



# Insomnia in children and adolescents with ASD - From science to clinical practice

## From research to practice



**Carmen M. Schroder, MD-PhD**

Professor for Child and Adolescent Psychiatry & European Board Certified Sleep Expert

Head of the Department of Child and Adolescent Psychiatry, Strasbourg, France

Head of the Excellence Centre for Autism and Neurodevelopmental Disorders STRAS&ND

CIRCSom, International Research Centre for ChronoSomnology, Strasbourg

CNRS UPR 3212, Institute for Cellular and Integrative Neurosciences, Strasbourg

University Clinics and Medical Faculty, Strasbourg, France

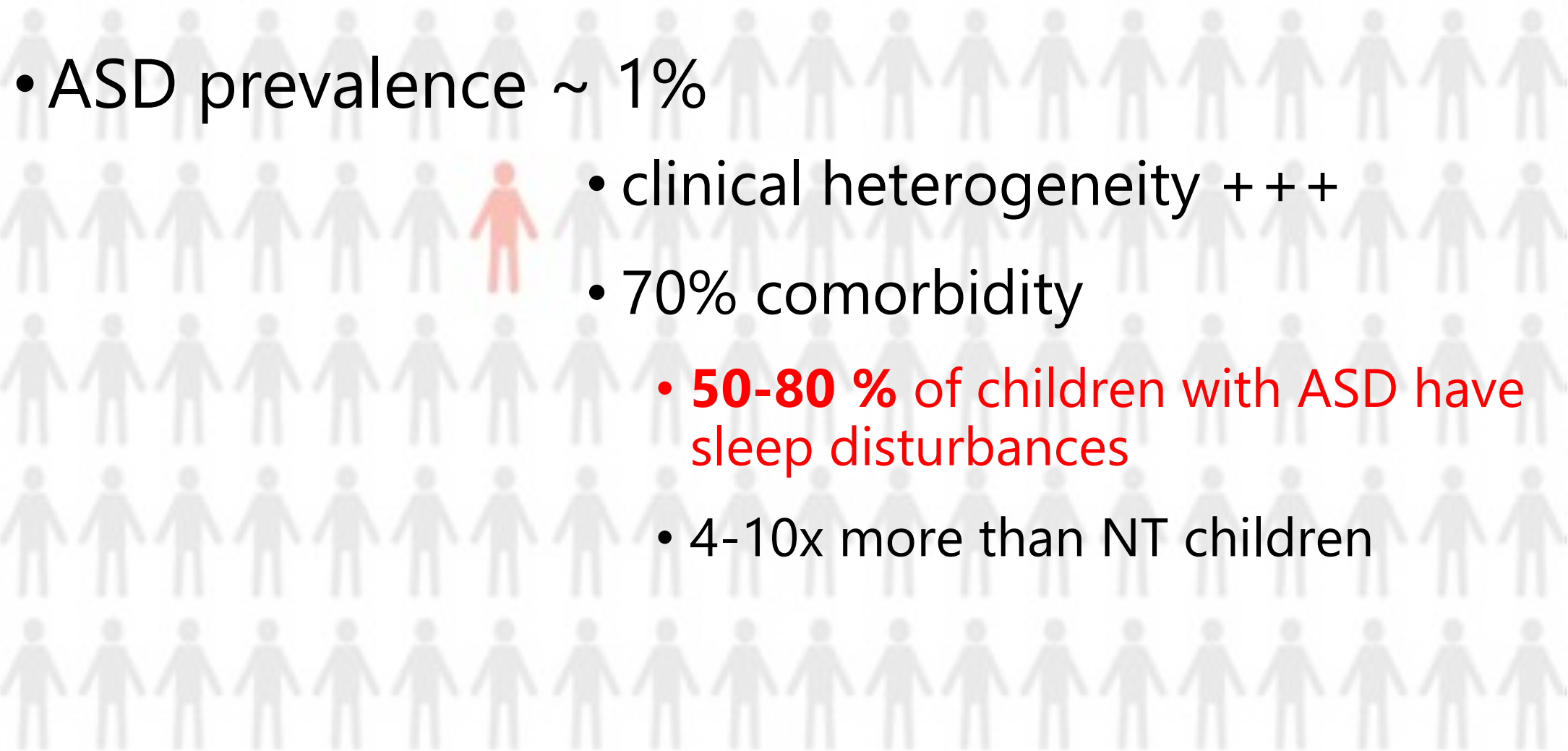


# Conflict of interest: Prof. CM Schröder

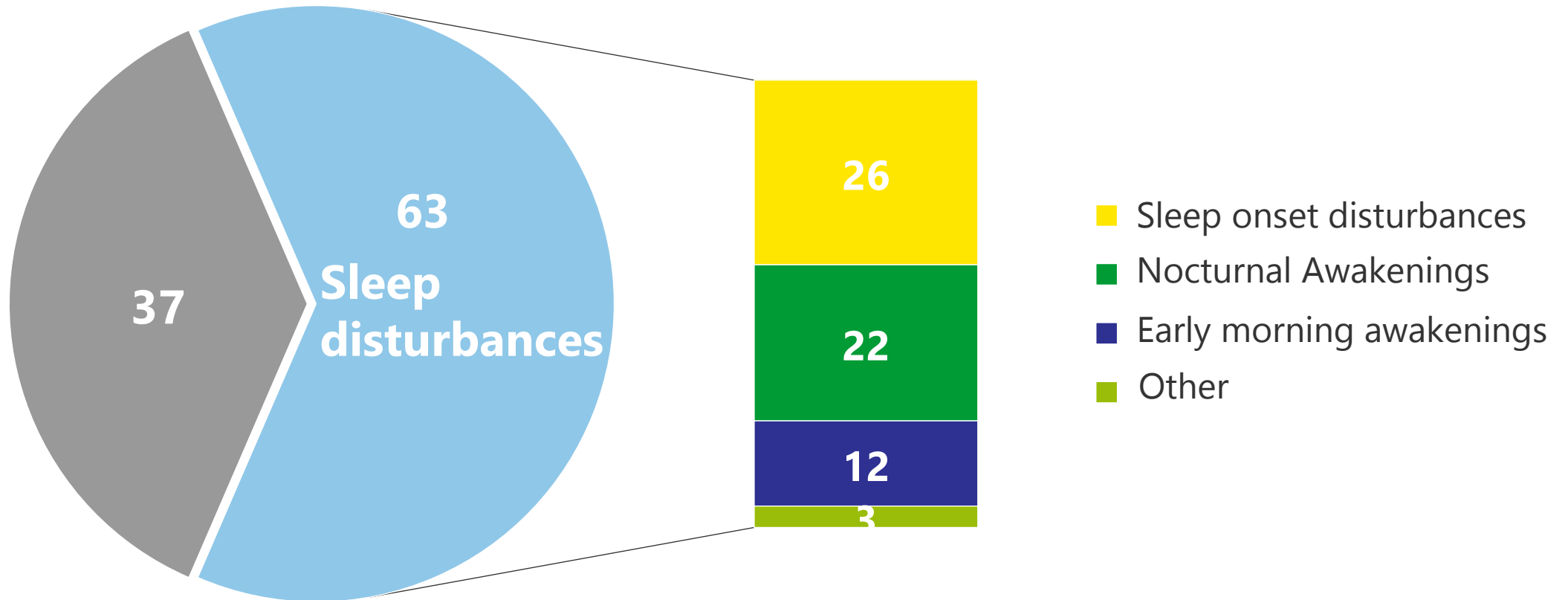
The authors wish to disclose the following potential conflicts of interest related to content in this lecture:

Type of Potential Conflict	Details of Potential Conflict
Grant/Research Support	Neurim (secondary investigator)
Consultant	Neurim, Biocodex
Speakers' Bureaus	N/A
Financial support	N/A
Honoraria	Neurim, Biocodex, Janssen, InfectoPhar, Takeda

# Autism Spectrum Disorder (ASD) and insomnia

- 
- ASD prevalence ~ 1%
  - clinical heterogeneity + + +
  - 70% comorbidity
    - **50-80 %** of children with ASD have sleep disturbances
  - 4-10x more than NT children

# Most frequent insomnia symptoms in ASD



Taira, M., M. Takase, and H. Sasaki, Sleep disorder in children with autism. *Psychiatry Clin Neurosci*, 1998. 52(2): p. 182-3. Krakowiak, P., et al., Sleep problems in children with autism spectrum disorders, developmental delays, and typical development: a population-based study. *J Sleep Res*, 2008. 17(2): p. 197-206.



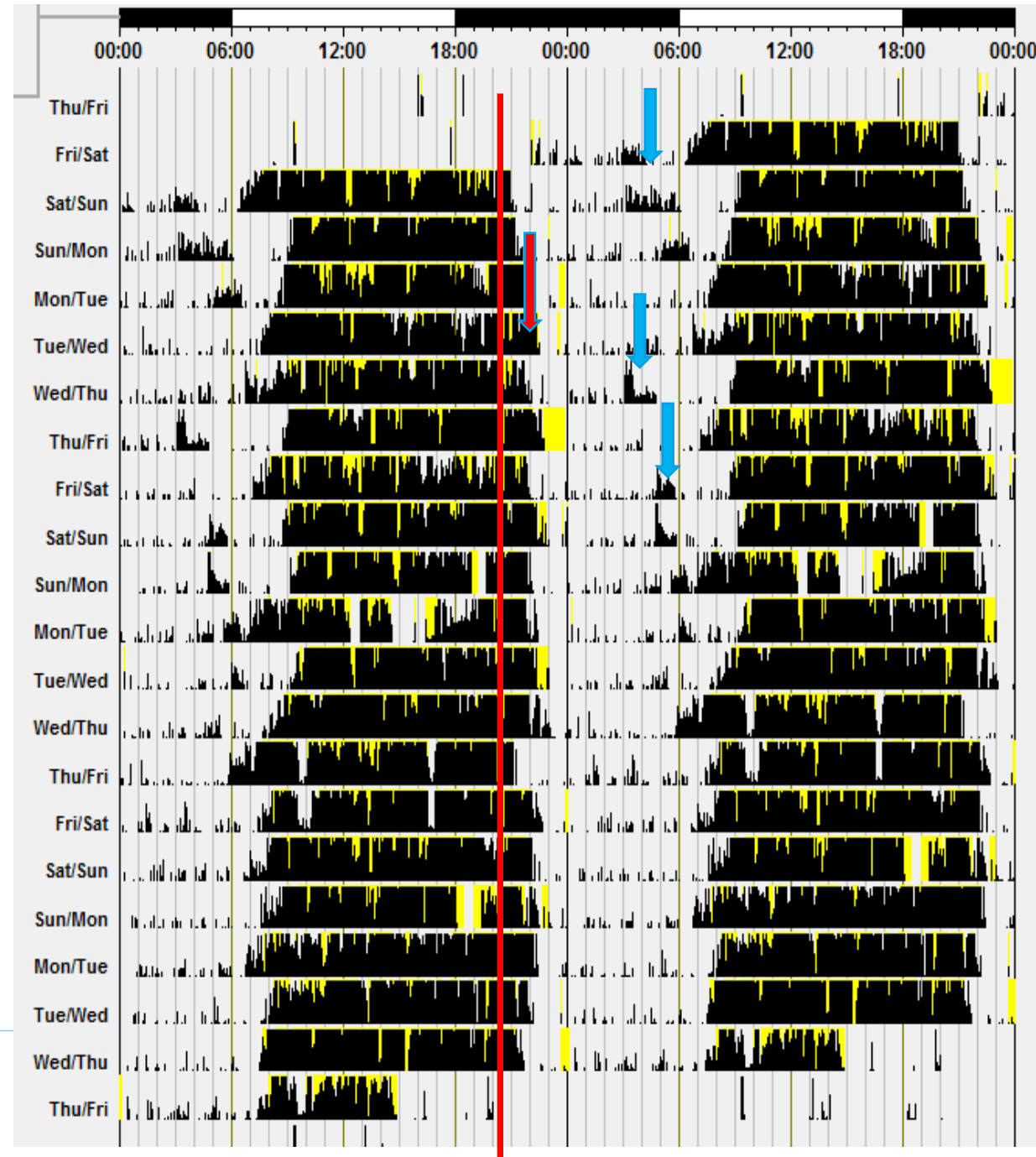
# The spectrum of insomnia disorders in children with ASD

