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ORIGINAL ARTICLE

In-field assessment of sodium oxybate effect in pediatric type 1 narcolepsy: an actigraphic study

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Abstract

Study Objectives: Sodium oxybate (SXB) is a GABAergic agent widely used as off-label treatment in pediatric type 1 narcolepsy (NT1). Here, we aimed at analyzing by wrist actigraphy the sleep/wake profile of NT1 children and adolescents in drug-naïve condition and after 1 year of SXB treatment. As secondary aim, we investigated changes on sleepiness, cataplexy, and children's anthropometric profile after 1 year of SXB treatment.

Methods: Twenty-four drug-naïve NT1 children underwent 7 days of actigraphy during the school week. Information on sleepiness, narcolepsy symptoms, and anthropometric features were collected during the same week with questionnaires and semistructured clinical interview. Children started SXB treatment and underwent a second evaluation encompassing actigraphy, clinical interview, questionnaires, and anthropometric assessment after 1 year of stable treatment.

Results: Actigraphy effectively documented an improvement of nocturnal sleep quality and duration coupled with a reduction of diurnal total sleep time, nap frequency, and duration at 1 year follow-up. Reduction of sleepiness, cataplexy frequency and severity, and weight loss, mainly in obese and overweight NT1 children, were also observed at the 1 year follow-up.

Conclusions: Actigraphy objectively documented changes in nocturnal sleep quality and diurnal napping behavior after 1 year of SXB treatment, thus representing a valid approach to ecologically assess SXB treatment effect on NT1 children's sleep/wake profile. NT1 symptoms severity and children's anthropometric features also changed as expected. Actigraphy offers the possibility to longitudinally follow up children and has potential to become a key tool to tailor treatment in pediatric patients.

Statement of Significance

Sodium oxybate (SXB) is a drug that currently displays a major role in the off-label treatment of pediatric type 1 narcolepsy (NT1) due to its effect on multiple symptoms simultaneously. Nonetheless, periodic follow-ups are required for optimal disease management, which so far have been conducted almost exclusively through subjective assessments. We showed, for the first time, that actigraphy could be a valid method for in-field assessment of SXB effect, as it depicts changes in NT1 children's sleep/wake profile consistent with those documented by sleep-laboratory tests in adult patients. Additionally, our study confirms that SXB treatment is associated with a reduction of sleepiness and cataplexy severity and significant weight loss in obese or overweight children.

Key words: type 1 narcolepsy; children; actigraphy; sodium oxybate; cataplexy; weight loss

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Introduction

Pediatric type 1 narcolepsy (NT1) is a chronic neurological disorder caused by the loss of the hypothalamic hypocretinergic neurons mirrored by low/undetectable levels of the neuropeptide hypocretin-1 in the cerebrospinal fluid (CSF Hcrt-1) [1, 2].

The loss of hypocretinergic signaling causes the inability to sustain wakefulness for long periods and daily episodes of undelayable sleep (excessive daytime sleepiness) [1], as well as the inability to maintain an uninterrupted nocturnal sleep (disrupted nocturnal sleep) [3], resulting in the loss of the boundaries between sleep and wake. Manifestations of full-blown or dissociated rapid eye movement (REM) sleep during wakefulness (sleep onset REM periods—SOREMPs, cataplexy, sleep paralysis, hypnagogic/hypnopompic hallucinations) complete the clinical pictures of NT1 [4].

NT1 most often arises during childhood or adolescence [5]. Currently, the pharmacological treatment of pediatric NT1 is based on off-label drugs [6], some of these registered to treat NT1 symptoms in adult patients [7–9]. Sodium oxybate (SXB) is a powerful GABAergic compound that affects multiple NT1 symptoms simultaneously (i.e. diurnal hypersomnolence, cataplexy, and disrupted nighttime sleep) [10] and has been approved by the US Food and Drug Administration and the European Medicine Agency. Several studies confirmed SXB effects in NT1 children, showing a safety profile comparable to that reported for adults [10–13]. Hence, SXB is increasingly being used as an off-label treatment in pediatric NT1, often associated with behavioral therapy (i.e. scheduled naps) [14].

SXB treatment in NT1 children and adolescents requires a tailored titration and, possibly, periodic objective assessment through nocturnal video-polysomnography and maintenance of wakefulness test as in adults. However, these expensive and time-demanding approaches can be difficult to perform on children and may not accurately inform on how children manage sleep and sleepiness in everyday life [15, 16].

