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RESEARCH ARTICLE

Negative impact of insomnia and daytime sleepiness on quality of life in individuals with the cyclin-dependent kinase-like 5 deficiency disorder

Jenny Downs[1,2] | Peter Jacoby[1] | Jacinta Saldaris[1] | Helen Leonard[1] | Tim Benke[3] | Eric Marsh[4] | Scott Demarest[3]

[1]Telethon Kids Institute, Centre for Child Health Research, The University of Western Australia, Perth, Australia

[2]Curtin School of Allied Health, Curtin University, Perth, Australia

[3]Children's Hospital Colorado, Paediatric Neurology, University of Colorado School of Medicine, Aurora, Colorado, USA

[4]Division of Neurology, Children's Hospital of Philadelphia, School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA

Correspondence
Jenny Downs, Telethon Kids Institute, University of Western Australia, PO Box 855, West Perth, Western Australia 6872, Australia.
Email: jenny.downs@telethonkids.org.au

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Summary

Cyclin-dependent kinase-like 5 (*CDKL5*) gene pathogenic variants result in CDKL5 deficiency disorder (CDD). Early onset intractable epilepsy and severe developmental delays are prominent symptoms of CDD. Comorbid sleep disturbances are a major concerning symptom for families. We aimed to explore the relationship between insomnia, daytime sleepiness, sleep medications and quality of life in children with CDD. Caregivers of 129 children with CDD in the International CDKL5 Disorder Database completed the Quality-of-Life Inventory-Disability (QI-Disability) questionnaire and "Disorders of Maintaining Sleep" (DIMS) and the "Disorders of Excessive Somnolence" (DOES) items of the Sleep Disturbance Scale for Children. Adjusting for covariates, a unit increase in DOES score was associated with reduced quality of life total (coefficient −3.06, 95% confidence interval [CI] 1.35–7.80), physical health (coefficient −7.20, 95% CI −10.64, −3.76) and negative emotions (coefficient −3.90, 95% CI −7.38, −0.42) scores. Adjusting for covariates, a unit increase in DIMS score was associated with reduced negative emotions (coefficient −6.02, 95% CI −10.18, −2.86). Use of sleep medications had small influences on the effect sizes. This study highlights the importance of sleep problems as a determinant of quality of life in children with CDD, consistent with effects observed for other groups of children with intellectual disability. Excessive daytime sleepiness was particularly associated with detrimental effects on quality of life. Further research in optimal behavioural and pharmaceutical management of sleep problems for this population is required.

KEYWORDS
developmental and epileptic encephalopathy, maintaining sleep, sleep disorders, sleep medications, sleepiness

1 | INTRODUCTION

Cyclin-dependent kinase-like 5 (*CDKL5*) deficiency disorder (CDD) is a developmental and epileptic encephalopathy (DEE) caused by pathogenic variants in the *CDKL5* gene. DEEs share common features beyond traditional criteria for intellectual disability or autism spectrum disorder such as treatment-resistant epilepsy, movement disorders, and autonomic dysfunction (Olson et al., 2019). Specifically, CDD is characterised by early infantile onset refractory epilepsy as well as developmental, intellectual, and motor disabilities. Other common features include hypotonia and cortical visual impairment (Brock et al., 2021; Mangatt et al., 2016; Olson et al., 2021).

Many children with an intellectual disability experience problems with initiating and maintaining sleep (insomnia), daytime somnolence (sleepiness), and sleep disordered breathing (Heussler & Hiscock, 2018; Pavlova & Latreille, 2019; Surtees et al., 2018). Sleep problems for individuals with intellectual disability can be more severe and persistent across their lifespan (Richdale & Baker, 2014; Wong et al., 2015). Using the Sleep Disturbance Scale for Children (Bruni et al., 1996), a recent study of 447 children with Down syndrome, Rett syndrome, cerebral palsy or autism and comorbid intellectual disability found that nearly half (47.7%) had abnormal insomnia scores and nearly a quarter (23.3%) had excessive daytime sleepiness scores (Gilbertson et al., 2021). Sleep disturbances also occurs commonly in CDD, identified by nearly 90% of 141 caregivers with a child with CDD aged 4 months to 29 years and who were registered with the International CDKL5 Disorder Database (ICDD) (Mangatt et al., 2016). The most common sleep disturbances included night waking reported for nearly 60% and excess daytime napping for nearly half of individuals with CDD (Mangatt et al., 2016). In a study with four genetically confirmed female patients with *CDKL5* mutations (age range 2–15 years), parents reported sleep disturbances, mainly disorders of initiating sleep, frequent awakenings, and excessive daytime napping, also using the Sleep Disturbance Scale for Children (Hagebeuk et al., 2012). In this small case series, the percentage of rapid eye movement (REM) sleep was low (9.7%–18.3%) and absent in one child (Hagebeuk et al., 2012), suggesting abnormal sleep architecture. In all children, the sleep efficiency was low (range 59%–78%) caused by frequent and long-lasting awakenings (range 7–52 times/night) (Hagebeuk et al., 2012).

