14th International CHARGE Syndrome Conference
Dallas, Texas • August 2-5, 2019

Professional Day **Friday, August 2, 2019**

Investigation of Two Methods for Treating Sleep Problems Among Children with CHARGE Syndrome

Benjamin Kennert, Central Michigan University CHARGE Lab

Presenter Information

Ben Kennert became interested in CHARGE syndrome during his graduate training at Central Michigan University, where he worked in the CHARGE Syndrome Research Lab under Tim Hartshorne. During his doctoral training in school psychology, Ben led or contributed to several research research projects including sleep in CHARGE, quality of life, and cognitive and emotional self-regulation, and worked as a mentor for other graduate and undergraduate students. Ben was a recipient of the Sandra Davenport CHARGE Syndrome Fellowship in 2015, and has presented in the past at the International CHARGE Syndrome Conference and at the Australasian conference. Ben completed his pre-doctoral internship in behavioral pediatrics and integrated primary care at the Munroe-Meyer Institute, and has since worked as a behavioral interventionist and consultant in both Missouri and Michigan. Ben currently resides in Traverse City, MI with his wife, Amber, and two children, Adrian and Lola.

Presentation Abstract

Sleep problems are common among children, especially those with developmental disabilities, visual impairments, and behavioral problems. Among children with CHARGE syndrome, recent research indicates a particularly high prevalence of clinically-relevant sleep problems for this group. This presentation will review a recent study using an explorative survey with parents of children with CHARGE syndrome in order to identify the types of sleep problems and the interventions most commonly used among this population. A follow-up study of two small sample groups of children will then be discussed, during which the treatment utility of two intervention strategies (i.e., melatonin treatment and a behavioral treatment package) were investigated, both separately and combined. Implications for results will be discussed.

Learning Objectives

- Review the types of sleep problems most commonly observed among children with CHARGE syndrome, what is most often done to address those problems, and how effective parents feel these strategies are.
- Discuss factors contributing to sleep problems among children with CHARGE.

INVESTIGATION OF TWO METHODS FOR TREATING SLEEP PROBLEMS AMONG CHILDREN WITH CHARGE SYNDROME

BENJAMIN KENNERT, M.A., DOCTORAL CANDIDATE, CENTRAL MICHIGAN UNIVERSITY

COMMITTEE CHAIR: TIMOTHY HARTSHRONE, PH.D.

COMMITTEE MEMBERS: CARL JOHNSON, PH.D., SANDRA KANOUSE, PH.D.

Research Questions

1. What types of sleep problems are most common among children with CHARGE syndrome, and what is typically done to address these sleep problems?
2. Can a structured treatment package, including positive bedtime routines, partial circadian rhythm management, and differential attention reduce sleeping difficulties for children with CHARGE syndrome related to initiation and maintenance of sleep?
3. Can melatonin treatment reduce sleeping difficulties for children with CHARGE syndrome related to initiation and maintenance of sleep?
4. Will a combination of melatonin treatment and structured treatment package, including positive bedtime routines, partial circadian rhythm management, and differential attention further reduce sleeping difficulties for children with CHARGE syndrome related to initiation and maintenance of sleep than these treatments alone?

Literature Review

- Sleep problems are common among children (~25%), and are even more common among children with:
  - Developmental disabilities
  - Visual impairments
  - Behavior problems
  - Pain
  - Anxiety
  - Poor self-regulation
  - Medication side-effects
  - CHARGE Syndrome
    - Craniofacial features often result in sleep-breathing difficulty
    - Sleep initiation and maintenance difficulties most common

Literature Review

- Sleep problems are important to address, due to association with:
  - Poorer quality of life
  - Poorer daily functioning
  - Missing school or arriving late, and poorer academic performance
  - Child behavior problems
  - Poorer general health
  - Reduced motivation and concentration
  - Poorer working memory
  - Poorer caregiver mental health
    - Depression, marital and familial discord, child abuse

Literature Review

- CHARGE Syndrome:
  - Multisensory impairment caused by genetic alteration on CHD7
  - Diagnosed by genetic testing or by clinical features
  - Major features: Coloboma of the eye; Choanal atresia or stenosis; Cranial nerve anomaly; Characteristic inner, outer, middle ear.
  - Minor features: Genital hypoplasia; Heart malformation; Growth deficiency; Orofacial cleft; Tracheoesophageal fistula; Renal anomalies; Distinctive facial features; Palmar crease; Behavioral profile

Literature Review

- No current research on non-medical treatments for sleep among children with CHARGE Syndrome
- Sleep problems likely to continue into adolescence and adulthood (~50%)
- Current professional recommendations:
  - Sleep hygiene
  - Regular bedtimes and routines
  - Sleep associations at bedtime and security objects present (i.e., stimulus control)

Methodology

- 3 studies:
  - Explorative survey of parents/caregivers
  - 2 single case design studies of treatments, and sleep initiation and maintenance outcomes