Recently, several studies have successfully applied actigraphy in the clinical work-up of adult and pediatric NT1 [17–19].

Actigraphy is a wearable technology that allows the indirect assessment of sleep in the participant's natural environment and has been widely used to assess drug-induced changes in sleep/wake and motor activity profile [20]. In the field of NT1, actigraphy proved reliable in assessing wake-promoting medication effects and has been proposed as an alternative to polysomnography to assess SXB effects in adult patients [21, 22].

The present study aims were as follows: (1) to explore whether at-home actigraphy can represent a valid method to objectively assess SXB effects on NT1 children's sleep/wake profile and (2) to assess changes associated with 1 year of SXB treatment on sleepiness, cataplexy, NT1-associated symptoms (sleep paralyses, hypnagogic/hypnopompic hallucinations, and nightmares), and children's anthropometric profile.

Methods

Participants

The study included 24 participants (13 males) aged <18 years (mean age: 12.20 ± 2.95 years, range: 7.10–17.03) with a final diagnosis of NT1 based on clinical history, neurophysiological (24 hr continuous PSG monitoring and multiple sleep latency test—MSLT) and biochemical (Hcrt-1) findings, according to the International Classification of Sleep Disorders, 3rd Edition (ICSD-3) criteria [1].

All children were drug-naïve at the time of evaluation and underwent our standardized diagnostic protocol, encompassing at least 7 days of at-home actigraphy before diagnostic hospitalization [17, 23]. Baseline actigraphic data from 12 NT1 patients from the present cohort were previously published in a study investigating the features of the circadian motor activity profile in pediatric NT1 [19].

All children had video-documented cataplexy [24], carried the human leukocyte antigen (HLA) DQB1*06:02, and displayed low (≤110 pg/mL) or undetectable CSF Hcrt-1 levels (lumbar puncture not performed in two children with in-laboratory documented cataplexy). Children and their relatives provided written informed consent. The study was approved by the Local Health Trust's Ethics Committee (Comitato Etico Interaziendale Bologna-Imola, CE-BI, Prot. Num. 17009).

Procedures

Children and a family member attended an educational session on SXB conducted by a sleep specialist (G.P. or F.P.), and on this occasion children completed questionnaires and underwent a semistructured clinical interview on cataplexy and NT1-associated symptoms. Anthropometric features (height, weight, and BMI) were collected by using a portable stadiometer (Harpenden Portable Stadiometer). Height, weight, and BMI z-score (BMI adjusted for sex and age) were calculated for all patients [25]. Underweight was defined as BMI < 5th percentile, normal weight as BMI > 5th and < 85th percentile, overweight between 85th and 95th percentile, and obesity as BMI > 95th percentile [26].

Patients started treatment with a dose of 1 + 1 g taken at bedtime and 3.5 hr away. SXB titration was made on the basis of weekly telephonic contacts between the children's relatives and the prescribing physician, and personalized until reaching an "optimal" dose (i.e. the dose that displayed the best balance between efficacy and tolerability). Detailed SXB dosing regimen for each patient is reported in Supplementary Table S1. Children were routinely followed up every 3 months through outpatient clinical evaluation and after 1 year of SXB treatment underwent a second evaluation comprising at-home actigraphy, questionnaires, semistructured clinical interview, and anthropometric assessment.

Actigraphy

Patients wore the Micro Motionlogger Watch actigraph (Ambulatory Monitoring, Inc., Ardsley, NY), consisting in a triaxial accelerometer with case temperature and environment light sensors, at the nondominant wrist. Devices were initialized in zero-crossing mode to quantify motor activity exceeding 0.01 *g* at a sampling frequency of 32 Hz, changes in acceleration were integrated and expressed in 1 min epochs, and sleep and wake epochs were estimated by using the validated algorithms developed by Sadeh [27].

Children were monitored during the school week and during the same season at both baseline and follow-up evaluations to minimize environmental influences; children were asked to

wear the device continuously across 24 hr, except when taking bath/shower, and to maintain their habitual sleep/wake schedule during the recording. In parallel, they had to fill in a daily sleep diary and mark time in and out of bed and diurnal naps by pressing the event-marker button on the device. At the 1 year follow-up evaluation, we also asked children to mark the moment when they took the first and the second dose of SXB by pressing the event-marker button.