Insomnia has negative impacts on the physical and mental health of all children, influencing their behaviour, social competence, and learning (Foley & Weinraub, 2017; Meijer et al., 2000). For adults with autism, sleep problems have been highlighted as important predictors of quality of life (QOL) (Deserno et al., 2019). For children with intellectual disability, insomnia and excessive daytime sleepiness are also associated with poorer QOL (Reddihough et al., 2021), measured with the Quality-of-Life Inventory-Disability (QI-Disability) (Downs et al., 2019). Healthy sleep practices and medications offer some relief for poor sleep in children with intellectual disability (Heussler & Hiscock, 2018) but these interventions often do not solve the problem (Gilbertson et al., 2021; Heussler & Hiscock, 2018). As for other groups of children with intellectual disability, the level of functional abilities and comorbidities influenced QOL in 129 individuals with CDD aged 3–29 years (Leonard et al., 2021). In adjusted regression models, more severe sleep disturbances were associated with lower QOL scores in the "physical health" and "negative emotions" domains of the QI-Disability measure (Leonard et al., 2021). In this study, sleep data were not separated by the type of sleep problem.

In the absence of data, we sought to explore the effects of the most common specific sleep problems of insomnia and sleepiness on QOL in CDD. Further, we evaluated the effect of sleep medications on QOL.

2 | METHODS

2.1 | Data source

The ICDD (Fehr et al., 2015) was the data source for this study. We used data from families who completed a follow-up questionnaire between April 2018 and August 2019 and whose child was aged ≥3 years with a confirmed pathogenic or likely pathogenic *CDKL5* variant.

2.2 | Dependent variable

The parent-report QI-Disability questionnaire is a 32-item parent-report measure assessing the QOL of children with intellectual disability and initial reliability and validity of the instrument has previously been published (Downs et al., 2019; Epstein et al., 2019). The questionnaire comprises six domains: "Social Interaction" (seven items), "Positive Emotions" (four items), "Negative Emotions" (seven items), "Physical Health" (four items), "Leisure and the Outdoors" (five items), and "Independence" (five items). Items were rated on a 5-point Likert scale and caregivers asked to recall observations of their child's well-being and enjoyment of life over the past month. Items were linearly transformed to a scale of 0–100, with higher scores representing better QOL. Domain scores were calculated by averaging item scores and total scores were calculated by averaging domain scores.

2.3 | Primary independent variables

Items from the "Disorders of Maintaining Sleep" (DIMS) and the "Disorders of Excessive Somnolence" (DOES) subscales of the Sleep Disturbance Scale for Children (Bruni et al., 1996) were used to describe sleep problems. All seven items of the DIMS subscale were included in the family questionnaire but only three of the five DOES items were included, because of uncertain appropriateness for parents to assess in children with such a severe disability as CDD (Table 1). Items were rated on a 5-point Likert scale (with higher scores indicating more frequent sleep problems) and average DIMS and DOES subscale scores were calculated for available items.

TABLE 1 Median (range) item scores on 5-point Likert scale for the sleep questionnaire items

Subscale	Item[a]	Median (range)
DIMS[b]	How many hours of sleep does your child get on most nights	2 (1–5)
	How long after going to bed does your child usually fall asleep	2 (1–5)
	The child goes to bed reluctantly	2 (1–5)
	The child has difficulty getting to sleep at night	3 (1–5)
	The child feels anxious of afraid when falling asleep	1 (1–5)
	The child wakes up more than twice per night	3 (1–5)
	After waking up in the night, the child has difficulty to fall asleep again	3 (1–5)
DOES[c]	The child is unusually difficulty to wake in the morning	2 (1–5)
	The child experiences daytime somnolence	3 (1–5)
	The child falls asleep suddenly in inappropriate situations	2 (1–5)

Note: Higher scores indicate more frequent problems.
[a]Sleep Disturbance Scale for Children items. The DOES items: "The child wakes in the morning feeling tired" and "The child feels unable to move when waking up in the morning" were not included in the questionnaire.
[b]DIMS, Disorders of Initiating and Maintaining Sleep subscale.
[c]DOES, Disorders of Excessive Somnolence subscale.