## - measured with actigraphy



## Example 1

Boy with high  
functioning ASD,  
age 9

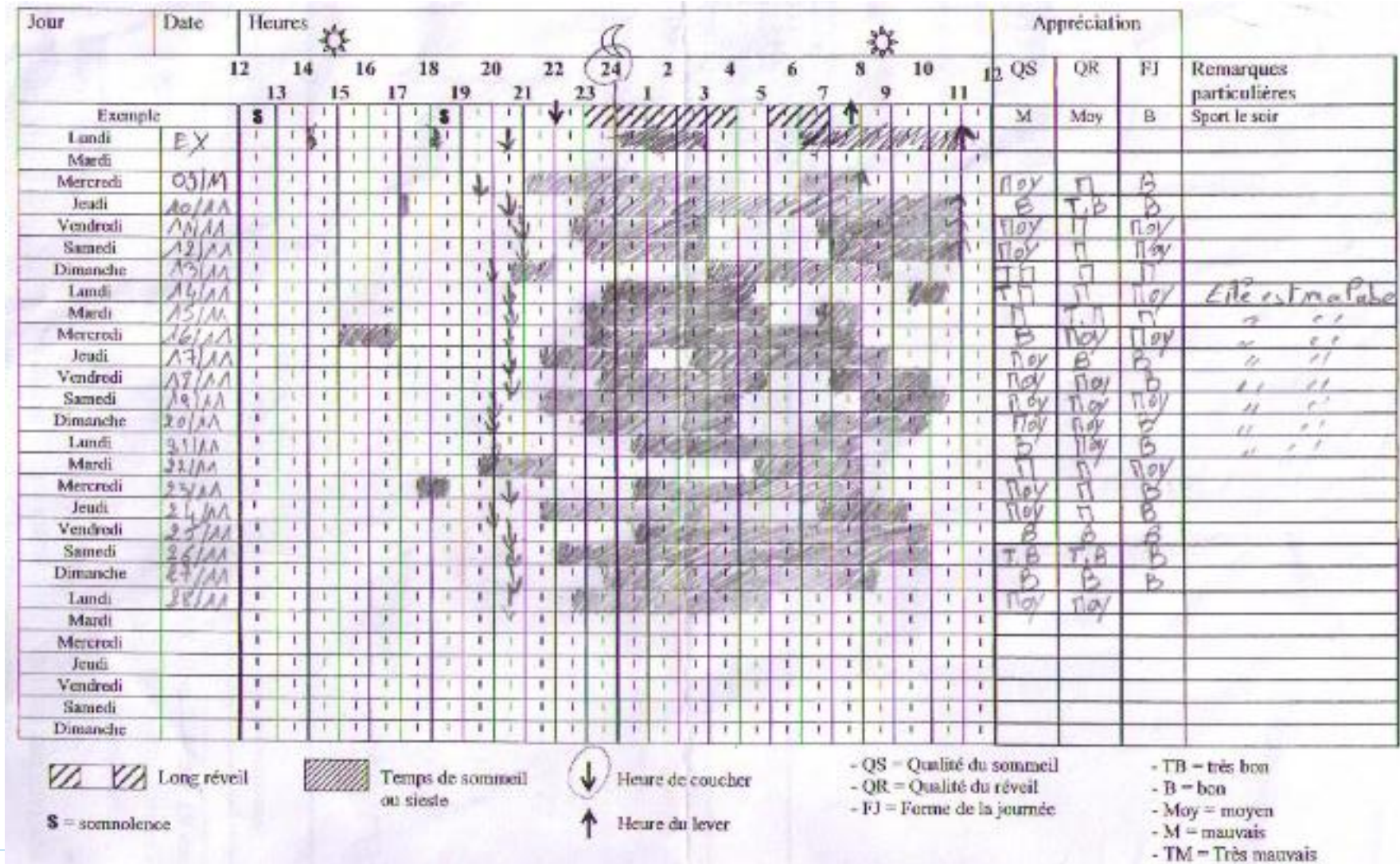




# Sleep diary

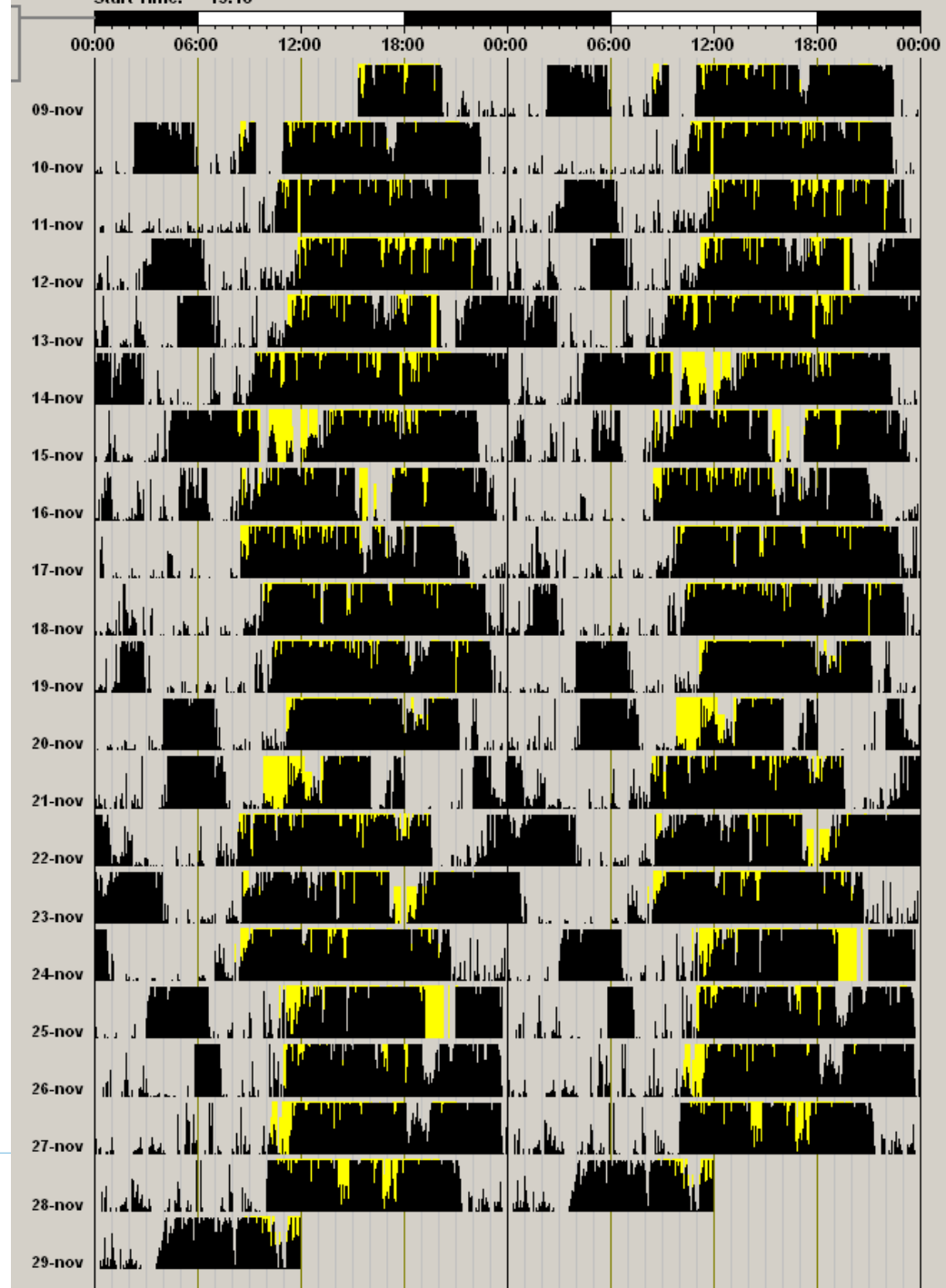
## Example 2

Girl with ASD and  
ID, age 6



## Example 2

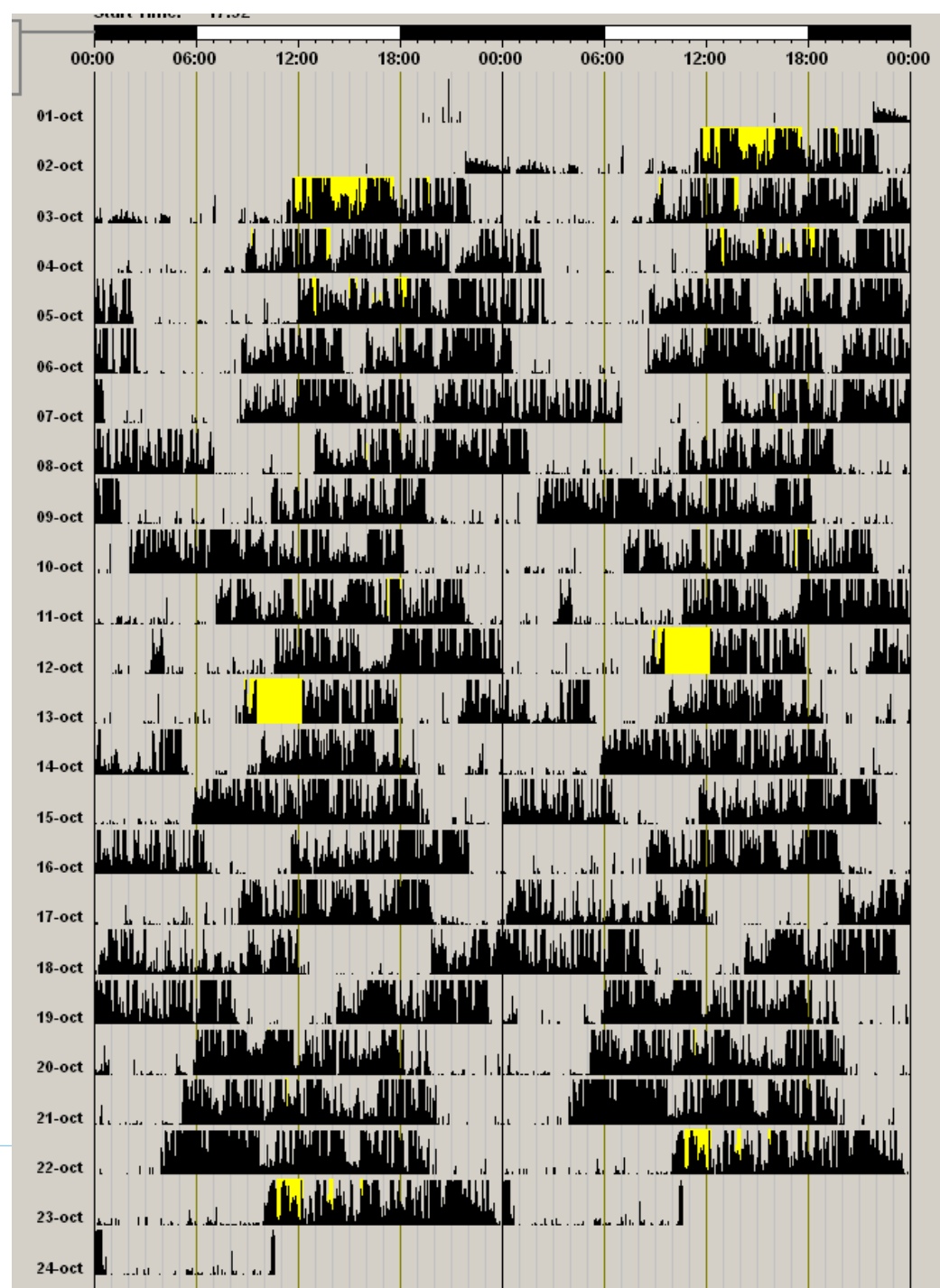
Girl with ASD and  
ID, age 6





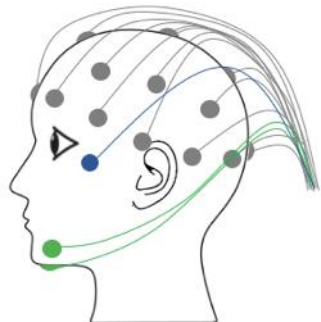
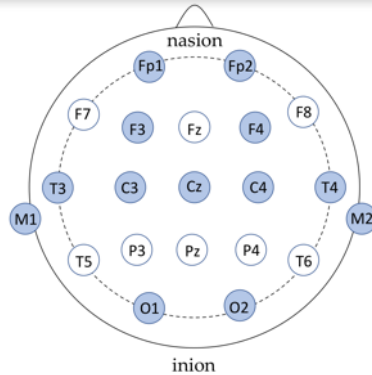
## Example 3

Boy with ASD, ID  
and genetic  
syndrome, age 7



# Validity of Actigraphy Compared to Polysomnography for Sleep Assessment in Children With Autism Spectrum Disorder

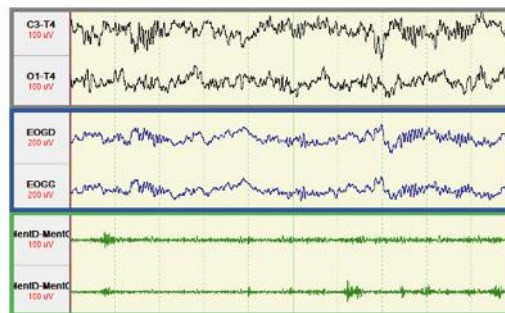
Enise Yavuz-Kodat<sup>1</sup>, Eve Reynaud<sup>1\*</sup>, Marie-Maude Geoffray<sup>2,3</sup>, Nadège Limousin<sup>4</sup>, Patricia Franco<sup>5</sup>, Patrice Bourgin<sup>1,6</sup> and Carmen M. Schroder<sup>1,6,7</sup>



EEG

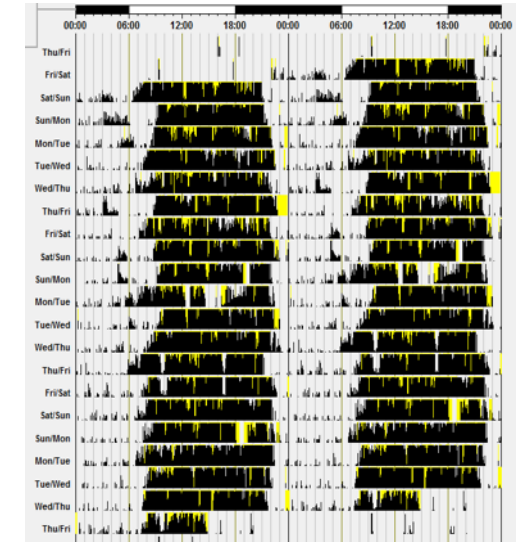
EOG

EMG



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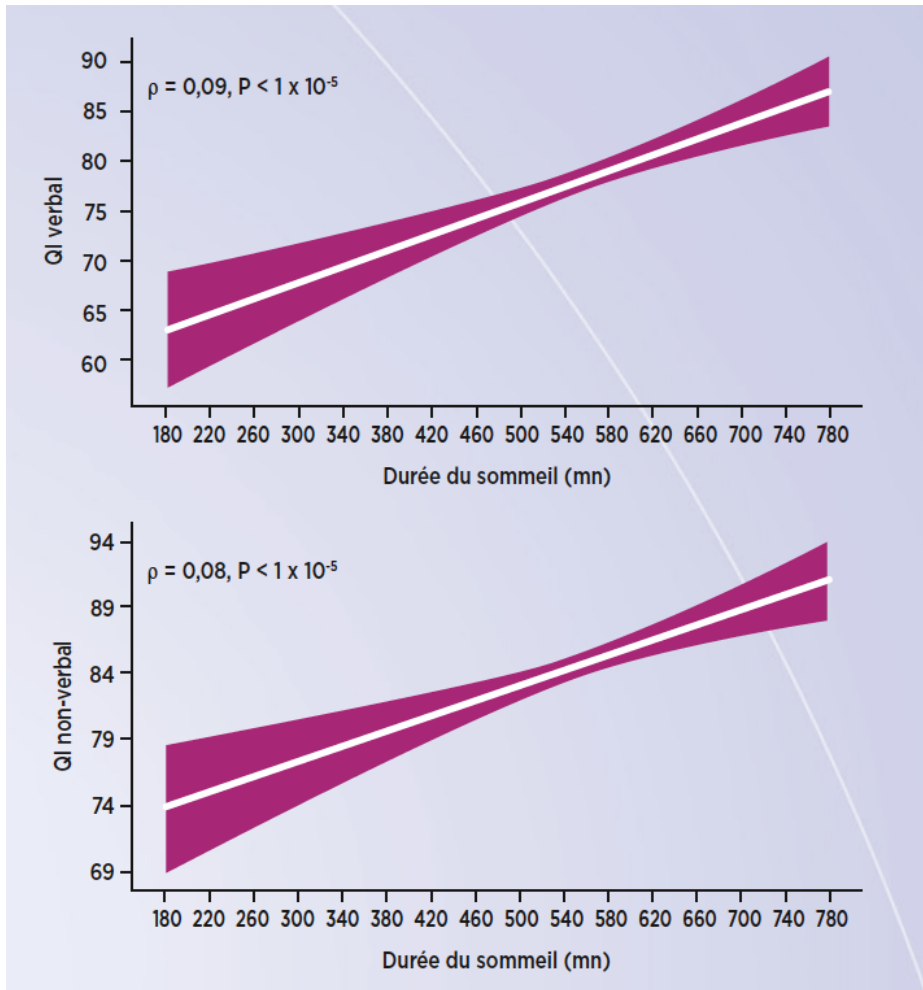
- TST
- SOL
- Effic.
- WASO