Parents were asked to assist children in completing the sleep diary and with the event-marker procedure, if necessary. Combining event-marked points and sleep diary information (if children omitted to push the event-marker), an experienced scorer identified the major nocturnal sleep period and the diurnal sleep episodes. Actigraphic recordings were split into nighttime and daytime periods based on individual bedtime and wake time, and mean actigraphic parameters were computed over 7 days in all participants for baseline and 1 year follow-up evaluations.

As previously reported [19], we considered the following actigraphic parameters: bedtime, wake time, midpoint, time in bed (TIB), estimated total sleep time (*e*TST), estimated wake after sleep onset (*e*WASO), estimated sleep efficiency, estimated nocturnal awakenings frequency, estimated prolonged (lasting more than 5 min) nocturnal awakenings frequency, estimated longest sleep (longest continuous episode scored as sleep), sleep motor activity (SMA), daytime motor activity (DMA), estimated daytime total sleep time (*e*DTST), estimated nap frequency (with a nap defined as an interval of at least 10 min up to 3 hr scored as sleep, preceded and followed by a period of at least 30 min scored as wake), estimated mean nap duration, and 24 hr estimated total sleep time (*e*24hTST—sum, in minutes, of all epochs scored as sleep in both nighttime and daytime periods). Finally, we carried out a nap analysis by dividing the daytime period into three segments (8:00–13:00, 13:00–18:00, and 18:00–22:00) and computing nap frequency and mean nap duration for each segment.

Questionnaires and semistructured interview

At baseline and at 1 year follow-up evaluations, children underwent a semistructured interview and completed the Epworth Sleepiness scale for children and adolescents (ESS-CHAD) [28], and the Italian version of the reduced Morningness–Eveningness questionnaire for children and adolescents (rMEQ-CA) [29].

The semistructured interview lasted 30–45 min and investigated cataplexy features, presence of NT1-associated symptoms, and occurrence of nocturnal enuresis and sleepwalking. Parents were present and authorized to assist the children in providing answers if needed.

The following cataplexy features were explored: frequency of cataplectic attack, expressed on a 5-point Likert scale (1: ≥1/day; 2: ≥1/week; 3: ≥1/month; 4: ≥1/in 3 months; 5: ≥1/in 6 months); cataplectic attack duration (1: ≤10 s; 2: from 30 to 60 s; 3: from 60 to 120 s), body-involvement during cataplectic attacks (partial: momentary weakness without postural dyscontrol; generalized: momentary weakness with fall to the ground), and questions (dichotomous) on the presence of falls to the ground and of "cataplectic status/facies" (long-lasting, continuous/subcontinuous, cataplectic attack with prominent facial involvement) [30].

Presence or absence of the following NT1 associated symptoms was explored: sleep paralysis, hypnagogic/hypnopompic hallucinations, automatic behaviors, and nightmares [31].

Statistical analysis

Data were explored with descriptive statistics (mean ± *SD* and frequency). To assess whether statistically significant changes occurred from baseline to 1 year follow-up in questionnaire scores, anthropometric features, and actigraphic parameters, the Student's *t*-test for paired-samples was performed; in case of statistically significant results, the effect size (Cohen's *d*) was computed. Differences from baseline to 1 year follow-up evaluation in chronotype and BMI category distribution were explored by means of the McNemar test. Regarding the semistructured interview data, we carried out the Wilcoxon signed-rank test for variables expressed on ordinal scale and the McNemar test for categorical variables. *p*-Values below 0.05 were considered statistically significant. All statistical analyses were conducted using IBM SPSS Statistics 19 software (SPSS, Inc., Chicago, IL).

Results

Actigraphic data at baseline and 1 year follow-up

Actigraphic parameters at baseline and 1 year follow-up are reported in Table 1. At 1 year follow-up, children woke up earlier and displayed a significant reduction of TIB, whereas no differences emerged in bedtime and midpoint of sleep. All nighttime actigraphic parameters showed significant changes from baseline to 1 year follow-up, with NT1 children displaying increased *e*TST and estimated sleep efficiency, reduced time spent in *e*WASO and SMA levels, decreased frequency of both brief and prolonged awakenings, and increased duration of the longest estimated nocturnal sleep. Regarding daytime period, at 1 year follow-up, NT1 children spent less time sleeping (*e*DTST) and took fewer and shorter naps, whereas DMA levels did not significantly change from baseline.