TABLE 2 Characteristics of individuals ($N = 129$) in the study

		N (%)
Age group	<12 years	78 (60.5)
	≥12 years	51 (39.5)
Gender	Female	109 (84.5)
	Male	20 (15.5)
Number of anti-seizure medications[a] ($N = 122$)	0 or 1	32 (26.2)
	2	33 (27.1)
	≥3	57 (46.7)
Respiratory problems	None	81 (62.8)
	Mild	14 (10.9)
	Severe	34 (26.4)
Sleep medications	None	91 (70.5)
	1 or 2	38 (29.5)
Hand function[b]	Grasp large and small objects	41 (32.3)
	Grasp large objects only	50 (39.4)
	No hand function	36 (28.4)
Walking	No assistance required	31 (24.0)
	Some assistance	14 (10.9)
	Unable to walk	84 (65.1)
Mutation type	No functional protein	34 (26.4)
	Missense/in-frame	34 (26.4)
	Truncations after aa172	36 (27.9)
	Truncations after aa781	19 (14.7)
	Mutations not grouped	6 (4.7)
		Mean (SD)
Sleep	DIMS score[c,d]	2.51 (0.77)
	DOES score[c,e]	2.37 (0.85)
Quality of life (scores/100)	Physical health	75.4 (18.7)
	Positive emotions	65.6 (23.1)
	Negative emotions	73.0 (17.9)
	Social interactions	50.1 (26.2)
	Leisure and the outdoors	61.6 (27.4)
	Independence	29.5 (25.2)
	Total	59.3 (16.2)

[a]Seven missing.
[b]Two missing.
[c]Mean item scores are presented.
[d]DIMS, Disorders of Initiating and Maintaining Sleep subscale.
[e]DOES, Disorders of Excessive Somnolence subscale.

2.4 | Confounding variables

The following potential confounding factors were included in the models as categorical variables: age (<12 years, ≥12 years), sex, respiratory problems (no symptoms, mild symptoms, severe symptoms), and the number of anti-seizure medications (0 or 1, 2, ≥3). Hand function (no hand function, ability to hold and pick up large objects only, ability to grasp small objects) and walking ability (walks unaided, assistance required, unable to walk) were indicators of functional ability. Medications that were specifically prescribed for sleep and seizures were identified. The number of sleep medications used was classified as none or any, and the number of seizure medications were classified as 0 or 1, 2, or ≥3.

2.5 | Statistical analysis

DIMS t scores were calculated based on normative data from typically developing children (Bruni et al., 1996). DOES t scores could not be calculated because not all relevant items were included in our dataset. Multivariate linear regression models were used to estimate the effect of sleep disorders (DIMS and DOES) on total and domain QI-Disability scores adjusting for confounding factors. Confounders were introduced in two stages, first: sex, age group, number of anti-seizure medications and respiratory problems, and second: sleep medication and functional abilities were included for additional adjustment. We used full information maximum likelihood (FIML) to account for the small amount of missing data in the confounding variables (Enders, 2001). This method produces similar results to multiple imputation but has many advantages, notably ease of implementation (Allison, 2012). Statistical analyses were performed using Stata 15.1 (StataCorp 2019).

TABLE 3 Sleep and anti-seizure medications prescribed

Sleep medication class	N	Specific sleep medications	N
Melatonin receptor agonists	19	Melatonin	19
Antihypertensive	11	Clonidine	11
Antidepressant	8	Trazodone	6
		Clomipramine	1
		Amitriptyline	1
Benzodiazepine	3	Clorazepate	2
		Nitrazepam	1
Hypnotic	3	Chloral hydrate	3
Antipsychotic	2	Levomepromazine	1
		Chlorprothixene	1
Calcium channel alpha-2 delta ligand	1	Gabapentin	1
Antihistamine	1	Diphenhydramine	1
Anti-seizure medication group	***N***	**Specific anti-seizure medications**	***N***
GABA enhancer	81	Clobazam	29
		Vigabatrin	20
		Clonazepam	11
		Phenobarbital	11
		Diazepam	6
		Clorazepate	4
Sodium channel blocker	66	Topiramate	20
		Lamotrigine	17
		Lacosamide	10
		Rufinamide	8
		Oxcarbazepine	5
		Carbamazepine	4
		Phenytoin	1
		Primidone	1
Poly - Na and Ca	44	Sodium valproate	44
Synaptic vesicle binding (SV2A)	23	Levetiracetam	18
		Brivaracetam	4
		Gabapentin	1
Cannabidiol receptors	13	Cannabidiol	10
		Other	3
Sodium/calcium	12	Zonisamide	12
AMPA receptor blocker	11	Perampanel	11
Poly—Na and NMDA	6	Felbamate	6
Carbonic anhydrase inhibitor	2	Acetazolamide	2
Hormone	1	Prednisolone	1
Other	1	Ataluren	1