Impact of poor  
sleep on **children**  
**with ASD**



# 'Impact' of poor sleep on autistic symptomatology and behaviour in children with ASD



- Impact on autism core symptomatology
  - Social communication
  - Stereotypical and repetitive behaviour
- Impact on comorbidities
  - Anxiety
  - Depression
  - Irritability
  - Aggressive behaviour (auto- & hetero)

n = 2 714 Children with ASD  
(Siemens Simplex Collection)

(Veatch et al. (2017))

(Cohen et al. (2014), Blackmer et al. (2016), Mazurek et al. (2016) Yavuz-Kodat et al. 2020)



# 'Impact' of poor sleep on daytime function in children with ASD

Disturbed sleep in attention-deficit hyperactivity disorder (ADHD) is not a question of psychiatric comorbidity or ADHD presentation

ANNE VIRRING<sup>1</sup>, RIKKE LAMBEK<sup>2</sup>, PER H. THOMSEN<sup>1</sup>, LENE R. MØLLER<sup>1</sup> and POUL J. JENNUM<sup>3</sup>  
<sup>1</sup>Centre for Child and Adolescent Psychiatry, Aarhus University Hospital Risskov, Aarhus, Denmark; <sup>2</sup>Department of Psychology and Behavioural Sciences, Aarhus University, Aarhus, Denmark; <sup>3</sup>Rigshospitalet, Danish Center for Sleep Medicine, Department of Clinical Neurophysiology, University of Copenhagen, Copenhagen, Denmark;

2016 European Sleep Research Society

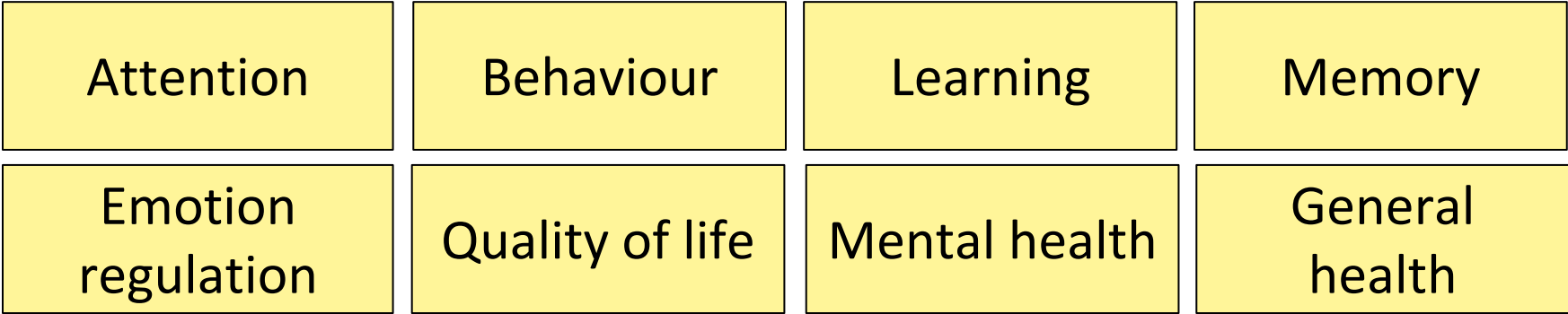
Exploring Sleep Quality of Young Children with Autism Spectrum Disorder and Disruptive Behaviors

Cynthia R. Johnson<sup>a</sup>, Tristram Smith<sup>b</sup>, Alexandra DeMand<sup>c</sup>, Luc Lecavalier<sup>d</sup>, Victoria Evans<sup>a</sup>, Matthew Gurka<sup>a</sup>, Naomi Swiezy<sup>e</sup>, Karen Bearss<sup>f</sup>, and Lawrence Scahill<sup>g</sup>

Sleep Dependent Memory Consolidation in Children with Autism Spectrum Disorder

Kiran Maski, MD<sup>1</sup>; Hannah Holbrook, BS<sup>2</sup>; Dara Manoach, PhD<sup>3</sup>; Ellen Hanson, PhD<sup>4</sup>; Kush Kapur, PhD<sup>5</sup>; Robert Stickgold, PhD<sup>1,7</sup>  
<sup>1</sup>Department of Neurology, Boston Children's Hospital, Boston, MA; <sup>2</sup>Department of Psychology, University of Vermont, Burlington, VT; <sup>3</sup>Department of Psychiatry, Massachusetts General Hospital, Boston, MA; <sup>4</sup>Department of Medicine, Boston Children's Hospital, Boston, MA; <sup>5</sup>Center for Health Statistics, Boston Children's Hospital, Boston, MA; <sup>6</sup>Department of Psychiatry, Beth Israel Deaconess Medical Center, Boston, MA; <sup>7</sup>Department of Psychiatry, Harvard Medical School, Boston, MA

*Sleep Med.* 2018 April



SHORTER SLEEP DURATION IS ASSOCIATED WITH SOCIAL IMPAIRMENT AND PSYCHIATRIC COMORBIDITIES IN AUTISM

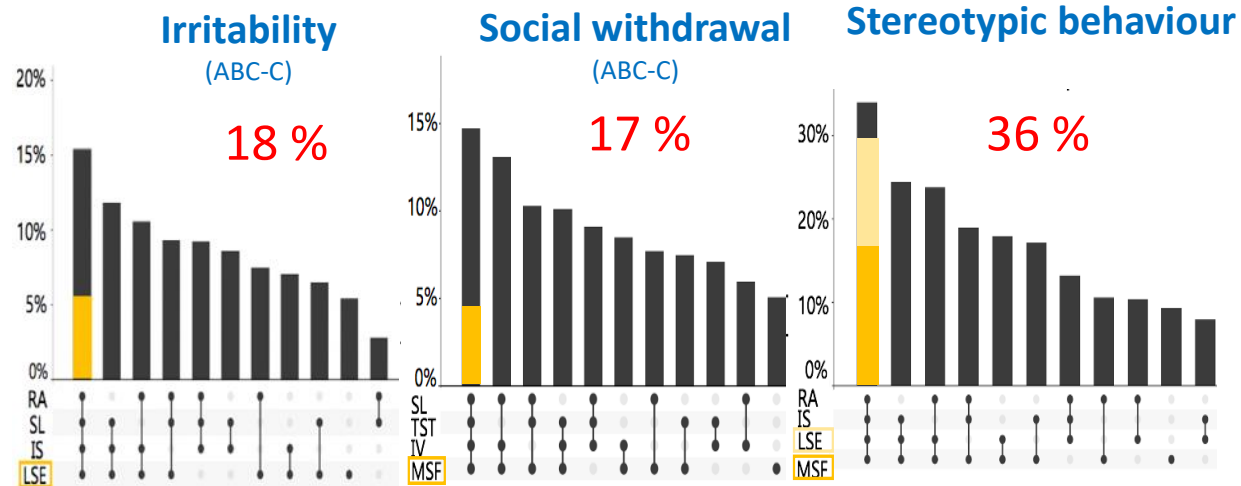
Veatch OJ<sup>1,2</sup>, Sutcliffe JS<sup>2</sup>, Warren ZE<sup>2</sup>, Keenan BT<sup>1</sup>, Potter MH<sup>2</sup>, Pack AI<sup>1</sup>, Malow BA<sup>2</sup>  
<sup>1</sup>University of Pennsylvania, Philadelphia, PA, <sup>2</sup>Vanderbilt University, Nashville, TN

# Link between sleep and circadian rhythm disturbances and daytime behaviour

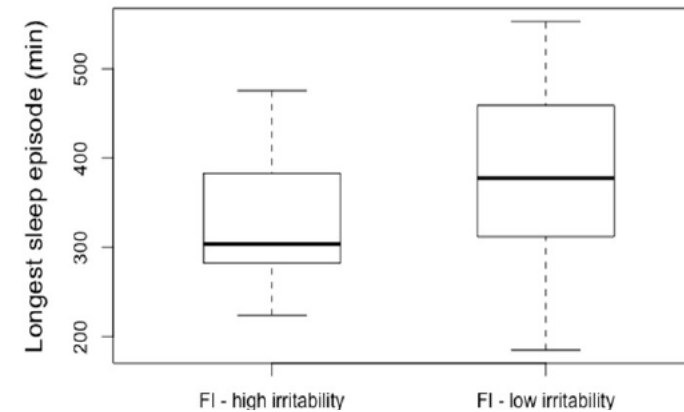
n= 52 children with ASD, 3-10 years (M 5.39 years)



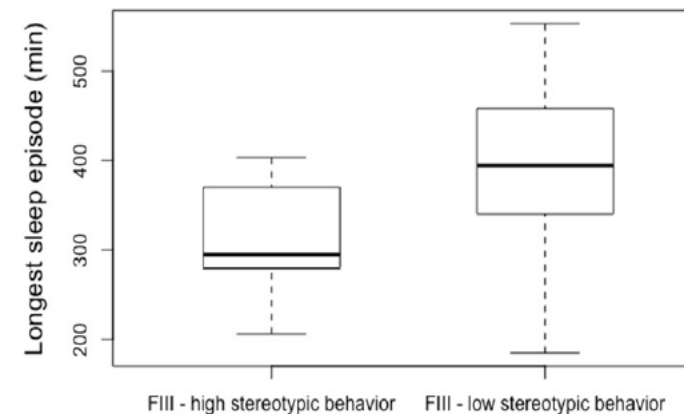
- Both sleep and circadian rhythm disturbances explain behavioural symptoms in children with ASD.



- Longer continuous sleep (LSE)** was associated with less irritability and stereotypical behaviour



$\Delta = 60 \text{ min}$



$\Delta = 75 \text{ min}$



Yavuz-Kodat et al. Disturbances of Continuous Sleep and Circadian Rhythms Account for Behavioral Difficulties in Children with Autism Spectrum Disorder, J. Clin. Med. 2020; doi:10.3390/jcm9061978



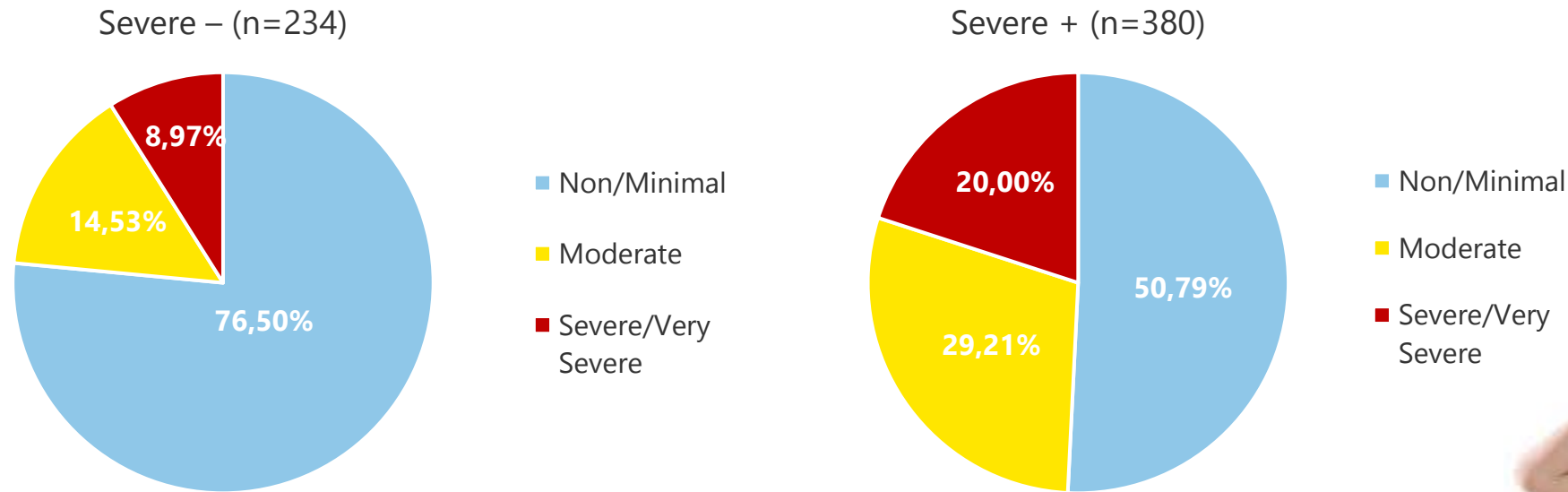
Journal of  
*Clinical Medicine*

# Quantifying insomnia burden in children with ASD – Autism Speaks survey 2019

# Quantifying insomnia burden in children with ASD - Autism Speaks survey 2019

Child behavior - CSDI and parent reported behavior

Children with sleep problems are more likely to have behavioral problems



Pearson  $\chi^2(2) = 40.1560$  Pr = 0.000

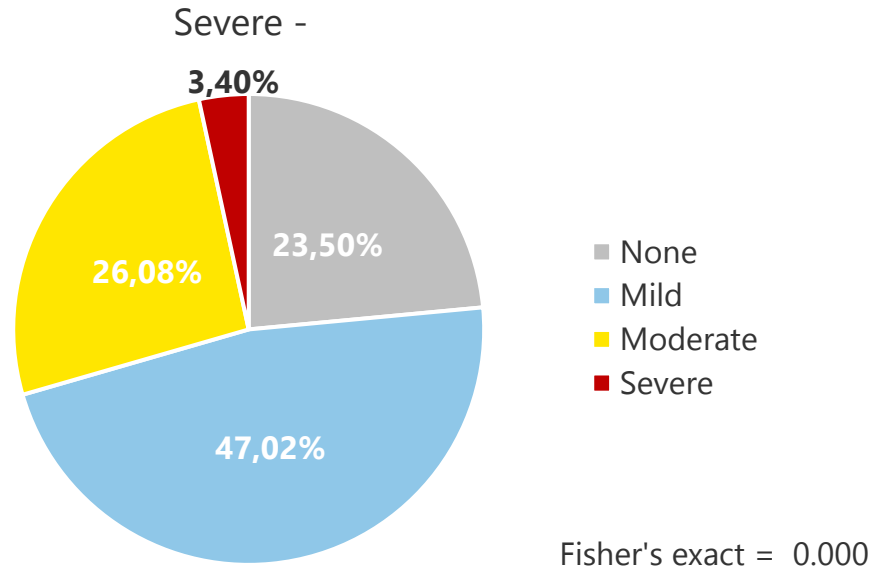




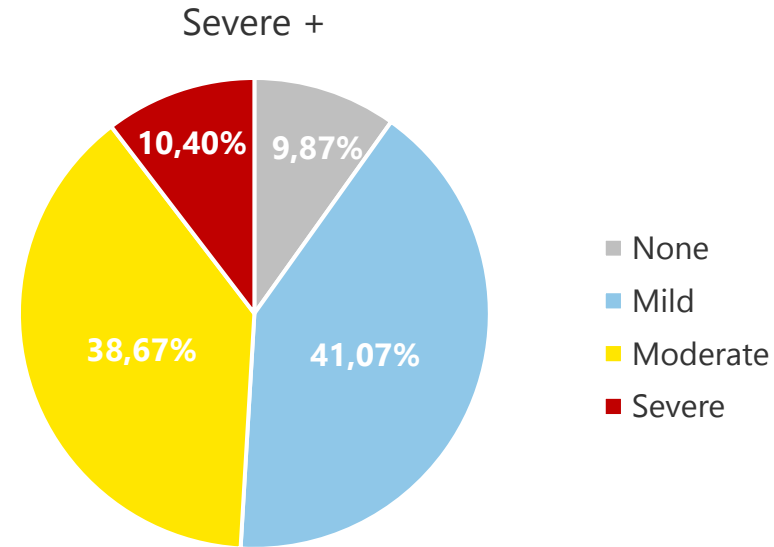
# Quantifying insomnia burden in children with ASD - Autism Speaks survey 2019