Methodology: Study 1

- 30 parents/caregivers of children with CHARGE (age 3-18)
  - Recruited on facebook group (6,400 members, but includes adults with CHARGE, professionals, etc.)
- 36 others completed the survey and were eliminated: incomplete data, completed by individuals with CHARGE, outside age group
- Analyzed using descriptive statistics, and results used to inform studies 2 and 3

Methodology: Study 1

- Survey completed on Survey Monkey
  - CHARGE Syndrome Demographic Questionnaire
  - CHARGE Syndrome Sleep Questionnaire
  - Sleep Disturbance Scale for Children
    - 5 point Likert-type scale
    - Subscales: Disorders of initiating and maintaining sleep; Sleep breathing disorders; Disorders of arousal/nightmares; Sleep wake transition disorders; Disorders of excessive somnolence; Sleep hyperhidrosis

Methodology: Study 2

- Invited to participate on facebook group (same as study 1)
- 3 participants:
  - Irene (10yo): sleep initiation concerns; behavior problems around going to sleep
  - Benny (4yo): sleep initiation concerns; exclusively co-sleeping with parent in a chair;
  - Lee (8yo): sleep initiation concerns
- All children in the past had a confirmed genetic test for CHARGE syndrome

Methodology: Study 2

- Non-concurrent multiple baseline design across participants
- Conditions: Baseline; Structured Treatment Package; Combined Structured Treatment Package and Melatonin (1.5-3 weeks per condition)
- Outcome measure: sleep diary
  - Bedtime, sleep onset, wake time, any nighttime awakenings and naps
  - Also functioned as integrity check for parents
  - Behavior problems around bed and wake times
  - Special circumstances: vacation, illness, etc.
- Social validity scale sent at end of combined treatment condition

Methodology: Study 2

- Parents asked to control for sleep hygiene across conditions
- Visual analysis for total nighttime sleep and sleep onset latency
  - Non-overlap of all pairs to calculate effect size
- Descriptive statistics for bed time, waking time, frequency of nighttime awakenings, duration of nighttime awakenings, frequency of daytime napping, duration of daytime napping, and presence of behavior problems around bedtime and wake times.

Methodology: Study 3

- Invited to participate on facebook group (same as study 1 and 2)
- 3 participants:
  - Mel (11yo): sleep initiation concerns; behavior problems around going to sleep
  - Ruth (12yo): sleep initiation concerns
  - Joe (10yo): sleep initiation concerns; behavior problems around going to sleep
- All children in the past had a confirmed genetic test for CHARGE syndrome

Methodology: Study 3

- Non-concurrent multiple baseline design across participants
- Conditions: Baseline; Melatonin; Combined Structured Treatment Package and Melatonin (1.5-3 weeks per condition)
- Outcome measure: sleep diary
  - Bedtime, sleep onset, wake time, any nighttime awakenings and naps
  - Also functioned as integrity check for parents
  - Behavior problems around bed and wake times
  - Special circumstances: vacation, illness, etc.
- Social validity scale sent at end of combined treatment condition

Methodology: Study 3

- Parents asked to control for sleep hygiene across conditions
- Visual analysis for total nighttime sleep and sleep onset latency
  - Non-overlap of all pairs to calculate effect size
- Descriptive statistics for bed time, waking time, frequency of nighttime awakenings, duration of nighttime awakenings, frequency of daytime napping, duration of daytime napping, and presence of behavior problems around bedtime and wake times.

Table 5. *CHARGE Syndrome Sleep Questionnaire Parent Reported Sleep Problems*

Type of Sleep Problem	**n**	**% of Parents Reporting**
Waking at night	24	80.0%
Not enough sleep	20	66.7%
Falling asleep	20	66.7%
Going to bed	12	40.0%
Difficult behaviors	11	36.7%
Tired after sleeping well	10	33.3%
Sleep breathing	10	33.3%
Waking in the morning	9	30.0%
Sleeps too much	1	3.3%

Table 6. *SDSC Sub-Categories of Sleep Problem Based on Cutoff Score*

Type of Sleep Problem	N	% of Participants
Sleep initiation and maintenance	28	93.3%
Sleep-wake transition problems	20	66.7%
Sleep breathing problems	19	63.3%
Sleep hyperthydrosis	18	60.0%
Excessive somnolence	14	46.7%
Disorders of arousal	5	16.7%

Table 7. *SDSC Reported Average Sleep Onset Latency (SOL)*

Average SOL Duration (Minutes)	**N**	**% of Participants**
Less than 15 minutes	5	16.7%
15-30 minutes	8	26.7%
30-45 minutes	3	10.0%
45-60 minutes	6	20.0%
More than 60 minutes	8	26.7%