Note: GABA, gamma-aminobutyric acid; AMPA, α-amino-3-hydroxy-5-methyl-4- isoxazolepropionic acid; SV2A, synaptic vesicle glycoprotein 2A.

3 | RESULTS

A questionnaire was completed by caregivers of 129 children with CDD aged >3 years. The median age was 10.2 years and 84.5% of the children were female (Table 2). Approximately two-thirds ($n = 84$, 65.1%) of children were unable to walk and 36 (28.4%) had no ability to grasp objects. The median DIMS t score was 72.8 and 52.7% of scores were higher than the threshold of 70 denoting clinical sleep

pathology. One-quarter ($n = 32$, 24.8%) of children were prescribed one sleep medication and six children were prescribed two sleep medications. Melatonin was the most commonly prescribed sleep medication. Approximately one-quarter (26.2%) were prescribed no or one anti-seizure medication, 27.1% two medications, and 46.7% three or more medications. Sodium valproate ($n = 44$), clobazam ($n = 29$) and topiramate ($n = 20$) of the 26 medications were most frequently prescribed. Sleep and anti-seizure medications are presented by the class of medication and specific medication in Table 3.

In the univariate analysis, a unit increase in the modified DOES score was associated with a mean reduction of 8.40 points (95% confidence interval [CI] 4.85–11.95, $p < 0.001$) for the physical-health domain, 4.80 points (95% CI 0.12–9.48, $p = 0.044$) for the positive-emotions and 3.98 points (95% CI 0.37–7.59, $p = 0.031$) for the negative-emotions domain scores, and 4.57 points (95% CI 1.35–7.80, $p = 0.006$) for the total score (Table 4). After adjustment for covariates, coefficients in both models remained reduced for both multivariate models but the effect of increasing DOES scores on the positive-emotions domain score was no longer statistically significant (Table 4).

Univariate analysis indicated that a unit increase in DIMS score was associated with a mean reduction of 7.87 points (95% CI 4.05–11.70, $p < 0.001$) on the negative-emotions domain score. Increased DIMS scores were not significantly associated with other domain scores and there was no clear pattern regarding the direction of effect. Coefficients from both multivariate models were broadly similar (Table 4).

4 | DISCUSSION

This study demonstrates the importance of sleep problems as a determinant of QOL in children with CDD. In our sample, excessive daytime sleepiness was associated with QOL indicated by poorer total and domain scores. Insomnia was associated with significantly lower negative-emotions domain scores. Results were consistent with findings that sleepiness and insomnia were predictors of QOL in 447 children with other intellectual disabilities (Reddihough et al., 2021). Further, sleep medications had only small influences on the effect sizes as also observed for 75 of 447 children with intellectual disability (Gilbertson et al., 2021). This is not necessarily surprising given the cross-sectional nature of the data in the present study and those on sleep medications could well have had worse sleep problems before sleep medication treatment.

Our data indicate that more than half of the individuals with CDD had insomnia scores above the threshold that denotes symptoms suggestive of sleep pathology (Bruni et al., 1996). The prevalence of insomnia in CDD (52.7%) was higher than observed for children with

TABLE 4 Model coefficients[a] with 95% confidence intervals (CIs) describing the association between insomnia, sleepiness, and quality of life

