthy age-matched controls with normal sleep, between June 2016 and July 2017. As shown in **Figure 1**, 2 eligible patients declined to participate; 31 screened patients were excluded because they did not have sleep disturbance, were already taking melatonin, or were younger than the predetermined age range for the study. All patients with Dravet syndrome completed the study. One participant in the control group, aged 4 years, withdrew from the study because

Table 2—Clinical features of patients with Dravet syndrome.

#	Sex	Age	Nature of Sleep Disturbance	Primary Seizure Types	Medications	Melatonin	Placebo
1	M	12 y	Initiation and maintenance of sleep; Sleep-wake transition; Excessive somnolence; Hyperhidrosis	GTC	TPM, VPA	Sleeping better.	–
2	F	12 y	Arousal; Sleep-wake transition	FIAS, GTC	CLB, TPM, VPA	Fewer nightmares and fewer nighttime wakings.	–
3	F	5 y	Initiation and maintenance of sleep	GTC, Hemiclonic	CLB, STP, TPM	Easier to get to sleep and happier in the mornings.	–
4	M	13 y	Initiation and maintenance of sleep; Sleep-wake transition	GTC, Hemiclonic	CLB, LEV, CLN, STP, TPM, CLO, ATO	–	Calmer during these two weeks.
5	M	13 y	Initiation and maintenance of sleep; Sleep breathing; Sleep-wake transition; Hyperhidrosis	GTC, ABS	LEV, PHT, STP, ZNS	No clear difference.	No clear difference.
6	F	6 y	Initiation and maintenance of sleep; Sleep-wake transition; Excessive somnolence	GTC, FIAS	CLB, STP, VPA	–	Did not go to sleep easier but easier to settle.
7	F	5 y	Initiation and maintenance of sleep; Sleep breathing; Sleep-wake transition; Arousal	FIAS, ABS, GTC	CLB, TPM, VPA	Sleep much improved.	–
8	F	13 y	Initiation and maintenance of sleep; Sleep breathing; Arousal; Sleep-wake transition; Excessive somnolence	GTC	VPA	Seemed to go to sleep a bit better.	–
9	M	6 y	Initiation and maintenance of sleep; Sleep-wake transition	ABS, GTC, Myoclonic	CLN, STP, TPM, VPA	More likely to sleep full night in bed; seemed to have cognitive improvement.	–
10	M	11 y	Initiation and maintenance of sleep; Arousal; Sleep-wake transition; Excessive somnolence	GTC	CLB, TPM	Sleep worse. More seizures	Sleep much improved.
11	F	38 y	Initiation and maintenance of sleep; Sleep breathing; Arousal	Tonic, Myoclonic, GTC	ACZ, CLN, LTG, VPA	No clear difference.	No clear difference.
12	F	14 y	Sleep breathing; Sleep-wake transition; Excessive somnolence	GTC	CLB, STP, VPA	Overall better. Gets to sleep easier, less daytime somnolence.	–
13	M	4 y	Initiation and maintenance of sleep	GTC, ABS, Myoclonic	CLB, ETX, KD, STP, TPM, VPA	Sleep and cognition better.	–

Nature of sleep disturbance is based on Sleep Disturbance Scale for Children, for all elements with T score ≥ 72. ABS = Absences, ACZ = Acetazolamide, ATO = Atomoxetine, CLB = Clobazam, CLN = Clonazepam, CLO = Clonidine, ETX = Ethosuximide, FIAS = focal impaired awareness seizures, GTC = generalized tonic-clonic, KD = Ketogenic diet, LEV = Levetiracetam, LTG = Lamotrigine, PHT = Phenytoin, STP = Stiripentol, TPM = Topiramate, VPA = valproic acid, ZNS = Zonisamide.

Table 3—Melatonin versus placebo in patients with Dravet syndrome.