Figure 1: SDSC Score Distribution

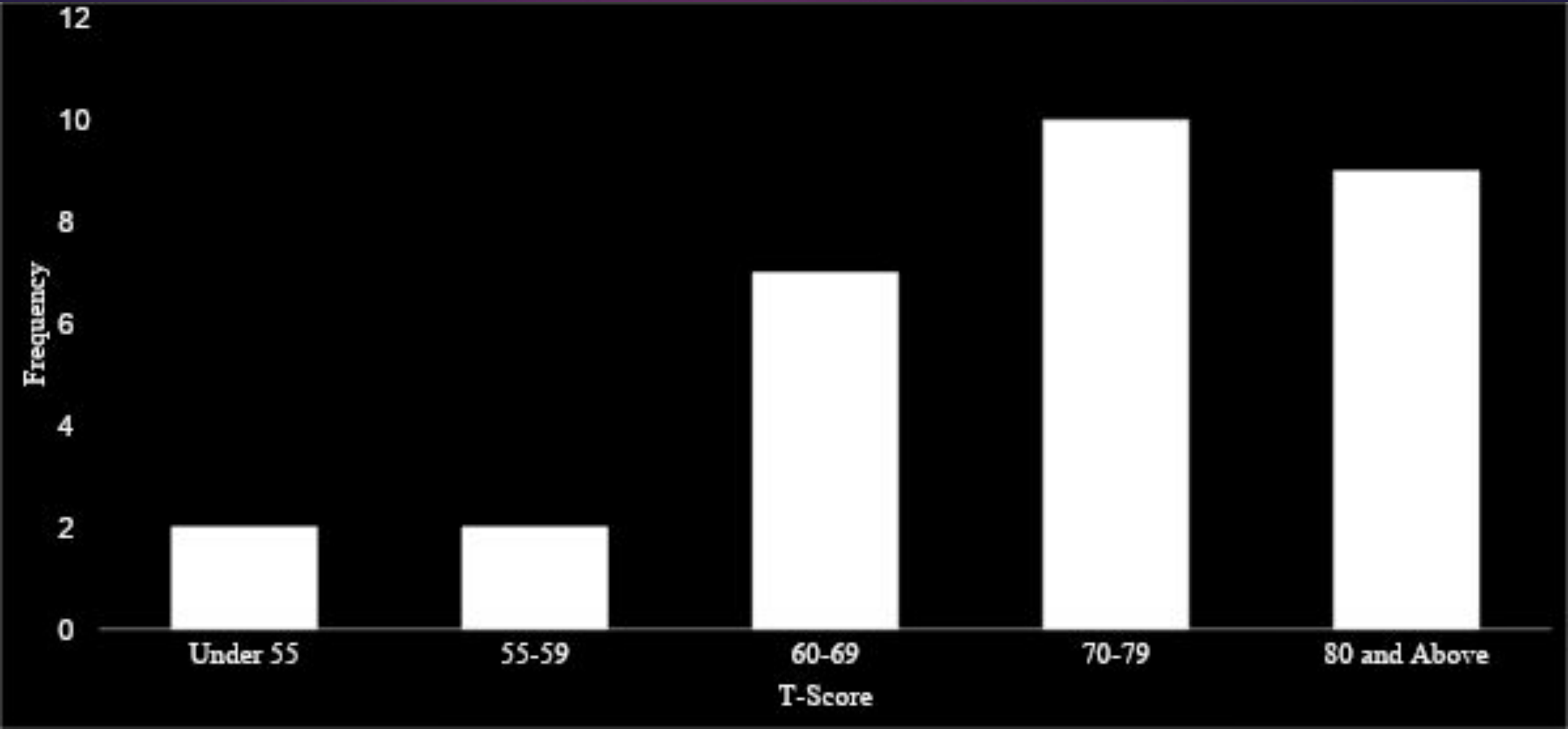


Table 8. *Parent Reported Factors Contributing to Sleep Problems*

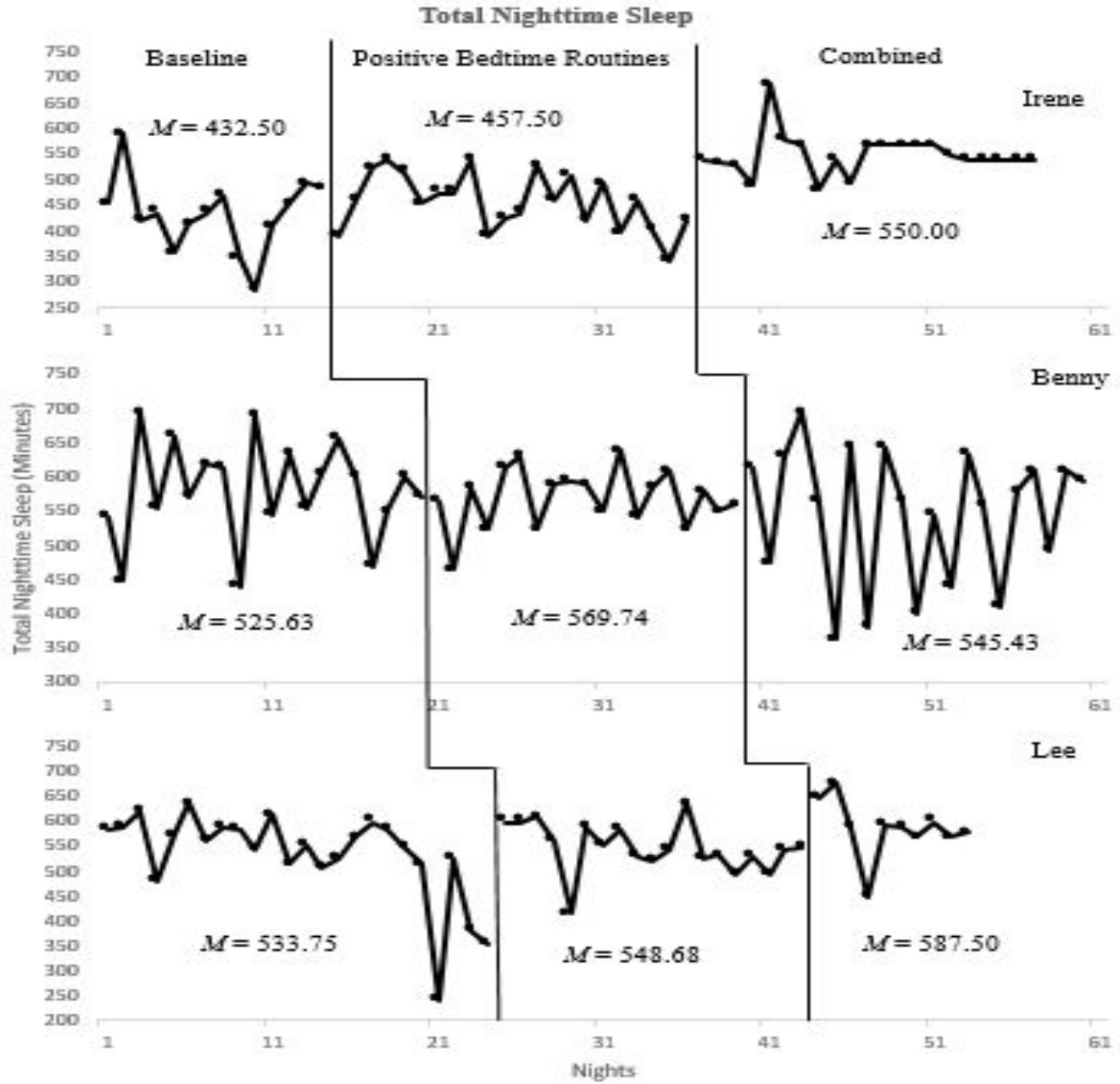
Factor	N	% of Participants
Self-regulation difficulties	13	43.3%
Teeth grinding	13	43.3%
Hormonal imbalance	12	40.0%
Problem behaviors	11	36.7%
Anxiety	11	36.7%
Breathing problems	9	30.0%
Pain	9	30.0%
Temperature regulation	8	26.7%
Muscular problems	6	20.0%
Sleep schedule problems	6	20.0%
Nightmares	0	0.0%
Bedwetting	0	0.0%
Sleep walking	0	0.0%
Night terrors	0	0.0%
Depression	0	0.0%

Table 9. *Parent Reported Intervention Strategies*

Intervention Strategy	N	% of Participants
Positive bedtime routines	19	63.3%
Melatonin treatment	15	50.0%
Weighted blanket	15	50.0%
Prescription medication	10	33.3%
Continuous positive airway pressure (CPAP)	8	26.7%
Over the counter medication	8	26.7%
Visual schedule	6	20.0%
Sleep diary	5	16.7%
Relaxing noise	4	13.3%
Surgery	3	10.0%
Meditation/Yoga/Tai Chi	3	10.0%
Bright light therapy	2	6.7%

Table 10. *Parent Reported Efficacy of Intervention Strategies*

Intervention Strategy	Average Rating	Description
Prescription medication	2.9	Moderately effective
Positive bedtime routine	2.47	Slightly effective
Melatonin treatment	2.33	Slightly effective
Continuous positive airway pressure (CPAP)	2.25	Slightly effective
Over the counter medication	2.25	Slightly effective
Sleep diary	2.2	Slightly effective
Visual schedule	2.17	Slightly effective
Weighted blanket	1.93	Slightly effective


Total Nighttime Sleep
Baseline
Positive Bedtime Routines
Combined
Irene
Benny
Lee
M = 432.50
M = 457.50
M = 550.00
M = 525.63
M = 569.74
M = 545.43
M = 533.75
M = 548.68
M = 587.50
Total Nighttime Sleep (Minutes)
Nights