	Insomnia (DIMS)					
	Univariate		Multivariate[b]		Multivariate[c]	
QI-disability domain	Coefficient (95% CI)	p	Coefficient (95% CI)	p	Coefficient (95% CI)	p
Physical health	−3.59 (−7.79, 0.62)	0.094	−1.36 (−5.03, 2.32)	0.470	−1.78 (−5.40, 1.84)	0.335
Positive emotions	1.03 (−4.23, 6.29)	0.699	2.72 (−2.42, 7.87)	0.299	1.44 (−3.39, 6.27)	0.559
Negative emotions	−7.87 (−11.70, −4.05)	<0.001	−7.24 (−10.97, −3.50)	<0.001	−6.52 (−10.18, −2.86)	<0.001
Social interactions	3.56 (−2.36, 9.47)	0.236	5.27 (−0.68, 1.22)	0.083	3.38 (−2.08, 8.84)	0.225
Leisure	2.71 (−3.50, 8.93)	0.389	4.12 (−1.69,9,93)	0.165	1.38 (−3.59, 6.34)	0.586
Independence	−0.25 (−6.02, 5.53)	0.933	−0.04 (−5.85, 5.76)	0.988	−2.49 (−7.10, 2.11)	0.289
Total	−0.66 (−4.33, 3.02)	0.724	0.66 (−2.83, 4.15)	0.711	−0.73 (3.77, 2.30)	0.636
	Sleepiness (DOES)					
	Univariate		Multivariate[b]		Multivariate[c]	
QI-disability domain	Coefficient (95% CI)	p	Coefficient (95% CI)	p	Coefficient (95% CI)	p
Physical health	−8.40 (−11.95, −4.85)	<0.001	−6.75 (−10.21, −3.29)	<0.001	−7.20 (−10.64, −3.76)	<0.001
Positive emotions	−4.80 (−9.48, −0.12)	0.044	−4.40 (−9.25, 0.45)	0.075	−4.09 (−8,68, 0.50)	0.081
Negative emotions	−3.98 (−7.59, −0.37)	0.031	−3.80 (−7.32, −0.28)	0.034	−3.90 (−7.38, −0.42)	0.028
Social interactions	−3.70 (−9.04, 1.63)	0.172	−3.50 (−9.11, 2.11)	0.221	−2.42 (−7.62, 2.77)	0.360
Leisure	−4.29 (−9.87, 1.30)	0.131	−3.88 (−9.36, 1.60)	0.165	−2.30 (−7.02, 2.43)	0.341
Independence	−1.68 (−6.88, 3.52)	0.525	0.14 (−5.34, 5.61)	0.961	1.82 (−2.56, 6.19)	0.416
Total	−4.57 (−7.80, −1.35)	0.006	−3.81 (−7.10, −0.53)	0.023	−3.06 (−5.94, −0.17)	0.038

[a]Coefficients describe the modelled change in QI-Disability score per unit change in sleep score.
[b]Adjusted for sex, other sleep problem, age group, number of anti-seizure medications and respiratory problems.
[c]Further adjustment for functional ability (walking and hand function) and being prescribed sleep medication.

Down syndrome (34.8%) but similar to those with autism spectrum disorder or cerebral palsy and intellectual disability and Rett syndrome (Gilbertson et al., 2021). We confirm that risk of insomnia is a transdiagnostic features of neurodevelopmental disorders (Barone et al., 2019; Heussler & Hiscock, 2018; Kamara & Beauchaine, 2020), including CDD.

Whilst there is not a deep understanding of mechanisms underlying sleep dysfunction in neurodevelopmental disorders (Barone et al., 2019; Kamara & Beauchaine, 2020), observed insomnia could reflect alterations in sleep architecture and circadian rhythm dysfunction (Chan, 2019; Hagebeuk et al., 2012; Kamara & Beauchaine, 2020), other abnormalities in neurobiological structures and functions such as abnormal sleep spindles (Kamara & Beauchaine, 2020) or synaptic function (Barone et al., 2019), or delay in achieving age-appropriate adaptive sleep behaviours (Chan, 2019). Epilepsy and anti-seizure medications, commonplace in CDD, can further disrupt sleep architecture (Chan, 2019; Lo Martire et al., 2017). The neuroimpairments in CDD are usually more severe in males than females, e.g., two-thirds of females and one-third of males learn to sit by 5 years of age (Fehr et al., 2015). We note that the effects of sleep on QOL were similar in the uni- and multivariate analyses, suggesting that the effects of the covariates of age and gender were small. Our sample ranged in age from 3 years to early adulthood, yet age did not have an appreciable effect on the relationship between the sleep and QOL variables.

The effects of excessive daytime sleepiness on QOL were greater than the effects of insomnia, consistent with the findings of Reddihough et al. (2021) in a large sample of children with different causes of intellectual disability. We know that sleep problems are pervasive in neurodevelopmental disorders and intellectual disability, and we would expect to see similar effects on the child's QOL for CDD, as for other disorders. We have previously demonstrated that the domains of QOL in CDD map to the domains of QOL represented in QI-Disability (Tangarorang et al., 2019), and this additional consistency of findings provides further evidence for the validity of QI-Disability as a measure of QOL in CDD.