## Sensitivity to sounds

Children with sleep problems are more likely to have sensitivity to sounds



Fisher's exact = 0.000



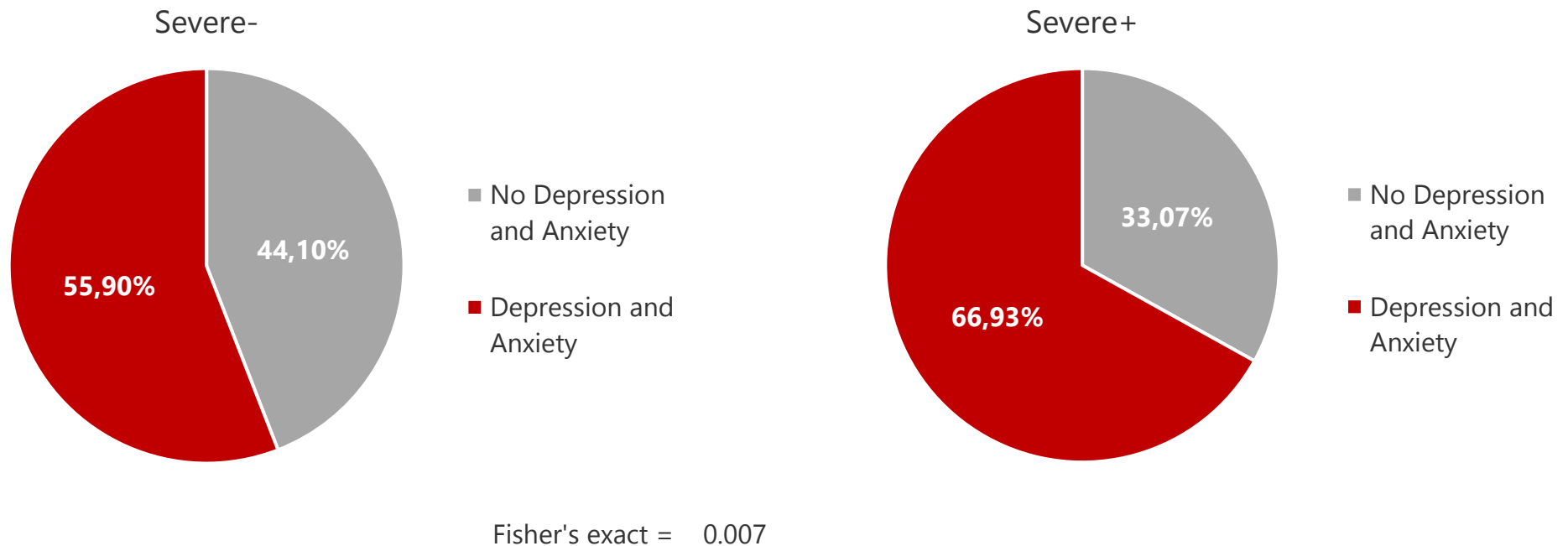
Impact of poor  
sleep on **families**  
of children with  
ASD



# Quantifying insomnia burden - Autism Speaks survey

## Parent health - anxiety and depression

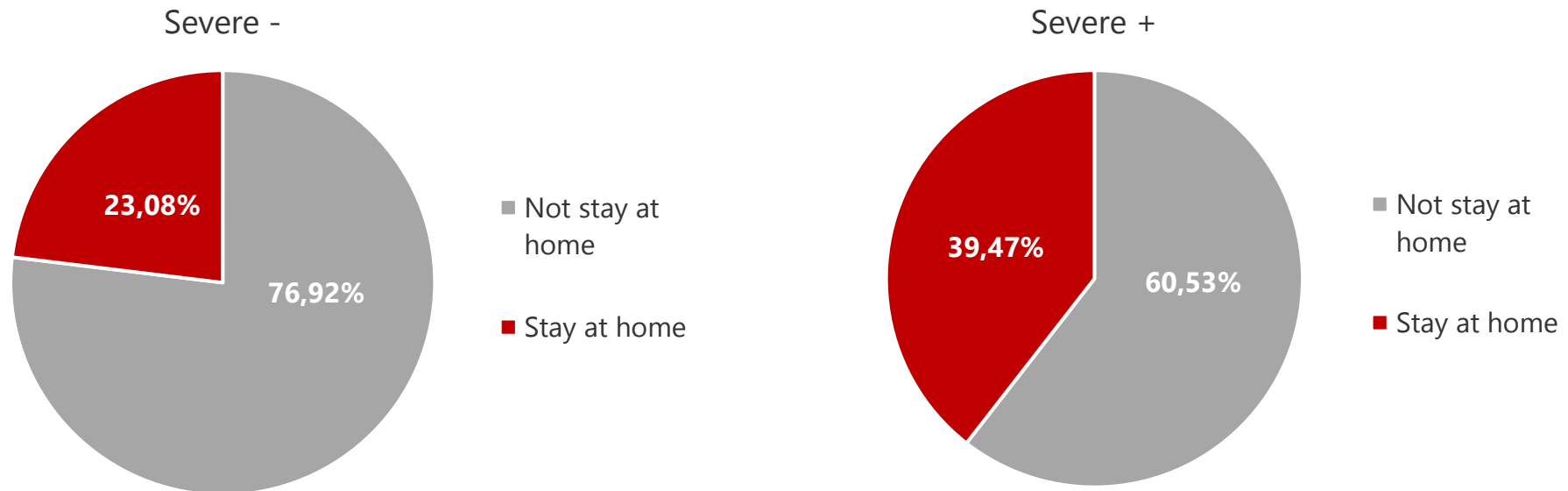
Parents to children with sleep problems are more likely to have a diagnosis of depression or anxiety.



# Quantifying insomnia burden - Autism Speaks survey

## Parent employment

Mothers to children with sleep problems are more likely to stay at home in order to care for the child than mothers to child without sleep problems



Fisher's exact = 0.000



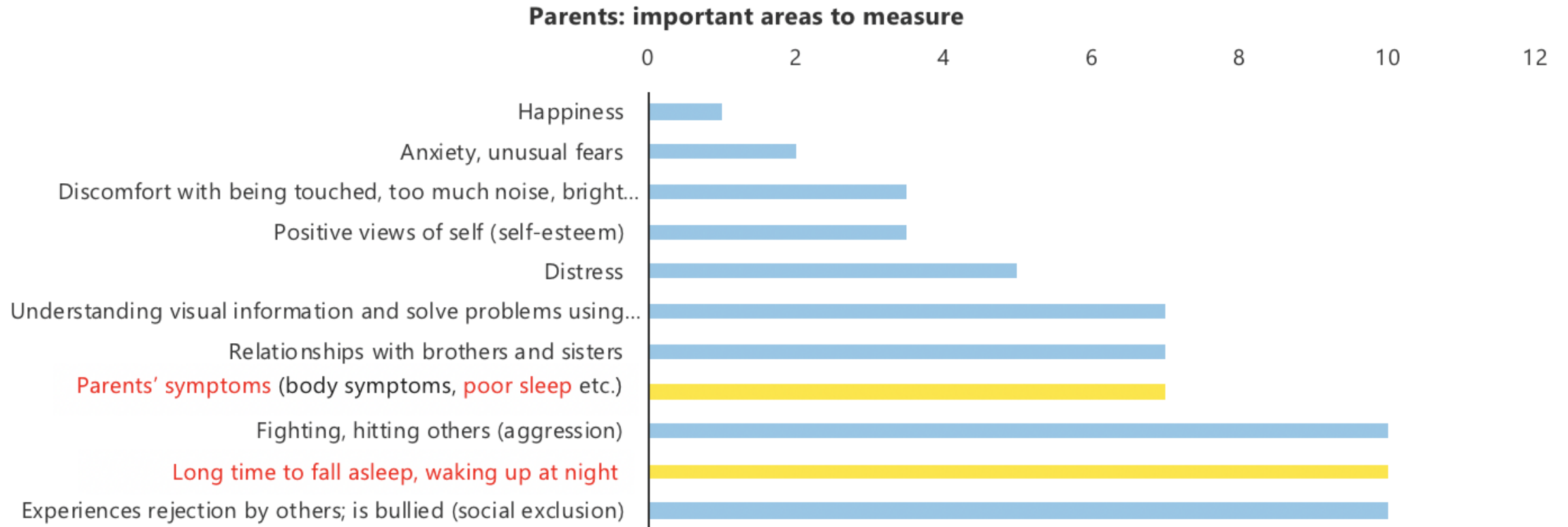
# Quantifying insomnia burden - Autism Speaks survey

## Work attendance

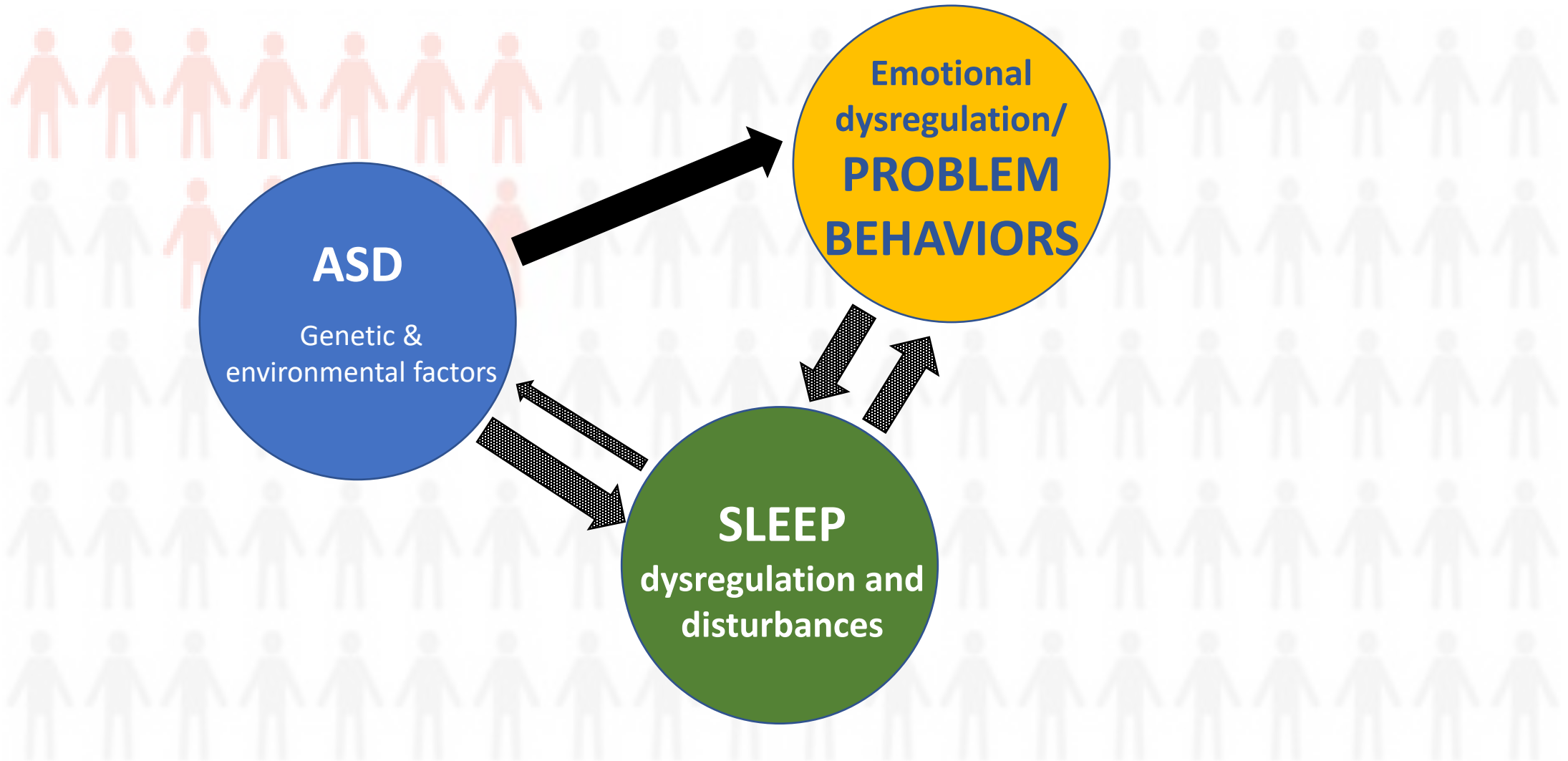
The proportion of working parents missing 5 or more days of work annually due to their child's ASD in the severe group was **more than double** the non-severe sleep problems (37% vs. 16%;  $\chi^2 (2) = 19.64, p = 0.000$ ).