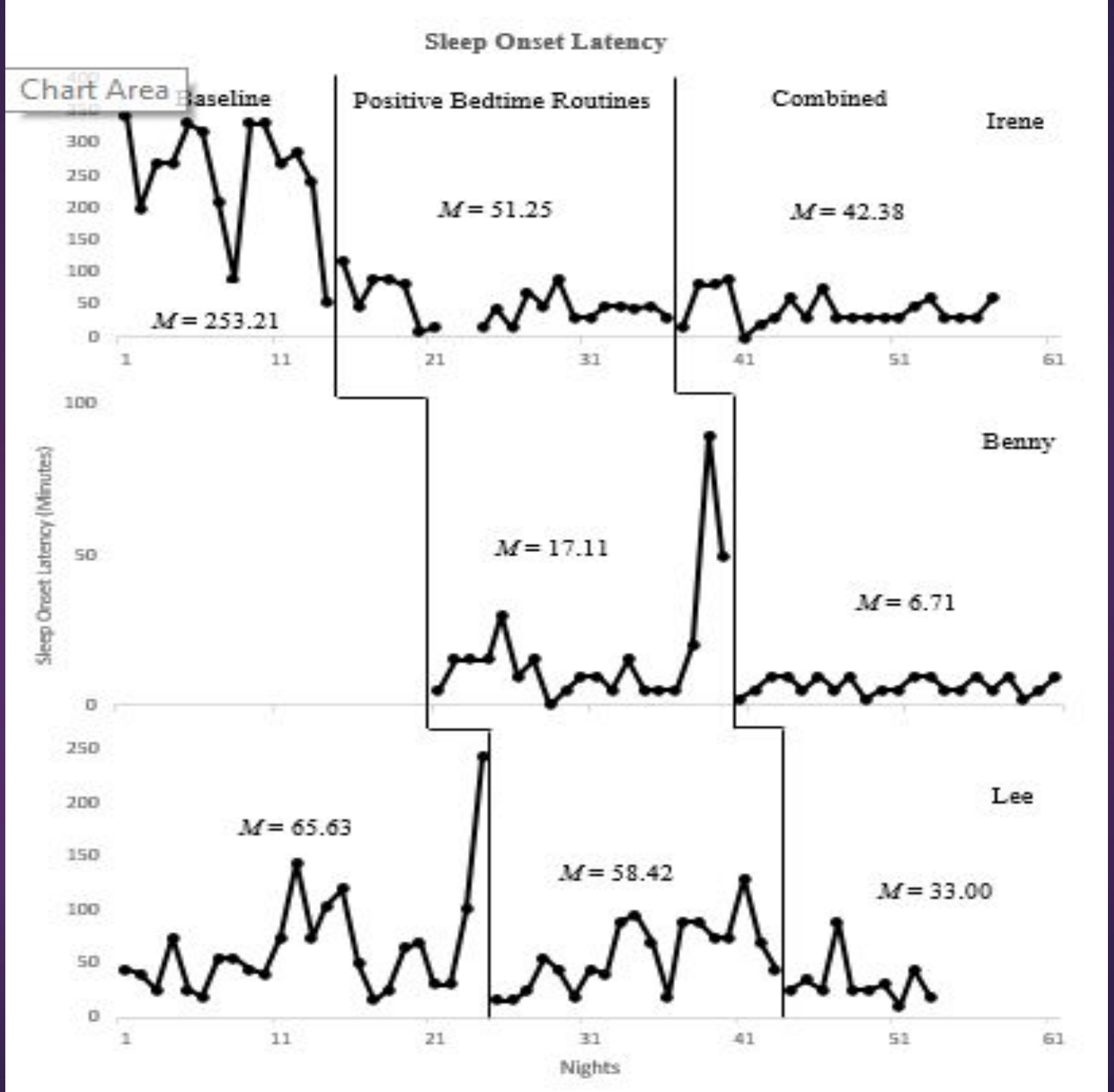

Sleep Onset Latency
Chart Area
Baseline
Positive Bedtime Routines
Combined
Irene
M = 253.21
M = 51.25
M = 42.38
Benny
M = 17.11
M = 6.71
Lee
M = 65.63
M = 58.42
M = 33.00
Sleep Onset Latency (Minutes)
Nights

Table 11. *Average Nighttime Awakenings and Daytime Naps Per Day*

	Nighttime Awakenings		Daytime Naps	
	Frequency	Duration (min)	Frequency	Duration (min)
Baseline				
Irene		0	0	0
Benny	0.20 (*SD*=0.41)	28.75 (*SD*=65.41)	0	0
Lee	0.38 (*SD*=1.24)	16.25 (*SD*=43.32)	0	0
PBR				
Irene	0	0	0	0
Benny	0.11 (*SD*=0.32)	15.26 (*SD*=47.18)	0	0
Lee	0.05 (*SD*=0.23)	7.89 (*SD*=34.41)	0	0
Combined				
Irene	0	0	0	0
Benny	0.67 (*SD*=1.35)	66.43 (*SD*=105.78)	0	0
Lee	0.10 (*SD*=0.32)	6.00 (*SD*=18.97)	0	0

Table 12. *Average Sleep and Wake Times by Condition*

	Irene		Benny		Lee	
Condition	Sleep Onset	Wake Time	Sleep Onset	Wake Time	Sleep Onset	Wake Time
Baseline	12:17am	7:30am	6:06pm	4:18am	9:48pm	7:05am
PBR	10:04pm	5:42am	5:46pm	3:31am	9:43pm	7:00am
Combined	10:02pm	7:10am	5:43pm	3:55am	9:28pm	7:00am