In our second multivariate model, we additionally adjusted for prescribed sleep medications. We previously reported that use of sleep medications was associated with persistently high effect sizes for the risk of insomnia and sleepiness in children with autism spectrum disorder, cerebral palsy, Rett syndrome and Down syndrome (Gilbertson et al., 2021), as we have also observed in an international sample of children and adults with Rett syndrome (Boban et al., 2018). This cannot provide causal evidence of effectiveness of sleep medications in CDD because the study designs are cross sectional. This more likely indicates that sleep medications are used for those with the most severe sleep dysfunction and if abnormal sleep continues, then the adverse effect on QOL would continue also. We note that melatonin was the most frequently used sleep medication in this group with CDD, which has been associated with some benefits for children with a neuro-disability in a recent systematic review of clinical trials (Parker et al., 2019). However in the present study, sleep problems appeared to be persistent despite use of these medications. There is much to learn regarding the optimal behavioural and pharmaceutical management of sleep problems for CDD.

4.1 | Strengths and limitations

The strengths of the present study related to the large sample size provided by recruitment from an established population database, the ICDD, and the range of characteristics with the sample. The Sleep Disturbance Scale for Children and QI-Disability are well-established measures. We acknowledge some limitations of the study, including the use of proxy-reported data and that there may be differences between parent and child reports (Davis et al., 2007). Whilst self-report is preferable where feasible, parent report in intellectual disability is essential for children with a severe disability such as CDD. The full set of items for DOES were not available in our dataset therefore we could not calculate a t score, which would provide the relevant cut-off for clinical abnormality. Finally, as this is a cross-sectional study design, causality and direction cannot be ascertained from the results, particularly for the relationship between sleep medications and QOL.

5 | CONCLUSION

Disturbances in sleep are commonly experienced by individuals with CDD. This is the first study to report the negative effects of specifically insomnia and daytime sleepiness on their QOL. Excessive daytime sleepiness was associated with lower total and domain scores, and insomnia was associated with significantly lower negative-emotions domain scores. Our findings highlight the importance of monitoring these sleep components amongst patients with CDD. Further research is needed to learn about the optimal behavioural and pharmaceutical management of sleep problems for this population.

AUTHOR CONTRIBUTIONS

Jenny Downs conceptualised and designed the study, contributed to data collection, conducted analyses, drafted, and revised the manuscript and approved the final manuscript as submitted. Peter Jacoby conceptualised and designed the study, conducted analyses, and revised the manuscript and approved the final manuscript as submitted. Jacinta Saldaris drafted and revised the manuscript and approved the final manuscript as submitted. Helen Leonard conceptualised and designed the study, contributed to data collection, revised the manuscript, and approved the final manuscript as submitted. Tim Benke conceptualised and designed the study and revised the manuscript and approved the final manuscript as submitted. Eric Marsh conceptualised and designed the study and revised the manuscript and approved the final manuscript as submitted. Scott Demarest conceptualised and designed the study and revised the manuscript and approved the final manuscript as submitted.

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CONFLICT OF INTERESTS

Jenny Downs: Consultancy for Marinus, Newron, Anavex, GW Pharmaceuticals, AveXis, Ultragenyx and Taysha; Clinical Trials with Newron and Anavex; All remuneration has been made to her department. **Helen Leonard**: Consultancy for Marinus, Newron, Anavex, GW Pharmaceuticals and AveXis; Clinical Trials with Newron and Anavex; All remuneration has been made to her department. **Tim A. Benke**: Consultancy for AveXis, Ovid, GW Pharmaceuticals, International Rett Syndrome Foundation, Takeda, Neurogene, Ultragenyx, Zogenix, GrinTherapeutics, Alcyone and Marinus; Clinical Trials with Acadia, Ovid, GW Pharmaceuticals, Marinus and RSRT; All remuneration has been made to his department. **Eric Marsh**: Consultancy for Stoke therapeutics, Cipla pharmaceuticals. Clinical trials with Acadia, GW pharma, Marinus, RSRT, Biopharm, Stoke therapeutics, Zogenix Pharmaceuticals. **Scott Demarest**: Consultancy for Upsher-Smith, Biomarin and Neurogene, Marinus and Ovid Therapeutics; All remuneration has been made to his department. Each of these disclosures relate to subject matter not contained in this manuscript. **Peter Jacoby** and **Jacinta Saldaris** report no disclosures or conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Jenny Downs https://orcid.org/0000-0001-7358-9037

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