Variable	Melatonin	Placebo	*P*
Total sleep hours, median (IR)	10.0 (0.9)	10.0 (0.7)	.28
WASO minutes, median (IR)	49 (23)	44 (35)	.79
Definite clinical improvement (caregiver impression)	8/11	3/11	.047
SDSC total score (IR)	−8.5 (10.3)	−2.0 (11.6)	.07
SDSC sleep initiation/maintenance (IR)	−4.5 (5.3)	−1.0 (4.3)	.046
SDSC sleep breathing disorder (IR)	0.0 (1.2)	0.0 (1.0)	–
SDSC arousal disorder (IR)	0.0 (1.0)	0.0 (1.0)	–
SDSC sleep-wake transition (IR)	−2.0 (3.5)	−0.5 (1.5)	.12
SDSC excessive somnolence (IR)	−0.5 (2.0)	−0.5 (2.0)	–
SDSC hyperhidrosis (IR)	0.0 (0.3)	0.0 (0.1)	–
QOLCE-55 total score (IR)	0.4 (8.6)	−1.6 (6.3)	.12
QOLCE-55 cognitive (IR)	2.2 (7.3)	0.2 (5.9)	.046
QOLCE-55 emotional (IR)	3.0 (11.3)	−0.3 (6.1)	.24
QOLCE-55 social (IR)	−5.4 (21.9)	−5.4 (17.9)	.33
QOLCE-55 physical (IR)	0.6 (12.0)	0.0 (5.5)	–
Convulsive Seizures During 2-Week Period, median (IR)	0 (2)	1 (1)	–

Scores on QOLCE-55 and SDSC represent median change from baseline measurement. The primary outcome measure was total sleep hours; all other variables are secondary outcomes. A dash in the *P* value column indicates thatthere were too few effective samples (too many of the paired data were equal) to perform the Wilcoxon signed-rank test. *P* value corrections for multiple tests have not been performed. IR = interquartile range, QOLCE-55 = Quality of Life in Children with Epilepsy-55, SDSC = Sleep Disturbance Scale in Children, WASO = wakefulness after sleep onset.

she found the actigraphy wristband annoying; she was replaced and is not included in the **Table 1** patient data.

We had intended to calculate sleep latency and sleep efficiency based on the light sensor on the actigraphy wristband; however, a number of patients had to have the wristband secured with duct tape or under clothing, which prevented collection of the light sensor data and determination of bedtime. Hence, we were unable to conduct sleep latency or sleep efficiency analyses.

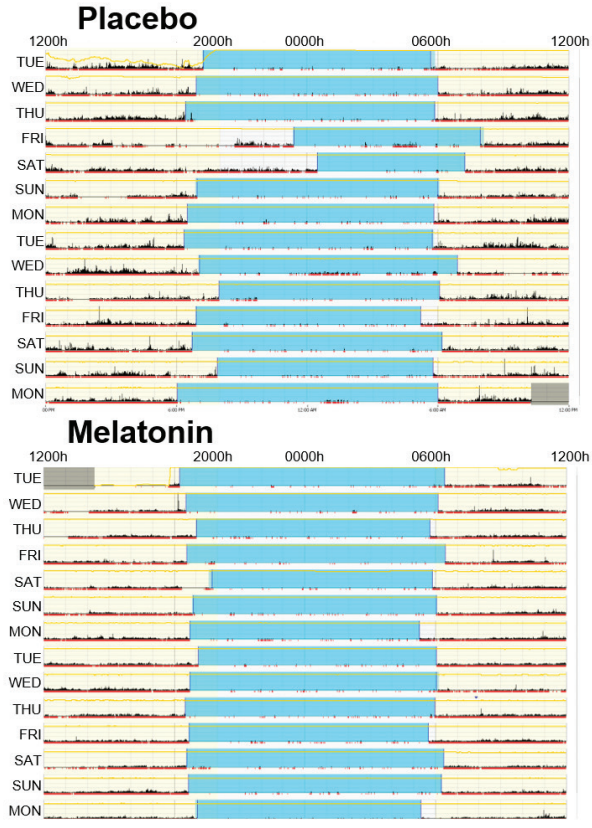
Melatonin Versus Placebo in Patients With Dravet Syndrome

The actigraphy did not demonstrate a significant difference in the primary outcome measure, total sleep, for melatonin compared to placebo in patients with Dravet syndrome, nor was there a significant difference in the secondary measure, WASO (**Table 3**). Although there was not an overall statistical difference in actigraphy qualitative measures, some patients showed clear objective improvement in sleep patterns while on melatonin (example given in **Figure 3**).

The total scores of the SDSC and QOLCE-55 did not show statistically significant improvement. However, there was improvement in Sleep Initiation/Maintenance on the SDSC ($P = .046$ without correction for multiple tests) consistent with the primary effect of melatonin.[10] There was also a borderline improvement observed in Cognitive Function on the QOLCE-55 ($P = .046$ without correction for multiple tests). There was no difference in convulsive seizure frequency, as expected.