Despite a slight increase at 1 year follow-up, no significant differences emerged in the total amount of time spent sleeping across 24 hr (*e*24hTST). Finally, children napping behavior displayed significant changes at 1 year follow-up, with a reduction in mean afternoon (13:00–18:00) nap duration and in evening (18:00–20:00) nap frequency; no further significant differences emerged.

Clinical and anthropometric data at baseline and 1 year follow-up

At baseline, 66 per cent of children were overweight or obese (33% obese and 33% overweight, respectively).

Demographics, clinical, anthropometric data and questionnaire scores at baseline, and 1 year follow-up are reported in Table 2. Significant changes from baseline to 1 year follow-up were observed in ESS-CHAD score but not in rMEQ-CA score, nor in chronotype distribution. Significant changes were observed in BMI, BMI and weight z-scores, and in the BMI category distribution with five (21%) overweight children at baseline, presenting with a BMI within the normal range at 1 year follow-up, three (13%) obese children at baseline presenting with a BMI within the overweight range at 1 year follow-up, and one (4%) obese patient at baseline presenting with a BMI within the normal range at 1 year follow-up.

Data of the semistructured interview are reported in Table 3. SXB treatment was associated with a significant reduction of

Table 1. Actigraphic nighttime, daytime, sleep timing, and napping behavior data of NT1 children at baseline and 1 year follow-up

	Drug-naïve NT1 children (n = 24) Mean ± SD	After SXB NT1 children (n = 24) Mean ± SD	P	ES
Sleep timing				
Bedtime	23:13 ± 01:09	23:16 ± 00:32	ns	
Wake time	08:01 ± 01:19	07:06 ± 00:38	<0.001	0.76
Midpoint	03:37 ± 01:09	03:10 ± 00:29	ns	
TIB, min	526.61 ± 55.24	470.77 ± 39.95	<0.0001	1.10
Nighttime period				
*e*TST, min	330.80 ± 53.77	373.97 ± 51	<0.001	–0.81
*e*Sleep efficiency	62.91 ± 8.89	79.65 ± 8.90	<0.0001	–1.61
*e*WASO, min	179.69 ± 48.83	81.61 ± 41.19	<0.0001	1.78
*e*Awakenings, *n*	32.88 ± 8.15	16.83 ± 4.08	<0.0001	2.44
*e*Prolonged awakenings, *n*	10.08 ± 2.57	5.17 ± 1.97	<0.0001	1.98
SMA, counts	33.69 ± 12.47	18.69 ± 7.34	<0.0001	1.15
*e*Longest sleep, min	64.27 ± 12.51	128.43 ± 31.46	<0.0001	–2.67
Daytime period				
DMA, counts	202.15 ± 22.47	198.63 ± 19.32	ns	
*e*DTST, min	67.90 ± 26.95	42.79 ± 18.24	<0.0001	1.01
*e*Nap, *n*	8.13 ± 3.42	6.46 ± 2.64	<0.05	0.43
*e*NapD, min	51.85 ± 13.05	36.94 ± 12.89	<0.001	0.79
*e*24hTST, min	398.71 ± 59.95	416.76 ± 48.57	ns	
Nap analysis				
Morning *e*Nap, *n*	2.38 ± 1.93	1.56 ± 2.22	ns	
Morning *e*NapD, min	24.99 ± 10.32	31.10 ± 9.57	ns	
Afternoon *e*Nap, *n*	5 ± 1.60	4.23 ± 1.77	ns	
Afternoon *e*NapD, min	58.45 ± 18.52	36.82 ± 14.55	<0.0001	1.08
Evening *e*Nap, *n*	2.56 ± 1.75	1.25 ± 1.39	<0.05	0.45
Evening *e*NapD, min	48.30 ± 12.26	44.88 ± 18.26	ns	

NT1 = type 1 narcolepsy; SXB = sodium oxybate; ES = Cohen's *d*; TIB = time in bed; *e*TST = estimated total sleep time; *e*WASO = estimated wake after sleep onset; SMA = mean activity counts during TIB; DMA = mean activity counts during daytime; *e*DTST = estimated daytime total sleep time; *e*NapD = mean nap duration; *e*24hTST = sum of all epoch scored as sleep in both nighttime and daytime periods.

cataplexy frequency and changes in its features, with predominantly partial body-involvement during attacks, decreased occurrence of falls to the ground and of spontaneous cataplectic status/facies, whereas typical cataplexy duration was unchanged. SXB treatment was associated with decreased occurrence of automatic behaviors and nightmares, whereas no significant effect was observed on sleep paralysis, hallucinations, and sleepwalking. Finally, SXB treatment was associated with increased occurrence of nocturnal enuresis.