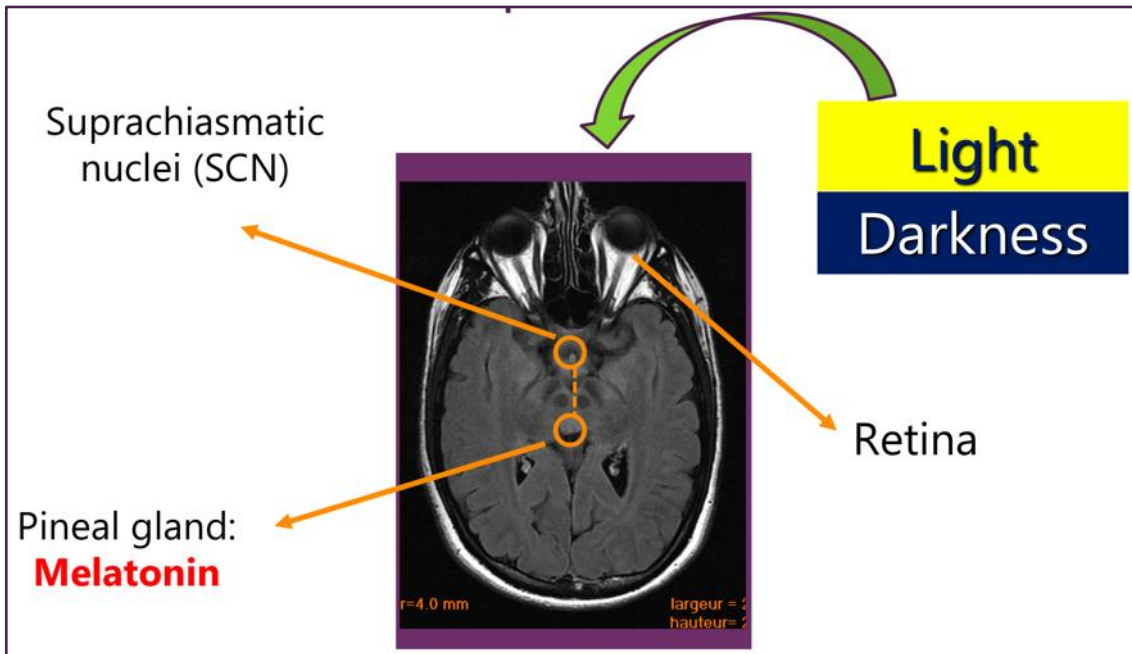
... thus: sleep is among parents' highest ranked outcomes  
(*focus groups, the MeASURE project – UK*)



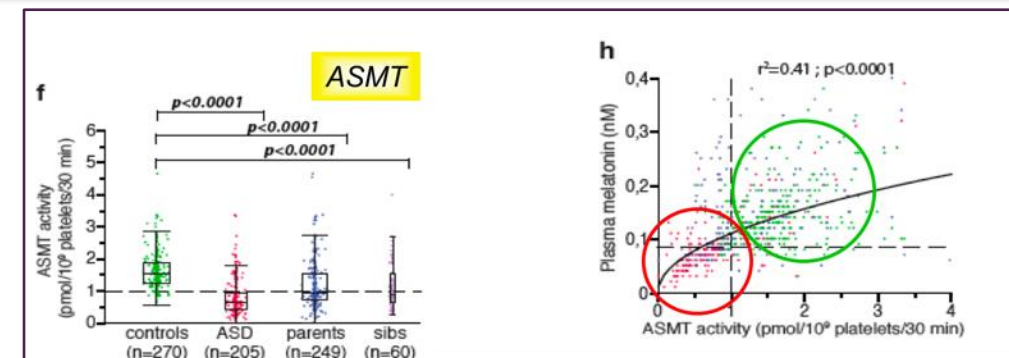
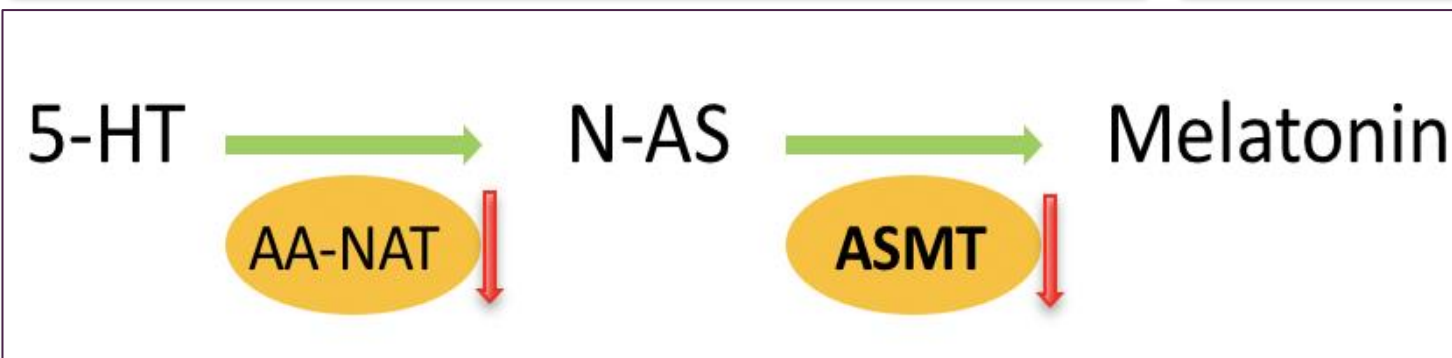
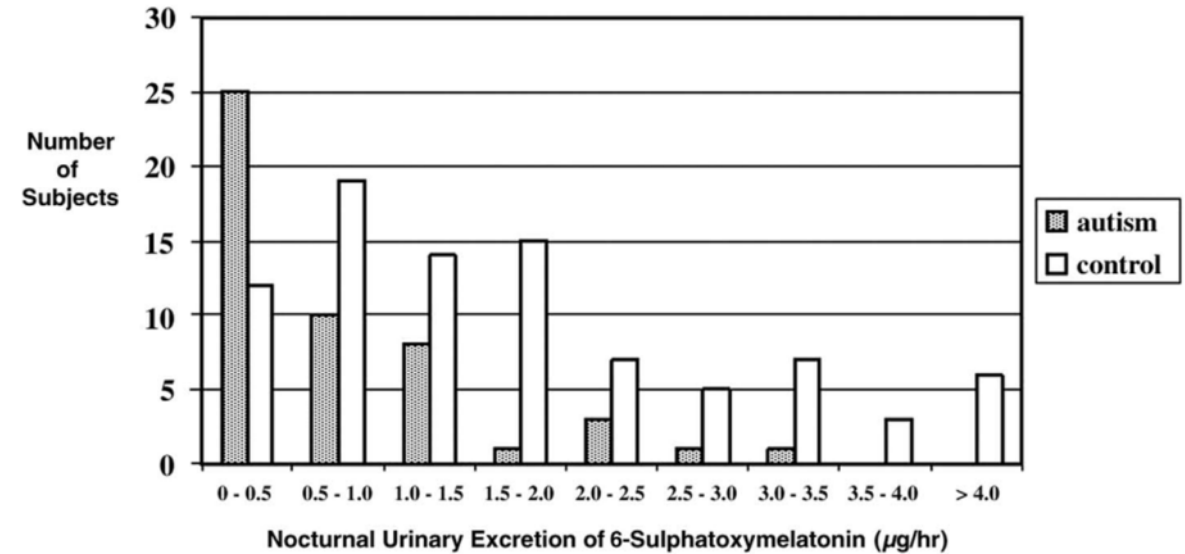
# ASD, sleep and behavioural disturbances



# What causes insomnia in children with ASD?



**63% of children  $<1/2$  of melatonin levels compared to controls**

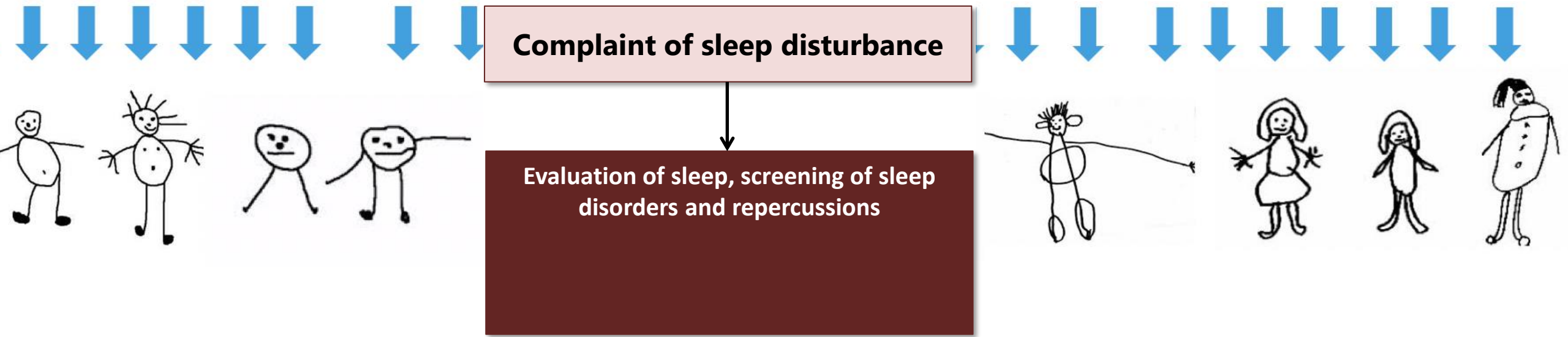


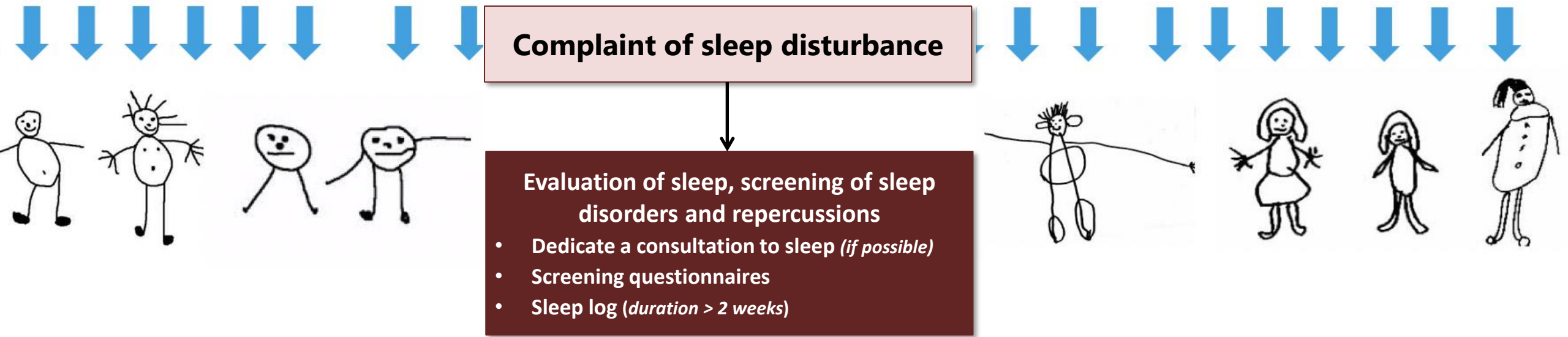
**Melatonin deficiency** is the main pathophysiological mechanism



How to evaluate  
and treat in clinical  
practice?









# Evaluation of sleep in children with ASD in primary care

*- when time is short*



Prof. Tobias Banaschewski  
Germany



Prof. Oliviero Bruni  
Italy



Prof. Joaquin Fuentes  
Spain



Dr. Cathy M Hill  
Great-Britain



Prof. Allan Hvolby  
Denmark



Prof. Maj-Britt Posserud  
Norway



Prof. Carmen Schroder  
France



# Evaluation of sleep in children with ASD in primary care

## - *when time is short*

### Novel screening tool for insomnia – modified DIMS (Part A) – **diagnose insomnia in 7 questions**

Part A: Insomnia Diagnosis: Child's sleep habits in the last 3 months		Score
Date	○ Child's name	○ Age
The Child goes to bed reluctantly	<ul style="list-style-type: none"> <li>○ Never (1)</li> <li>○ Occasionally (1-2 per month or less) (2)</li> <li>○ Sometimes (once or twice per week) (3)</li> <li>○ Often (3-5 times per week) (4)</li> <li>○ Always (daily) (5)</li> </ul>	○
The child has difficulty getting to sleep at night	<ul style="list-style-type: none"> <li>○ Never (1)</li> <li>○ Occasionally (1-2 per month or less) (2)</li> <li>○ Sometimes (once or twice per week) (3)</li> <li>○ Often (3-5 times per week) (4)</li> <li>○ Always (daily) (5)</li> </ul>	○
The child feels anxious or afraid when falling asleep	<ul style="list-style-type: none"> <li>○ Never (1)</li> <li>○ Occasionally (1-2 per month or less) (2)</li> <li>○ Sometimes (once or twice per week) (3)</li> <li>○ Often (3-5 times per week) (4)</li> <li>○ Always (daily) (5)</li> </ul>	○
The child wakes up more than twice per night	<ul style="list-style-type: none"> <li>○ Never (1)</li> <li>○ Occasionally (1-2 per month or less) (2)</li> <li>○ Sometimes (once or twice per week) (3)</li> <li>○ Often (3-5 times per week) (4)</li> <li>○ Always (daily) (5)</li> </ul>	○