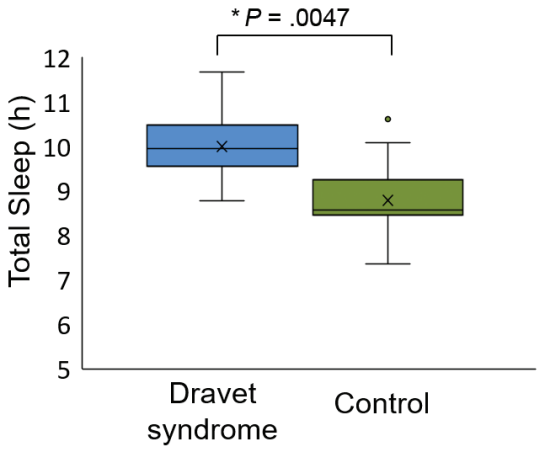
The caregivers reported a clear difference in response between the two treatments in 11 of 13 cases. Eight improved with melatonin, whereas three observed improvement with placebo ($P < .05$). The subjective observations of the caregivers when

Figure 3—Actigraphy data from a 5-year-old patient with Dravet syndrome showing a positive response to melatonin.



Blue represents the nocturnal sleep period identified and black reflects patient activity. During the 2 weeks on melatonin, the time-to-sleep and time-to-wake is much more consistent, and there is less activity detected during the sleep period.

Figure 4—Actigraphy comparison of individuals with Dravet syndrome and healthy individuals in the control group.



The patients with Dravet syndrome on placebo had greater total sleep than those in the control group.

comparing the two treatments are given for each patient in **Table 2**. Although the formal study design did not incorporate an open label extension phase, four families were so impressed with the clinical effect that they insisted on continuing therapy despite not yet being unblinded. One family reported that melatonin's effects had "changed their lives" as the patient's sleep disruption had been the major source of stress for the family.

No significant adverse events were reported by caregivers with either treatment. In only one patient were drug levels assessed at the conclusion of both treatment periods; he was on valproate and had an asymptomatic elevation in serum level of 199 μg/mL (normal range 50–125) while receiving melatonin. This level dropped to 126 μg/mL when measured at the conclusion of the placebo period without a change in the patient's valproate dosing. One patient was reported by caregivers to have worse sleep and more seizures while on melatonin; however, caregivers also thought this was within the child's typical week-to-week fluctuations and thus not a significant change from baseline.

Comparison of Actigraphy Among Individuals With Dravet Syndrome and Individuals in the Control Group

When comparing actigraphy from patients with Dravet syndrome on placebo with healthy participants in the control group, mean total sleep was significantly greater in the Dravet group, at 9.99 hours compared to 8.78 hours in the control group ($P = .0047$, **Figure 4**). There was no difference in mean WASO, with 56.7 minutes for the Dravet group and 54.2 minutes for controls ($P = .76$).

DISCUSSION

This randomized, double-blind, placebo-controlled, crossover trial comparing melatonin to placebo for sleep disturbance in Dravet syndrome did not find a significant difference in the predetermined primary outcome variable, total sleep measured by actigraphy. However, the data provide important insights into the nature of sleep disturbance in Dravet syndrome, as well as the possible benefits of melatonin for some patients. The study had a number of limitations including: smaller sample size than planned (though still larger than prior trials with similar designs that found statistically significant results), wide age range of study participants, lack of sleep latency data, and the potential for selection bias and confounding effects of antiepileptic medications.

When comparing patients with Dravet syndrome to healthy individuals in the control group, somewhat surprisingly, we found that the patients with Dravet syndrome had a greater total sleep time measured by actigraphy. This finding was unexpected as our previous study reported sleep disturbance in 75% of patients with Dravet syndrome based on parental questionnaire.[3] Longer total sleep time may reflect a lower quality of sleep in Dravet syndrome; however, this possibility has not been thoroughly investigated. A study of sleep in a mouse model of Dravet syndrome found marked sleep impairment with frequent arousals and electrographic abnormalities in both rapid eye movement and non-rapid eye movement sleep.[17] However, a case series of polysomnography studies in human patients with Dravet syndrome failed to show consistent abnormalities, though abnormal non-rapid eye movement sleep microarchitecture was noted.[6] Though the nature of sleep disturbance in Dravet syndrome remains unclear, one possibility is that the abnormalities occur because of subtle baseline physiologic abnormalities that may be exacerbated by nocturnal seizures and the effects of antiepileptic polypharmacy. Our data should be considered with caution, as we compared patients over a broad age range, and sleep patterns change considerably through the lifespan.