Discussion

This study is the first that evaluated SXB effect in pediatric NT1 patients by means of in-field actigraphy.

Our actigraphic findings are comparable with previous PSG studies on adult NT1 in showing that SXB treatment is associated with a significant improvement in nocturnal sleep continuity (decreased *e*WASO and awakenings frequency, increased sleep efficiency, and estimated longest nocturnal sleep duration) and duration (increased *e*TST) [9, 32]. The lack of neurophysiological studies investigating SXB-induced changes on NT1 children diurnal profile precludes the possibility to directly compare our in-field findings with literature data. Our results documented that SXB treatment is associated with a reduction in time spent asleep during daytime without any effect on DMA levels. Nap analysis further characterized SXB-induced changes on NT1 children daytime behavior, disclosing a decrease in mean afternoon nap duration and in evening nap frequency, with the latter most likely reflecting the enhancement of homeostatic process.

NT1 children were assessed during school week and analogous season at both baseline and 1 year follow-up evaluations; this strengthens our results inasmuch minimize possible variations in sleep duration, timing of circadian phase, and daytime behavior related to seasonal changes.

Changes in NT1 children's actigraphic sleep/wake profile associated with SXB treatment were paralleled by changes in sleepiness, cataplexy, and anthropometric features. Indeed, SXB treatment was associated with a reduction of subjective sleepiness level, automatic behaviors, and of cataplexy frequency and severity.

We also confirmed the overrepresentation of obesity (33.3%) and overweight (33.3%) among drug-naïve NT1 children [33–35], compared with the general Italian population (obesity 9.8% and overweight 20.9%, respectively) [36]. Moreover, our results confirm that 1 year of SXB treatment is associated with a significant weight loss in obese and overweight children, without affecting the anthropometric profile of normal-weight NT1 children [35].

Since DMA levels did not significantly change from baseline to 1 year follow-up, weight reduction can likely be ascribed to different SXB-induced changes such as the stimulation of lipolysis or the restoration of slow-wave sleep, rather than to changes in daytime behavior [32, 37].

Treatment with SXB was not associated with decreased occurrence of sleep paralysis and hypnagogic/hypnopompic hallucinations, but with a reduced occurrence of nightmares: in this regard, previous studies highlighted an increased frequency of nightmares in NT1 that can prove very burdensome in adult patients and reasonably even more in children [31].

Table 2. Demographic, clinical, and anthropometric data of NT1 children at baseline and 1 year follow-up

	Drug-naïve NT1 children (*n* = 24)	After SXB NT1 children (*n* = 24)		
	Mean ± *SD*	Mean ± *SD*	*P*	ES
Male/female	13/11			
Age at NT1 onset, years	9.09 ± 3.03			
Age at observation, years	12.20 ± 2.95	13.19 ± 2.98		
Diagnostic delay, years	3.10 ± 3.21 range 0.02–11.10			
MSLT-sl, min	3.35 ± 2.89	n/a		
SOREMP, *n*	4.54 ± 0.78	n/a		
CSF Hcrt-1, pg/mL (*n* = 22)	14.7 ± 17.21 range 0–44.6	n/a		
HLA DQB1*0602 positivity	24/24			
Height, cm	1.56 ± 0.16	1.61 ± 0.15		
Weight, kg	65.58 ± 24.70	60.90 ± 20.78		
BMI	26.17 ± 7.14	23.08 ± 5.43	<0.0001	1.00
Height z-score	0.55 ± 1.09	0.66 ± 1.03	*ns*	
Weight z-score	1.46 ± 1.23	0.82 ± 1.33	<0.0001	1.05
BMI z-score	1.38 ± 1.12	0.59 ± 1.33	<0.0001	1.24
BMI category (underweight|normal|over|obese)	0|8|8|8	0|14|6|4	0.029†	
Questionnaire				
ESS-CHAD	15.71 ± 2.56	10.29 ± 3.52	<0.0001	1.33
rMEQ-CA	15.17 ± 3.97	16 ± 3.08	*ns*	
Chronotype (*m*|*i*|*e*)	7|13|4	7|16|1	*ns*†	

NT1 = type 1 narcolepsy; SXB = sodium oxybate; ES = Cohen's *d*; MSLT-sl = mean sleep latency at MSLT; SOREMPs = sleep-onset REM periods at MSLT; CSF Hcrt-1 = cerebrospinal fluid hypocretin-1; BMI = body mass index; ESS-CHAD = Epworth sleepiness scale for children and adolescent; rMEQ-CA = reduced Morningness–Eveningness questionnaire for children and adolescent; Chronotype (*m* = morning type; *i* = intermediate type; *e* = evening type). †McNemar's test.