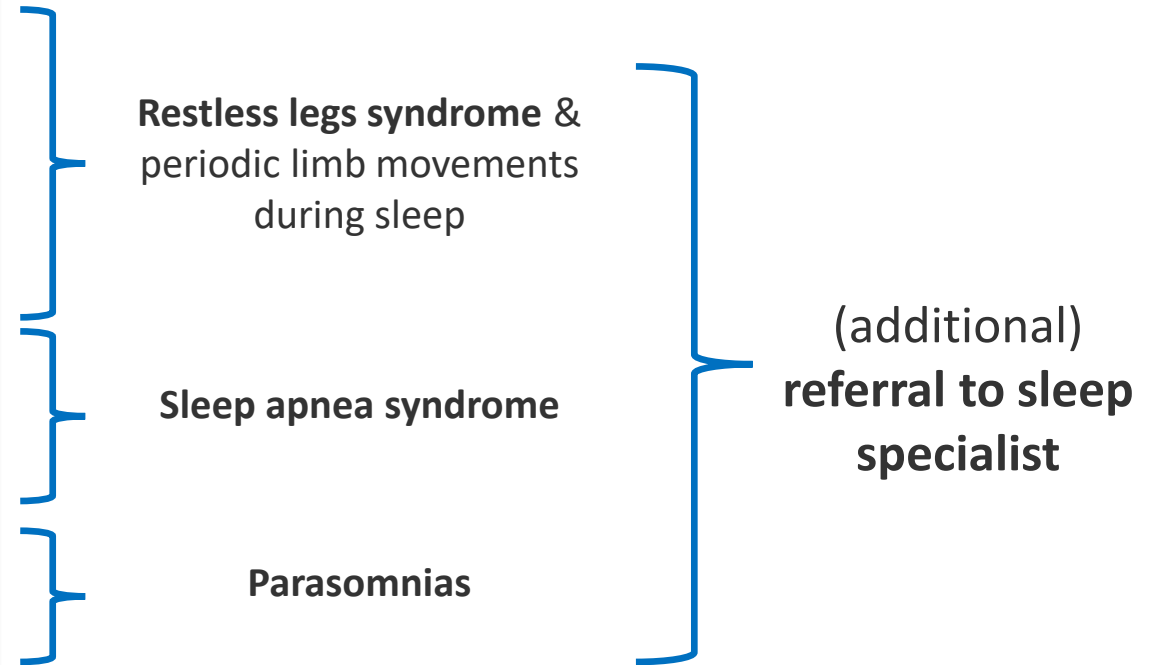
After waking up in the night, the child has difficulty to fall asleep again	<ul style="list-style-type: none"> <li>○ Never (1)</li> <li>○ Occasionally (1-2 per month or less) (2)</li> <li>○ Sometimes (once or twice per week) (3)</li> <li>○ Often (3-5 times per week) (4)</li> <li>○ Always (daily) (5)</li> </ul>	○
How many hours of sleep does your child get on most nights?	<ul style="list-style-type: none"> <li>○ 9-11 h (1)</li> <li>○ 8-9 h (2)</li> <li>○ 7-8 h (3)</li> <li>○ 5-7 h (4)</li> <li>○ Less than 5 h (5)</li> </ul>	○
How long, after going to bed, does your child usually fall asleep?	<ul style="list-style-type: none"> <li>○ Less than 15 minutes (1)</li> <li>○ 15-30 minutes (2)</li> <li>○ 30-45 minutes (3)</li> <li>○ 45-60 minutes (4)</li> <li>○ More than 60 minutes (5)</li> </ul>	○
<b>Total Score (sum of subscale scores)</b> Score 10 or lower: unlikely to have insomnia Score 11-16: at risk of having insomnia Score 17 or higher: insomnia		○

# Evaluation of sleep in children with ASD in primary care

## - *when time is short*

### Novel screening tool for insomnia – modified DIMS (Part B) – **rule out other sleep disorders**

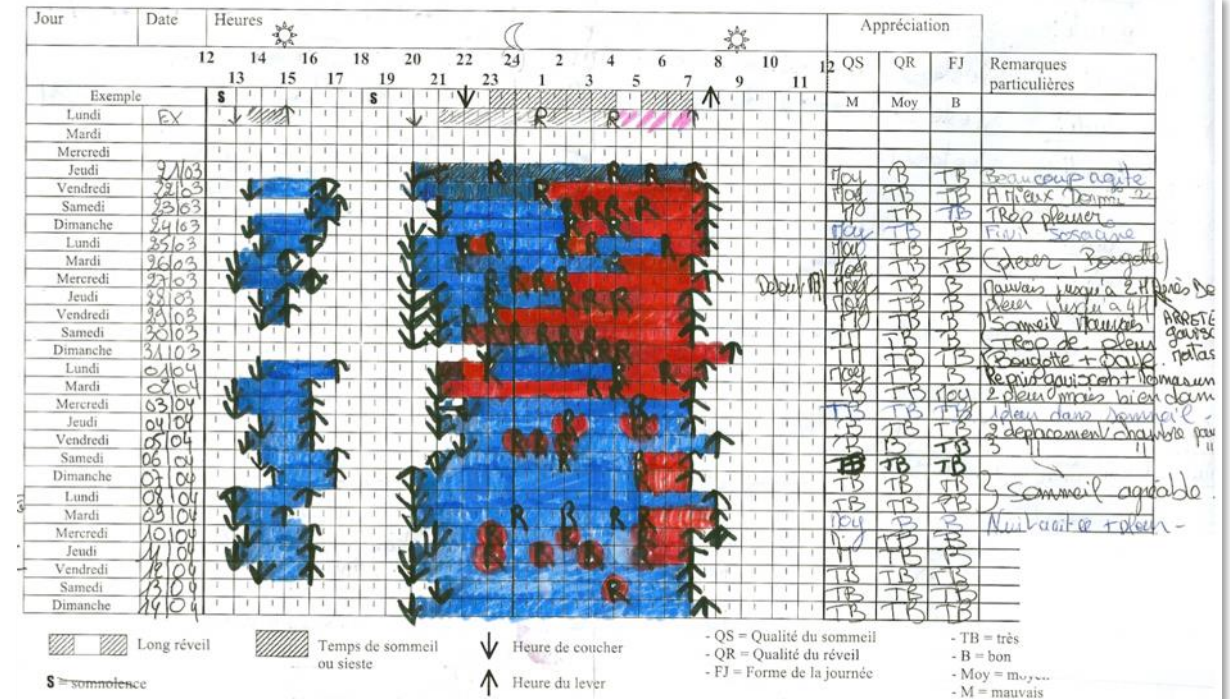
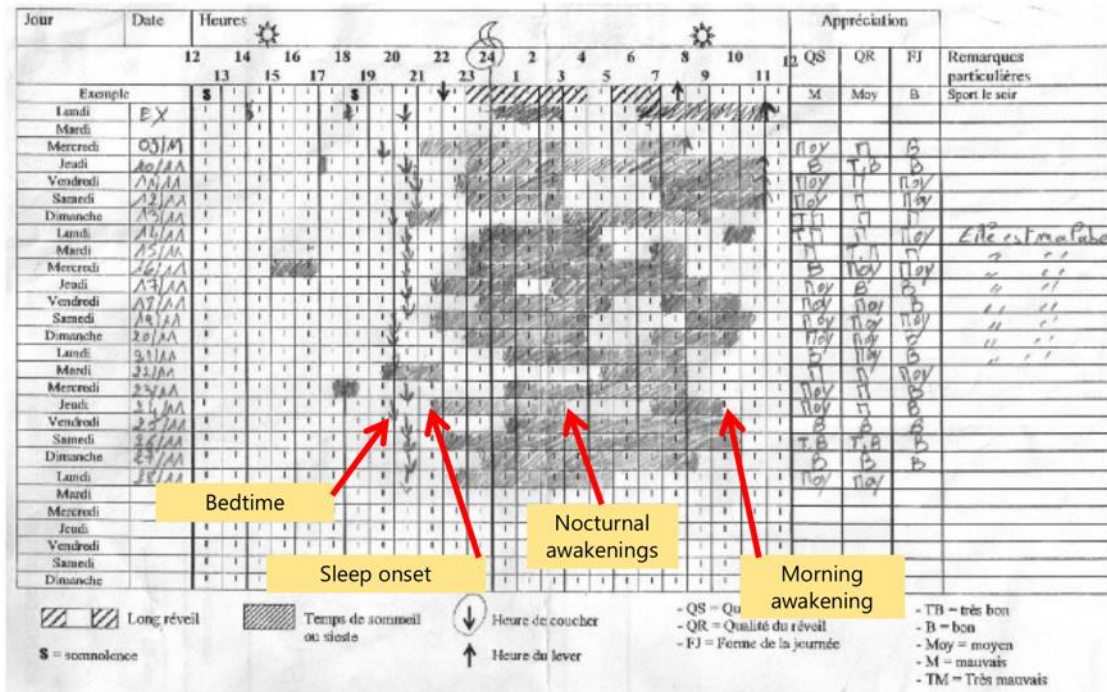
Part B: Discussion/Referral to sleep specialist:		Score
The Child shows one or more of the following: <ul style="list-style-type: none"><li>• startles or jerks parts of the body while falling asleep and/or while asleep</li><li>• often changes position</li><li>• kicks the covers off the bed</li><li>• shows repetitive actions such as rocking or head banging while falling asleep</li></ul>	<ul style="list-style-type: none"><li>○ Never (1)</li><li>○ Occasionally (1-2 per month or less) (2)</li><li>○ Sometimes (once or twice per week) (3)</li><li>○ Often (3-5 times per week) (4)</li><li>○ Always (daily) (5)</li></ul>	○
The child snores loudly and/or has difficulty breathing during the night	<ul style="list-style-type: none"><li>○ Never (1)</li><li>○ Occasionally (1-2 per month or less) (2)</li><li>○ Sometimes (once or twice per week) (3)</li><li>○ Often (3-5 times per week) (4)</li><li>○ Always (daily) (5)</li></ul>	○
The Child shows one or more of the following: wakes up from sleep screaming or confused sleep walks has recurrent nightmares	<ul style="list-style-type: none"><li>○ Never (1)</li><li>○ Occasionally (1-2 per month or less) (2)</li><li>○ Sometimes (once or twice per week) (3)</li><li>○ Often (3-5 times per week) (4)</li><li>○ Always (daily) (5)</li></ul>	○
Score 3 or higher on any item: consider discussion and or referral to sleep specialist	Number of scores $\geq 3$	



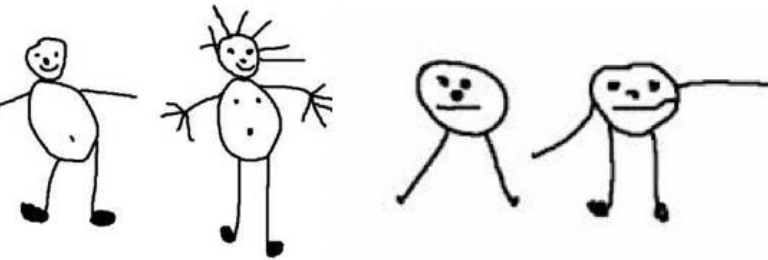
# Complaint of sleep disturbance

## Evaluation of sleep, screening of sleep disorders and repercussions

- Dedicate a consultation to sleep (if possible)
- Screening questionnaire
- Sleep log (duration > 2 weeks)



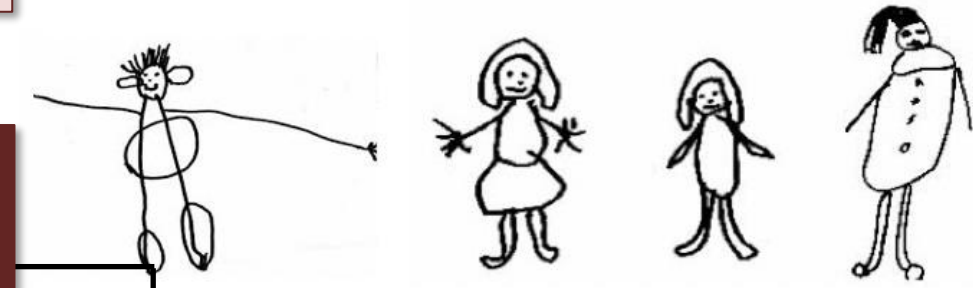




## Complaint of sleep disturbance

### Evaluation of sleep, screening of sleep disorders and repercussions

- Dedicate a consultation to sleep (*if possible*)
- Screening questionnaire
- Sleep log (*duration > 2 weeks*)

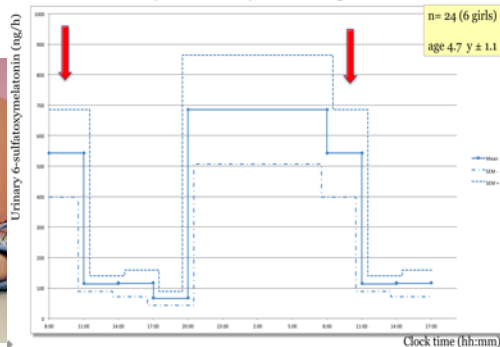


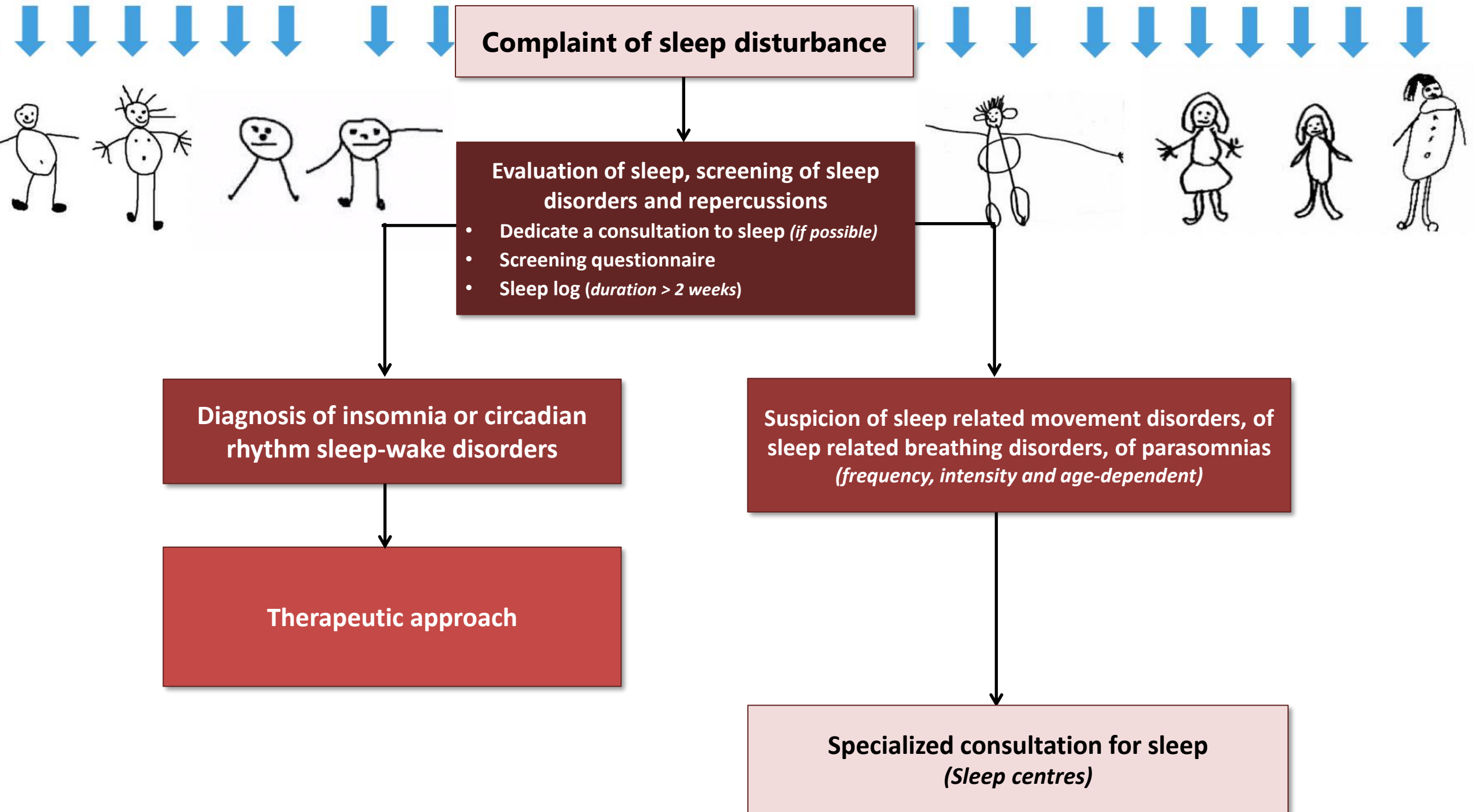
Suspicion of sleep related movement disorders, of sleep related breathing disorders, of parasomnias  
(*frequency, intensity and age-dependent*)