Table 13. *Problematic Behaviors at Bed and Wake Times*

	Average Nights Per Week that Problematic Behaviors Were Reported	
Factor	Bedtime	Wake Time
Baseline		
Irene	5.50	0.50
Benny	0	0
Lee	4.37	0.87
PBR		
Irene	5.10	0.32
Benny	0	0
Lee	5.17	1.84
Combined		
Irene	1.67	0
Benny	0	0

Table 15. *Treatment Integrity as Percentage of Days Implemented as Instructed*

	Irene			Benny			Lee		
Component	BL	PBR	Com	BL	PBR	Com	BL	PBR	Com
Sleep diary completed and submitted	100%	100%	100%	100%	100%	100%	100%	100%	100%
Melatonin administered within 30 minutes of scheduled time	-	-	100%	-	-	95%	-	-	90%
Positive bedtime routines started at least 60 minutes before bedtime	-	95%	95%	-	100%	95%	-	89%	90%
All positive bedtime routines activities completed	-	95%	95%	-	95%	95%	-	74%	80%
Bedtime within 30 minutes of scheduled time	-	91%	95%	-	100%	95%	-	89%	90%
Awakened within 30 minutes of scheduled time	-	86%	100%	-	100%	90%	-	84%	80%

Figure 4. *Total Nighttime Sleep Across Participants*

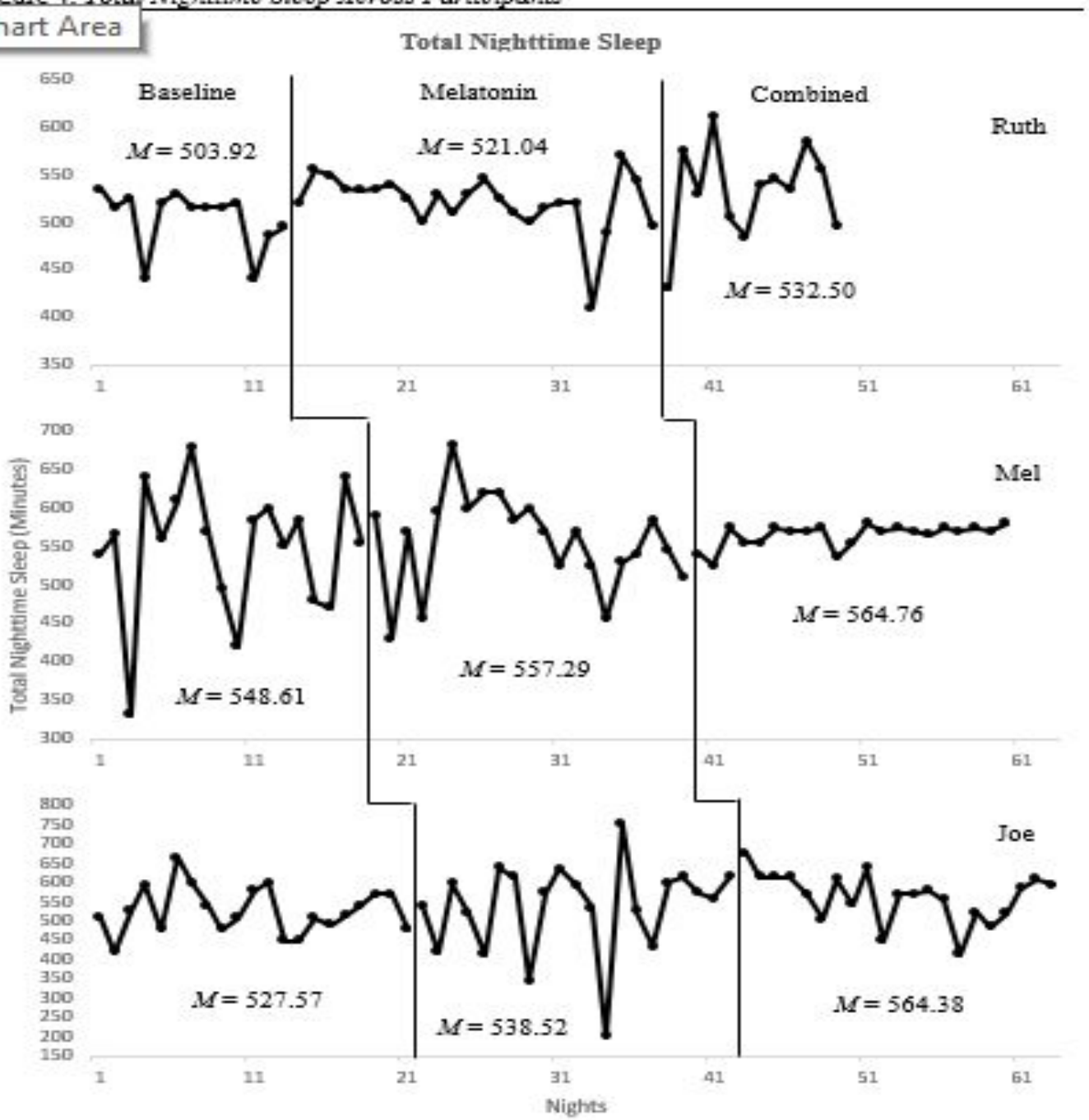


Figure 5. *Sleep Onset Latencies Across Participants*

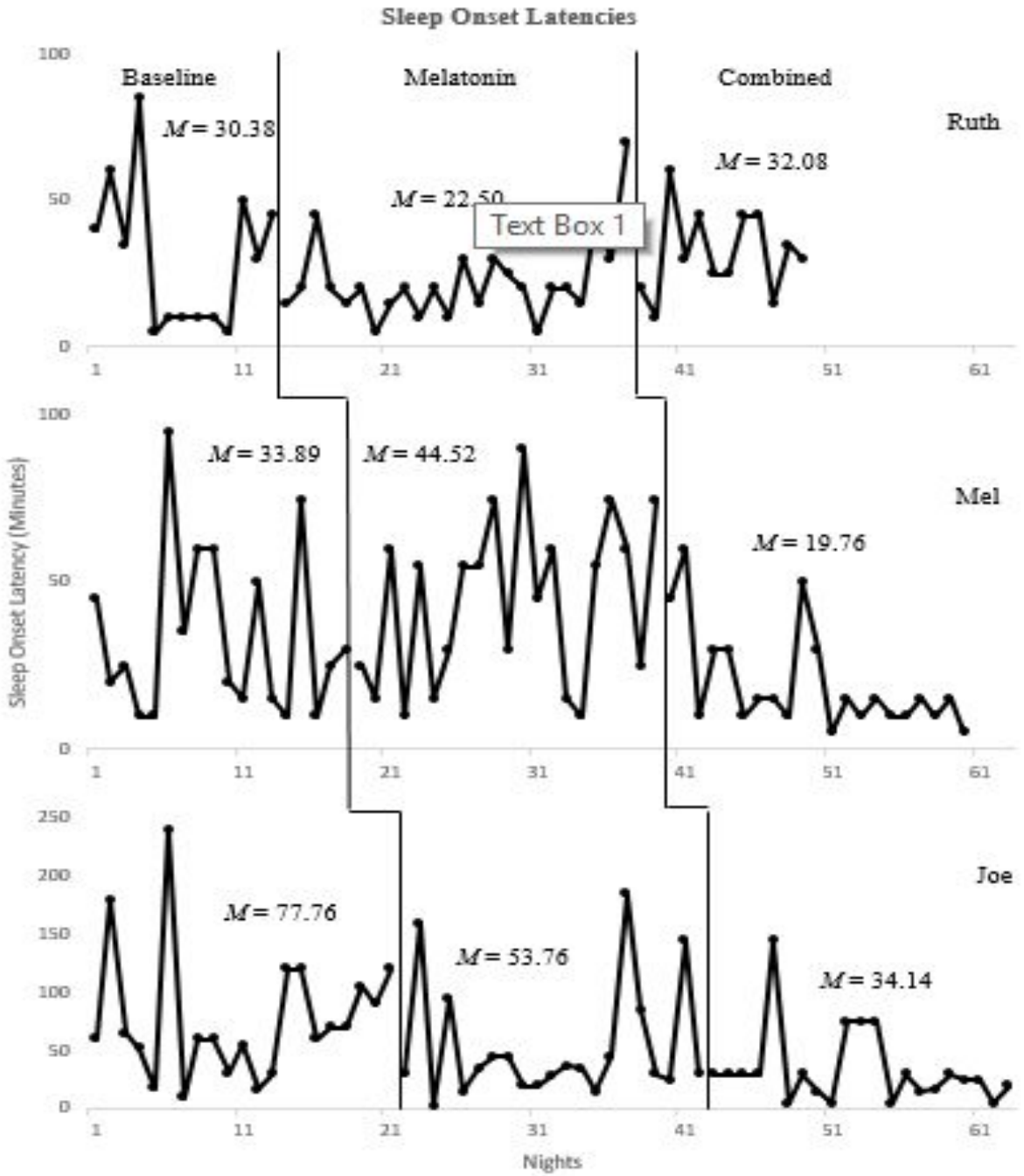


Table 16. *Average Nighttime Awakenings and Daytime Naps Per Day*

	Nighttime Awakenings		Daytime Naps	
Factor	Frequency	Duration (min)	Frequency	Duration (min)
Baseline				
Joe	0	0	0	0
Mel	0.44 (*SD*=0.70)	41.67 (*SD*=91.67)	0.44 (*SD*=0.78)	20.56 (*SD*=38.42)
Ruth	0.15 (*SD*=0.38)	5.00 (*SD*=16.58)	0	0
Melatonin				
Joe	0	0	0	0
Mel	0.24 (*SD*=0.44)	17.14 (*SD*=44.74)	0.24 (*SD*=0.54)	7.62 (*SD*=17.00)
Ruth	0.21 (*SD*=0.51)	1.71 (*SD*=4.62)	0	0
Combined				
Joe	0	0	0	0
Mel	0	0	0	0
Ruth	0.33 (*SD*=0.49)	19.17 (*SD*=36.79)	0	0