In our sample, SXB treatment did not turn out to be associated with increased occurrence of sleepwalking, but we confirm an association with nocturnal enuresis (up to 25% of children with at least one episode) [10, 12].

In our study, treatment compliance was excellent: SXB was overall well tolerated by NT1 children and, apart from nocturnal enuresis, the most commonly reported side effect was irritability which, however, was not deemed burdensome enough (by the physician and/or children/parents) to withdraw treatment.

Although SXB proved effective in all evaluated NT1 children, with an outstanding reduction of sleepiness and cataplexy and a major impact on children's sleep/wake profile, a significant portion of our sample (50%) still presented with an ESS-CHAD score of >10 (a validated cutoff) at 1 year follow-up [38], and all children had daily long-lasting naps in the early afternoon, though with shorter duration compared with baseline. These results highlight two common issues in pediatric NT1 management: first, in up to 50 per cent of NT1 children SXB monotherapy is not sufficient to flatten hypersomnolence to nonpathological levels. In these cases, the co-administration of wake-promoting drugs has been shown to be overall well tolerated and more efficacious than each drug alone [39]. Second, although during both the SXB educational

Table 3. Semistructured interview data at baseline and at 1 year follow-up

		Drug-naïve NT1 children (*n* = 24)	After SXB NT1 children (*n* = 24)	*P*
Cataplexy frequency, (%)	≥ 1/day	83.3	8.3	<0.0001†
	≥ 1/week	12.5	41.7	
	≥ 1/month	4.2	25.0	
	≥ 1/in 3 months	0	8.3	
	≥ 1/in 6 months	0	16.7	
Cataplexy duration, (%)	< 10 s	79.2	95.8	*ns*†
	30 to 60 s	16.7	4.2	
	60 to 120 s	4.2	0	
Cataplectic facies/status, affected (%)		62.5	16.7	<0.001‡
Partial/Generalized cataplexy, presence (%)		20.8/79.2	95.8/4.2	<0.0001‡
Falls to the ground, presence (%)		70.80	4.2	<0.0001‡
Automatic behaviors, affected (%)		79.2	29.2	<0.0001‡
Sleep Paralyses, affected (%)		33.3	12.5	*ns*‡
Hallucinations, affected (%)		41.7	20.8	*ns*‡
Sleepwalking, affected (%)		8.3	12.5	*ns*‡
Nocturnal enuresis, affected (%)		0	25	<0.05‡
Nightmare, affected (%)		45.8	20.8	<0.05‡

NT1 = type 1 narcolepsy; SXB = sodium oxybate.
†Wilcoxon signed-rank test; ‡McNemar's test.

session and routine follow-up evaluations children and their parents received general instruction on the diurnal sleep schedule [40], actigraphy documented that the spontaneous establishment of a napping strategy has been rather scarce, with children continuing to display long-lasting sleep episodes in the afternoon, immediately after lunch. Illustrative actigram of a patient at baseline and 1 year follow-up is reported in Supplementary Figure S1. Although behavioral therapy is required for optimal symptom control, our data suggest that NT1 children need to be trained to a regular napping schedule in the framework of a comprehensive educational program. This issue, together with the possible impact of physical activity programs, should be explored by further longitudinal studies in patients with and without treatment.

Some limitations of the present work should be acknowledged. First, SXB effect was assessed by integrating different sources of information (i.e. self-assessment questionnaire and semistructured interviews). Recently, a narcolepsy severity scale has been developed to quantify the main narcolepsy symptoms (cataplexy, hypnagogic/hypnopompic hallucinations, sleep paralysis, and disrupted nighttime sleep) and their changes with treatment in adult NT1 [41]. The authors planned to validate this scale also for NT1 children and adolescent, but unfortunately it was not yet available at the time of our study.