Specialized consultation for sleep  
(*Sleep centres*)



Urinary 6-Sulfatoxymelatonin profile







## Complaint of sleep disturbance

### Evaluation of sleep, screening of sleep disorders and repercussions

- Dedicate a consultation to sleep (*if possible*)
- Screening questionnaire
- Sleep log (*duration > 2 weeks*)

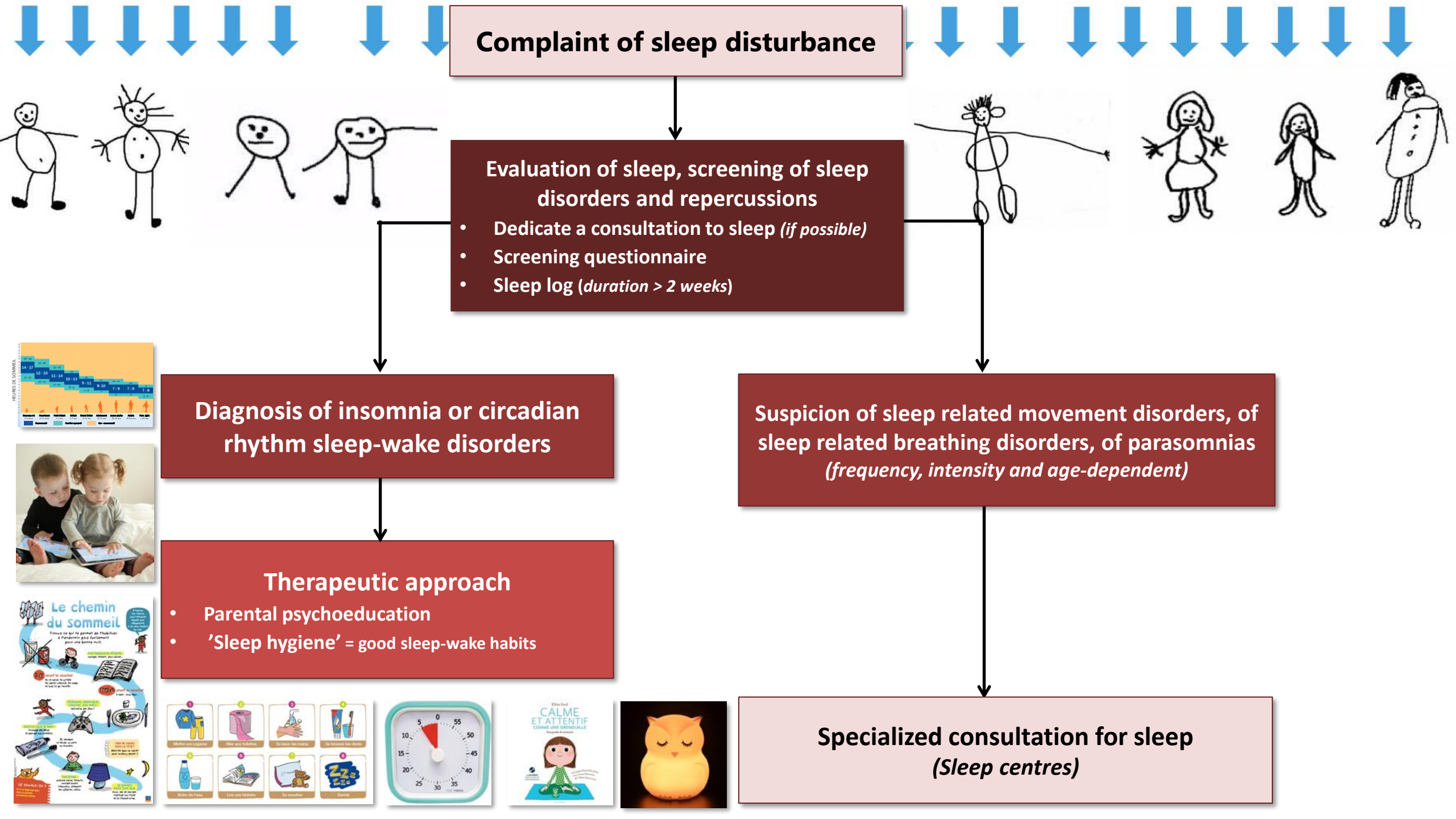
### Diagnosis of insomnia or circadian rhythm sleep-wake disorders

### Therapeutic approach

- Parental psychoeducation
- 'Sleep hygiene' = good sleep-wake habits

### Suspicion of sleep related movement disorders, of sleep related breathing disorders, of parasomnias (*frequency, intensity and age-dependent*)

### Specialized consultation for sleep (*Sleep centres*)



## Strategies to Improve Sleep in Children with Autism Spectrum Disorders

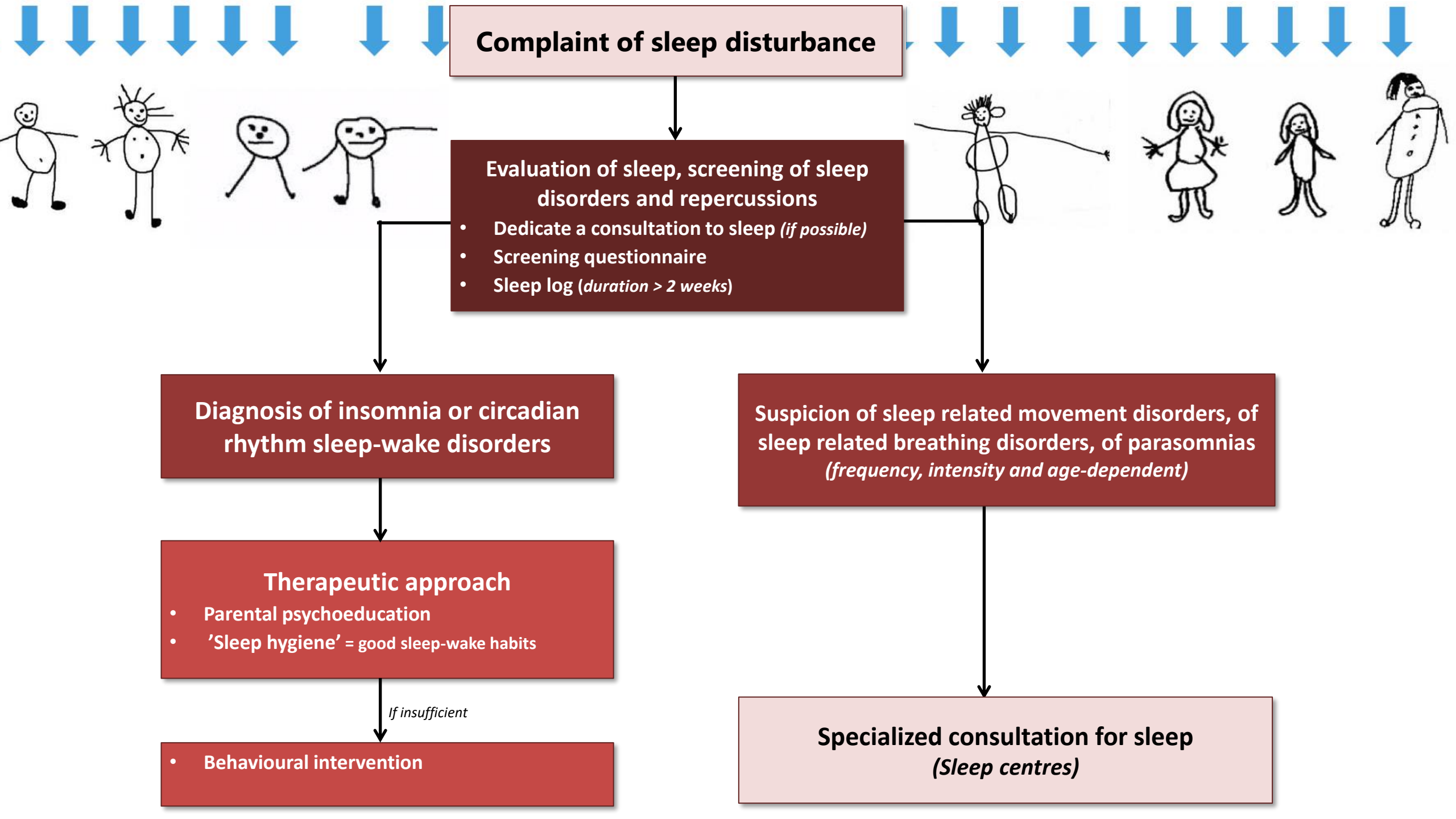


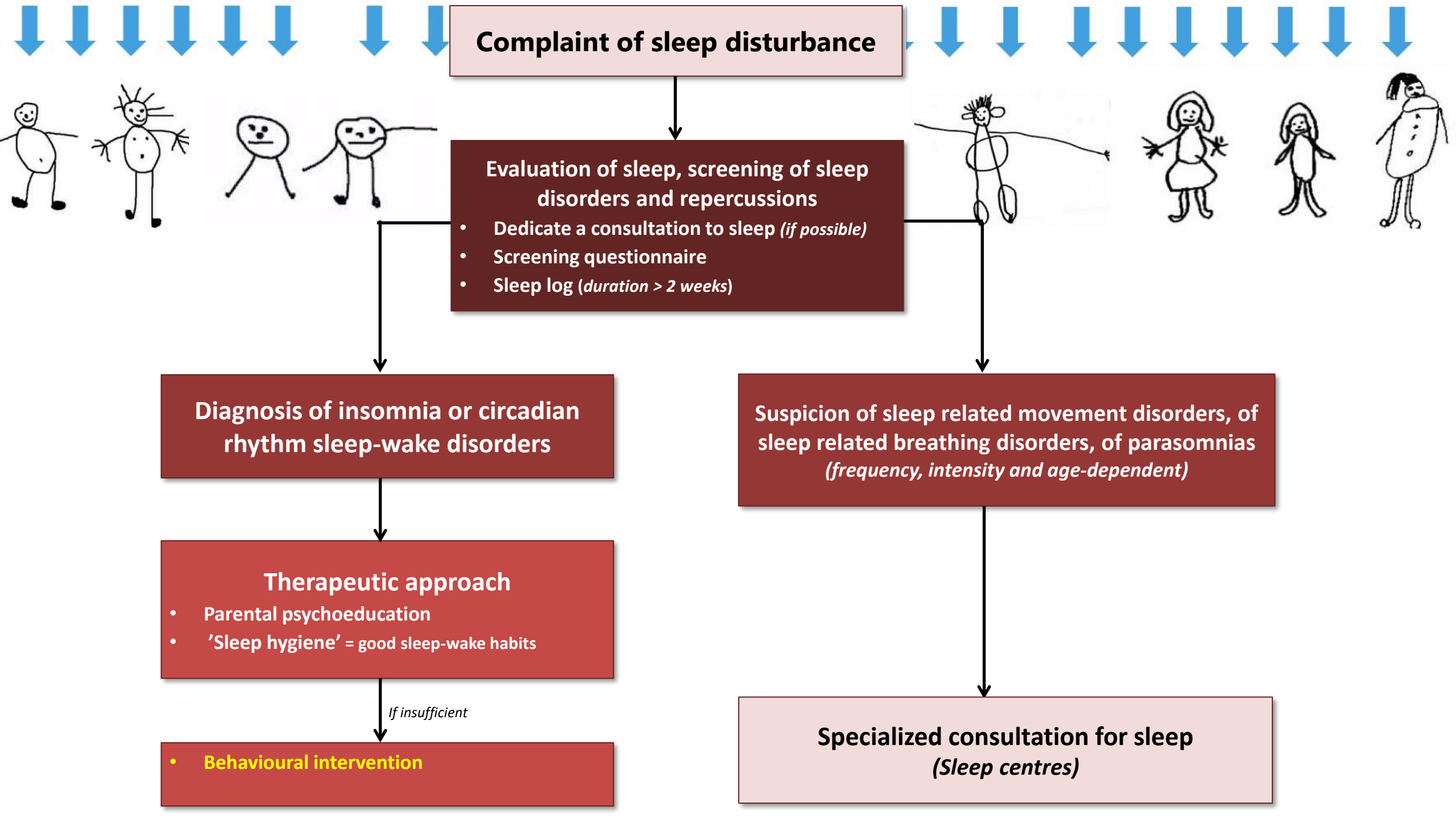
*A Parent's Guide*



These materials are the product of a project of the Autism Speaks Autism Treatment Network (ATN). The project is supported by Autism Speaks. It is supported by grant #11054 through the U.S. Department of Health and Human Services.