Given the baseline increased total sleep duration in the group of patients with Dravet syndrome, it is less surprising that melatonin failed to increase this as our primary outcome measure. However, the reports from caregivers indicated that melatonin is highly beneficial for some patients. Of the 11 patients for whom caregivers thought there was a significant difference between treatments, 8 reported improvement when receiving melatonin ($P < .05$). The parental reports of clinical benefit described subjective improvements in sleep initiation and maintenance, with parents also thinking there were concomitant improvements in cognitive function and quality of life.

The effect of melatonin on sleep latency would have been an interesting and valuable outcome measure, and we had planned to estimate this using the light sensor on the actigraphy bracelet. Unfortunately, this was not possible for practical reasons because many of the patients with Dravet syndrome had to have their bracelets secured with tape or under wristbands or sleeves for behavioral reasons, obscuring the light sensor. On the basis of parental report, sleep latency considerably improved in some patients, but we could not prove this with quantitative data.

From a safety perspective, although no significant adverse effects were reported by caregivers, one patient had a measured serum valproate level in the toxic range while on melatonin. Though this is only a single case, the finding emphasizes that clinicians should consider potential interactions

with melatonin and antiepileptic drugs. In vitro data indicate melatonin is metabolized by cytochrome P450 enzymes, primarily CYP1A2, CYP1A1, and CYP2C19, and may inhibit these and other enzymes.[18] These are potentially relevant properties for young epilepsy populations, as some patients with Dravet syndrome are on antiepileptic medications partially metabolized by CYP2C19 (eg, phenytoin, phenobarbital, primidone), serum levels of which could be affected with introduction of melatonin. In addition, although melatonin does not affect serum levels of another anti-epileptic drug, carbamazepine, both antiseizure activity and side effects appear to be potentiated when the two medications are combined.[19] A final issue related to metabolism is that many people with epilepsy have comorbid mood issues treated with antidepressants, which may be metabolized by a variety of cytochrome P450 enzymes including CYP2C19 and CYP1A1. There is at least one report of an individual on a regimen of antidepressants who experienced severe sedation when melatonin was added.[16]

Although our double-blind trial did not find a significant difference in total sleep time, the overall impression from parental report was that melatonin is very beneficial in some patients. The negative outcome of our trial likely relates to a few issues. First, total sleep was likely not the optimal parameter choice for our primary outcome measure, given that individuals with Dravet syndrome on placebo had greater total sleep than healthy individuals in the control group. Second, recruitment was challenging because of multiple factors including long travel distances to our clinic, and that many patients were already receiving melatonin. This meant that our findings were underpowered, and a larger cohort size may have delivered more definitive findings.

Nevertheless, parental reports of improvement were dramatic and more likely on melatonin than placebo. It may be that these improvements relate to both the quality and timing of sleep, which we did not examine in a quantitative manner. The likely benefits include more rapid sleep initiation and enhanced sleep maintenance, leading to improved cognitive function and, importantly for families, improved quality of life for both parents and caregivers. Sleep is a critical modifiable comorbidity for people with epilepsy, especially those with the severe developmental and epileptic encephalopathies. Sleep deserves consideration at each clinical appointment because optimal management can be life-changing for both the patient and his or her family.

CONCLUSIONS

This study did not show significant differences in the primary outcome measure, total sleep, or any of the secondary outcome measures, when patients with Dravet syndrome were receiving melatonin versus placebo. However, the data also indicate that melatonin is a safe therapy for patients with Dravet syndrome and sleep disturbance, and elicits marked clinical improvement in a subset. The underlying nature of sleep disturbance in Dravet syndrome is complex, and may involve the combined effects of nocturnal seizures, antiepileptic drug effects, and inherent cerebral dysfunction related to *SCN1A* mutation.

ABBREVIATIONS

QOLCE-55 = Quality of Life in Children with Epilepsy 55
SDSC = Sleep Disturbance Scale For Children
WASO = wakefulness after sleep onset

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DISCLOSURE STATEMENT

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