Second, at 1 year follow-up, neurophysiological evaluations were not performed, precluding the possibility of exploring whether changes in the 24 hr activity profile correlated with documented changes in nocturnal sleep dynamics and diurnal sleep propensity.

In conclusion, in this study we show that in-field actigraphy is a valid method to ecologically assess SXB-associated changes on NT1 children's sleep/wake profile. Actigraphy has the potential to become a key tool to tailor treatment in children suffering from this chronic disease; furthermore, the modification of children's sleep/wake profile might be considered a potential outcome measure in controlled pharmacological studies. Further studies are required to explore whether actigraphy can be sufficiently sensitive for assessing effects of pharmacological polytherapy in pediatric NT1.

Supplementary Material

Supplementary material is available at *SLEEP* online.

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Notes

Conflict of interest statement. Dr. Plazzi participated in advisory board for Jazz Pharmaceuticals outside the submitted work. The other authors have no potential financial conflict of interest to disclose. For the sake of clarity and transparency, we specify that Jazz Pharmaceuticals is the manufacturer of Xyrem (sodium oxybate). Marco Filardi, Elena Antelmi, Raffaele Ferri, and Vincenzo Natale have no potential conflicts of interest relevant to this article to disclose; Fabio Pizza reports personal fees from UCB Pharma and Bioprojet, outside the submitted work; and Giuseppe Plazzi participated in advisory board for UCB Pharma, Jazz pharmaceuticals, and Bioprojet, outside the submitted work.

References

1. American Academy of Sleep Medicine. *International Classification of Sleep Disorders*, 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014.
2. Thannickal TC, *et al*. Reduced number of hypocretin neurons in human narcolepsy. *Neuron*. 2000;**27**(3):469–474.
3. Roth T, *et al*. Disrupted nighttime sleep in narcolepsy. *J Clin Sleep Med*. 2013;**9**(9):955–965.
4. Scammell TE. Narcolepsy. *N Engl J Med*. 2015;**373**(27):2654–2662.
5. Thorpy MJ, *et al*. Delayed diagnosis of narcolepsy: characterization and impact. *Sleep Med*. 2014;**15**(5):502–507.
6. Barateau L, *et al*. Management of Narcolepsy. *Curr Treat Options Neurol*. 2016;**18**(10):43.
7. Broughton RJ, *et al*. Randomized, double-blind, placebo-controlled crossover trial of modafinil in the treatment of excessive daytime sleepiness in narcolepsy. *Neurology*. 1997;**49**(2):444–451.
8. Szakacs Z, *et al*.; HARMONY-CTP Study Group. Safety and efficacy of pitolisant on cataplexy in patients with narcolepsy: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol*. 2017;**16**(3):200–207.
9. Boscolo-Berto R, *et al*. Narcolepsy and effectiveness of gamma-hydroxybutyrate (GHB): a systematic review and meta-analysis of randomized controlled trials. *Sleep Med Rev*. 2012;**16**(5):431–443.
10. Aran A, *et al*. Clinical and therapeutic aspects of childhood narcolepsy-cataplexy: a retrospective study of 51 children. *Sleep*. 2010;**33**(11):1457–1464.
11. Murali H, *et al*. Off-label treatment of severe childhood narcolepsy-cataplexy with sodium oxybate. *Sleep*. 2006;**29**(8):1025–1029.
12. Mansukhani MP, *et al*. Sodium oxybate in the treatment of childhood narcolepsy-cataplexy: a retrospective study. *Sleep Med*. 2012;**13**(6):606–610.
13. Wang Y, *et al*. A double-blind, placebo-controlled, randomized-withdrawal, multicenter study on the efficacy and safety of Sodium Oxybate in pediatric subjects with Narcolepsy with Cataplexy. *Ann Neurol*. 2017;**82**:S339–S339.
14. Lecendreux M. Pharmacological management of narcolepsy and cataplexy in pediatric patients. *Paediatr Drugs*. 2014;**16**(5):363–372.
15. Bonnet MH. ACNS clinical controversy: MSLT and MWT have limited clinical utility. *J Clin Neurophysiol*. 2006;**23**(1):50–58.
16. Wise MS. Objective measures of sleepiness and wakefulness: application to the real world? *J Clin Neurophysiol*. 2006;**23**(1):39–49.
17. Filardi M, *et al*. Actigraphic assessment of sleep/wake behavior in central disorders of hypersomnolence. *Sleep Med*. 2015;**16**(1):126–130.
18. Alakuijala A, *et al*. Polysomnographic and actigraphic characteristics of patients with H1N1-vaccine-related and sporadic narcolepsy. *Sleep Med*. 2015;**16**(1):39–44.
19. Filardi M, *et al*. Circadian rest-activity rhythm in pediatric type 1 Narcolepsy. *Sleep*. 2016;**39**(6):1241–1247.
20. Stanley N. Actigraphy in human psychopharmacology: a review. *Hum Psychopharmacol*. 2003;**18**(1):39–49.
21. Bruck D, *et al*. Diurnal actigraphy and stimulant efficacy in narcolepsy. *Hum Psychopharmacol*. 2005;**20**(2):105–113.