Text Box 1

Table 17. *Average Sleep and Wake Times by Condition*

	Joe		Mel		Ruth	
Condition	Sleep Onset	Wake Time	Sleep Onset	Wake Time	Sleep Onset	Wake Time
Baseline	10:54pm	7:44am	10:33pm	8:15am	10:49pm	7:17am
Melatonin	10:23pm	7:22am	10:33pm	8:05am	10:27pm	7:10am
Combined	10:06pm	7:32am	10:34pm	7:59am	9:36pm	6:47am

Table 18. *Problematic Behaviors at Bed and Wake Times*

	Average Nights Per Week that Problematic Behaviors Were Reported	
	Bedtime	Wake Time
Baseline		
Joe	3.00	0.67
Mel	2.33	0
Ruth	0	0
Melatonin		
Joe	2.33	1.00
Mel	0	0
Ruth	0	0
Combined		
Joe	2.00	0.67
Mel	0	0

Table 20. *Treatment Integrity as Percentage of Days Implemented as Instructed*

	Joe			Mel			Ruth		
Component	BL	Mel.	Com	BL	Mel.	Com	BL	Mel.	Com
Sleep diary completed and submitted	100%	100%	100%	100%	100%	100%	100%	100%	100%
Melatonin administered within 30 minutes of scheduled time	-	100%	100%	-	100%	100%	-	100%	75%
Positive bedtime routines started at least 60 minutes before bedtime	-	-	95%	-	-	95%	-	-	100%
All positive bedtime routines activities completed	-	-	95%	-	-	100%	-	-	100%
Bedtime within 30 minutes of scheduled time	-	-	95%	-	-	95%	-	-	75%
Awakened within 30 minutes of scheduled time	-	-	52%	-	-	100%	-	-	83%

Discussion: Research Question 1

- In-line with previous research, sleep initiation identified as major problem.
- Common to use melatonin, positive bedtime routines, and weighted blankets:
  - Easy, cost-effective, recommended by professionals, availability, melatonin and PBR have evidence base with other populations
- Melatonin and PBR rated as most effective.

Discussion: Research Question 2

- Positive bedtime routines, partial CRM, and differential attention package is a viable treatment option for sleep initiation.
- Why?
  - Stronger stimulus control
  - Regulated circadian rhythms
  - Predictability
- Implemented by parents effectively at low cost, with brief and discontinuous training, and without direct professional intervention.
  - Parents disliked when on vacation or when schedules changed.
  - Weaker outcome for Lee, whose parent reported lower treatment integrity.

Discussion: Research Question 3

- Melatonin may be a viable treatment option for sleep initiation, but effect sizes were small.
- More variability for Ruth, whose parent reported short gaps in implementation.
  - Not regulated by FDA, so may be differences in product?
- Reduction in behavior problems around bedtime
- Why?
  - Visual impairment may result in melatonin deficiency
  - Regulated circadian rhythms

Discussion: Research Question 3

- Side effects: only 1 reported by Lee (increase in OCD-like behaviors during daytime). Stopped when treatment ended.
  - Not likely to be harmful short-term
    - Long-term tolerance, withdrawal, dependency issues not tested but should be kept in mind
  - Did not make sleep worse for anyone
- Parents approve, though questioned whether helpful for sleep
- Easy to implement, low cost, and little training needed

Discussion: Research Question 4

- Combined treatment resulted in the best outcomes for sleep initiation, especially when structured treatment package came first.
  - Improving stimulus control, (possibly) reducing anxiety, and teaching sleep-compatible behaviors first is important.
  - While melatonin helps to make you sleepy, it does not deal with other issues around sleep (e.g., sleep cues, anxiety).
  - When melatonin added to this group, sleep increased, then decreased, then stabilized. Suggests a brief adjustment period.
- Increased variability in total nighttime sleep for Benny. May be related to co-sleeping at baseline.
- Difficult to test sleep maintenance, due to already being treated or few nighttime awakenings at baseline.

Discussion: Research Question 4

- Behavior problems reduced.
- Two participants dropped early in combined phase:
  - Lee: reported increase in OCD-like behavior in daytime
  - Ruth: concerns about maintaining implementation due to schedule
- Parents approve and would recommend to a friend, and felt it worked.
- Low cost, easy to implement, discontinuous and indirect training to implement.
  - Good news for pediatric primary care setting.

Limitations

- Small sample
- Reliance on parent report, with no inter-observer reliability
  - Indirect outcome measure
- Variability in implementation due to indirect training
- No long-term follow-up
- Variability in melatonin

Future Directions

- Replication with controlled, direct measure of outcomes: actigraphy, polysomnography, video recording.
- Effectiveness of other behavioral intervention strategies for children with CHARGE syndrome (e.g., graduated extinction, excuse-me drill, sleep fairy).
- Variable melatonin: dosage, extended release, tablet or capsule.
- Replication with measure of anxiety.
- Impact of anxiety intervention on sleep.
- Outcomes for sleep maintenance difficulties among children who awaken during the night more frequently.