22. Poryazova R, *et al*. Sodium oxybate in narcolepsy with cataplexy: Zurich sleep center experience. *Eur Neurol*. 2011;**65**(3):175–182.
23. Pizza F, *et al*. Daytime continuous polysomnography predicts MSLT results in hypersomnias of central origin. *J Sleep Res*. 2013;**22**(1):32–40.
24. Vandi S, *et al*. A standardized test to document cataplexy. *Sleep Med*. 2017 Oct 9. doi:10.1016/j.sleep.2017.08.021.
25. Cacciari E, *et al*. Italian cross-sectional growth charts for height, weight and BMI (2 to 20 yr). *J Endocrinol Invest*. 2006;**29**(7):581–593.
26. Wang Y. Cross-national comparison of childhood obesity: the epidemic and the relationship between obesity and socioeconomic status. *Int J Epidemiol*. 2001;**30**(5):1129–1136.
27. Sadeh A, *et al*. Actigraphic home-monitoring sleep-disturbed and control infants and young children: a new method for pediatric assessment of sleep-wake patterns. *Pediatrics*. 1991;**87**(4):494–499.
28. Wang YG, *et al*. Assessing narcolepsy with cataplexy in children and adolescents: development of a cataplexy diary and the ESS-CHAD. *Nat Sci Sleep*. 2017;**9**:201–211.
29. Tonetti L, *et al*. Measures of circadian preference in childhood and adolescence: a review. *Eur Psychiatry*. 2015;**30**(5):576–582.
30. Serra L, *et al*. Cataplexy features in childhood narcolepsy. *Mov Disord*. 2008;**23**(6):858–865.
31. Pisko J, *et al*. Nightmares in narcolepsy: underinvestigated symptom? *Sleep Med*. 2014;**15**(8):967–972.
32. Black J, *et al*. The nightly use of sodium oxybate is associated with a reduction in nocturnal sleep disruption: a double-blind, placebo-controlled study in patients with narcolepsy. *J Clin Sleep Med*. 2010;**6**(6):596–602.
33. Kotagal S, *et al*. A putative link between childhood narcolepsy and obesity. *Sleep Med*. 2004;**5**(2):147–150.
34. Inocente CO, *et al*. Impact of obesity in children with narcolepsy. *CNS Neurosci Ther*. 2013;**19**(7):521–528.
35. Ponziani V, *et al*. Growing up with type 1 Narcolepsy: its anthropometric and Endocrine features. *J Clin Sleep Med*. 2016;**12**(12):1649–1657.
36. Nardone P, *et al*. Surveillance system OKkio alla SALUTE: 2014 results. 2016;**9**. http://www.iss.it/binary/publ/cont/ONLINE_Okkio.pdf. Accessed September 13, 2017.
37. Donjacour CE, *et al*. Glucose and fat metabolism in narcolepsy and the effect of sodium oxybate: a hyperinsulinemic-euglycemic clamp study. *Sleep*. 2014;**37**(4):795–801.
38. Janssen KC, *et al*. Validation of the epworth sleepiness scale for children and adolescents using rasch analysis. *Sleep Med*. 2017;**33**:30–35.
39. Black J, *et al*. Sodium oxybate improves excessive daytime sleepiness in narcolepsy. *Sleep*. 2006;**29**(7):939–946.
40. Rogers AE, *et al*. A comparison of three different sleep schedules for reducing daytime sleepiness in narcolepsy. *Sleep*. 2001;**24**(4):385–391.
41. Dauvilliers Y, *et al*. Measurement of narcolepsy symptoms: the Narcolepsy severity scale. *Neurology*. 2017;**88**(14):1358–1365.