<https://www.autismspeaks.org/tool-kit/atnair-p-strategies-improve-sleep-children-autism>





# Behavioural interventions: *overview*

1

**Consistant bedtime rituals**

2

**Appropriate bed-sleep associations**

3

**Relaxation techniques**

4

**Positive reinforcement of adaptive behaviours**

5

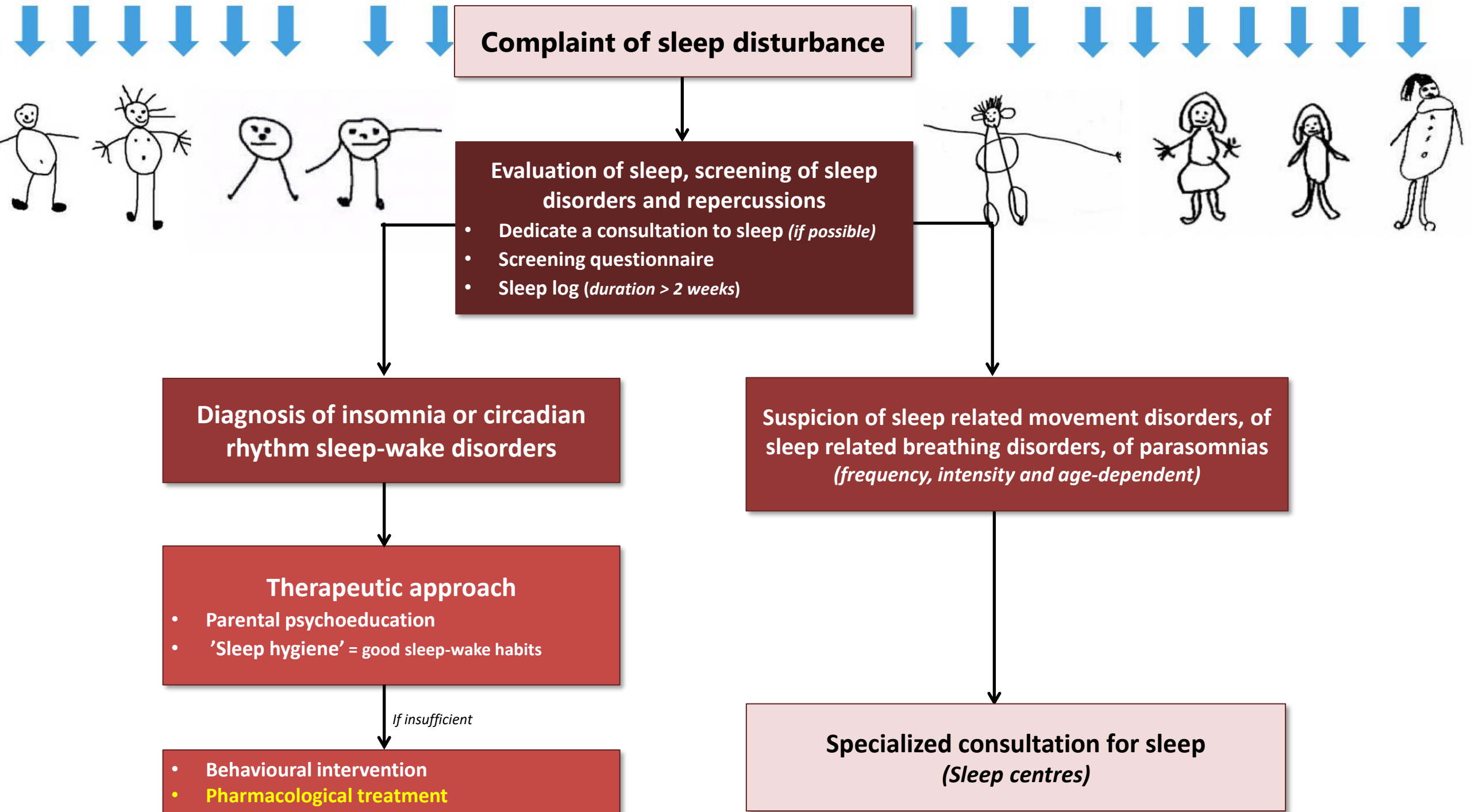
***Bedtime fading***

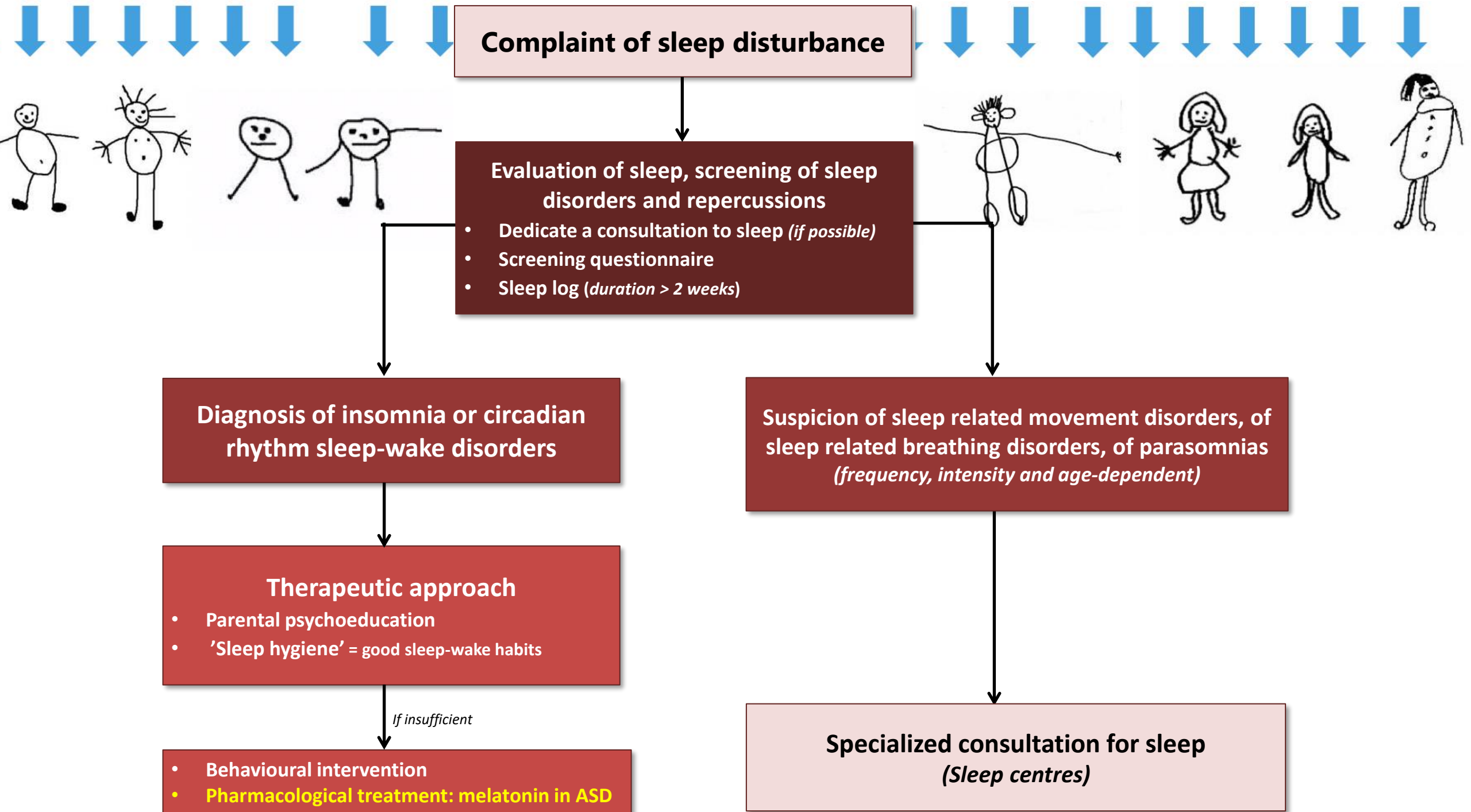
6

**Gradual extinction**

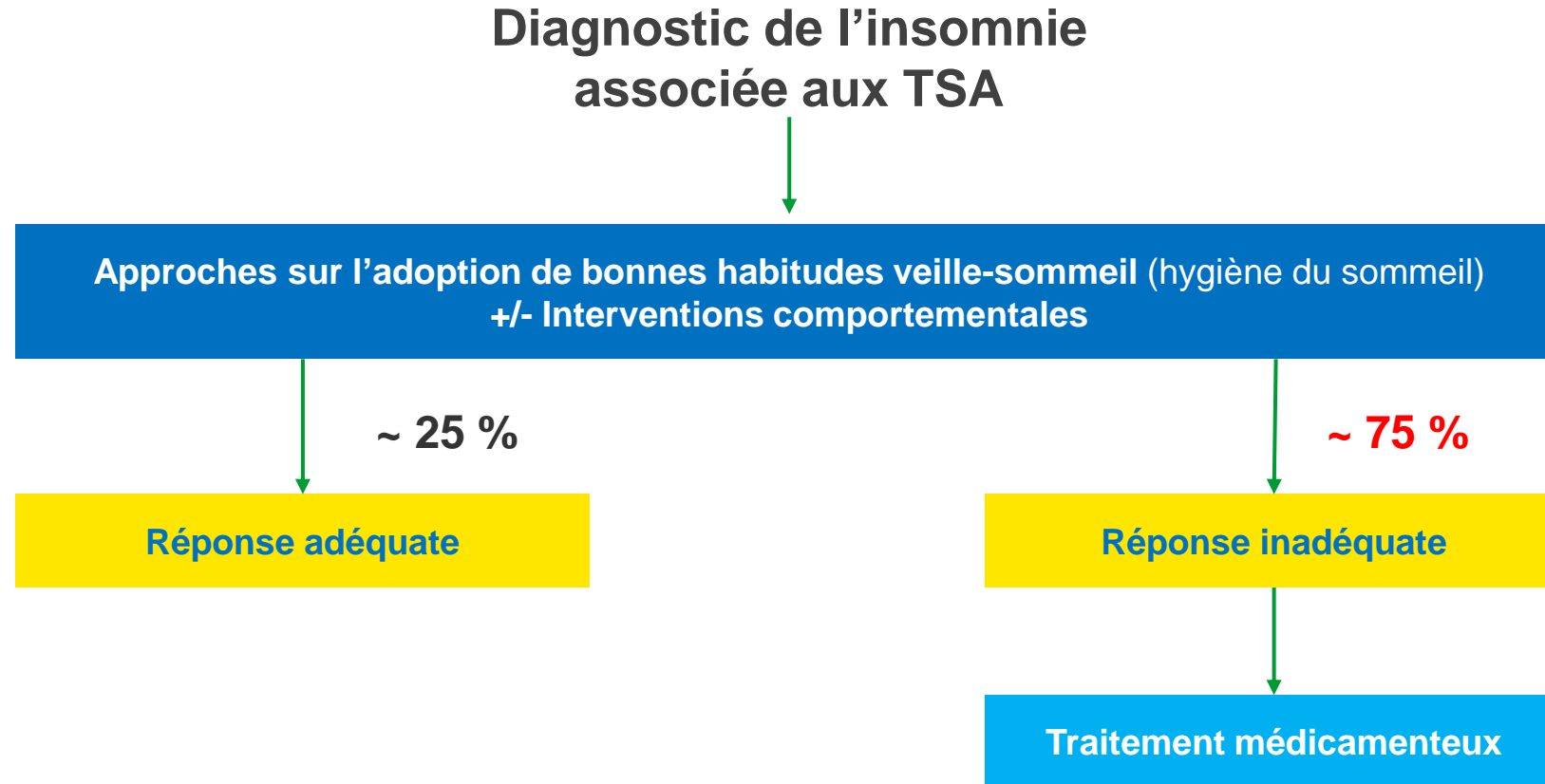








# Limites des interventions comportementales chez l'enfant avec TSA

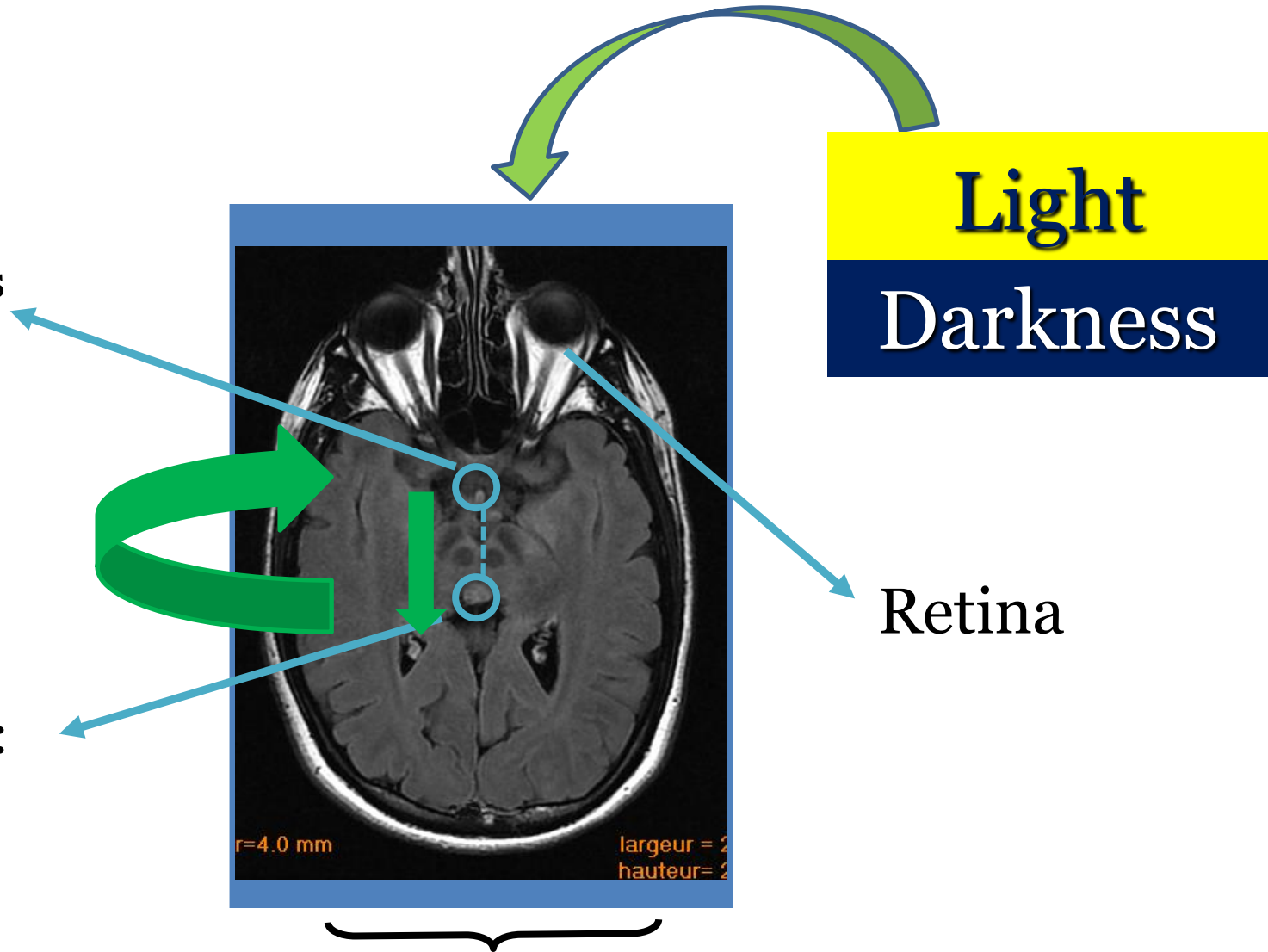


+

# Melatonin as a pharmacological treatment

Suprachiasmatic  
Nuclei (SCN):  
MT1 and MT2 receptors

Pineal gland:  
Melatonin



**Light**  
**Darkness**

Retina

Rhythms & behaviours : sleep-wake

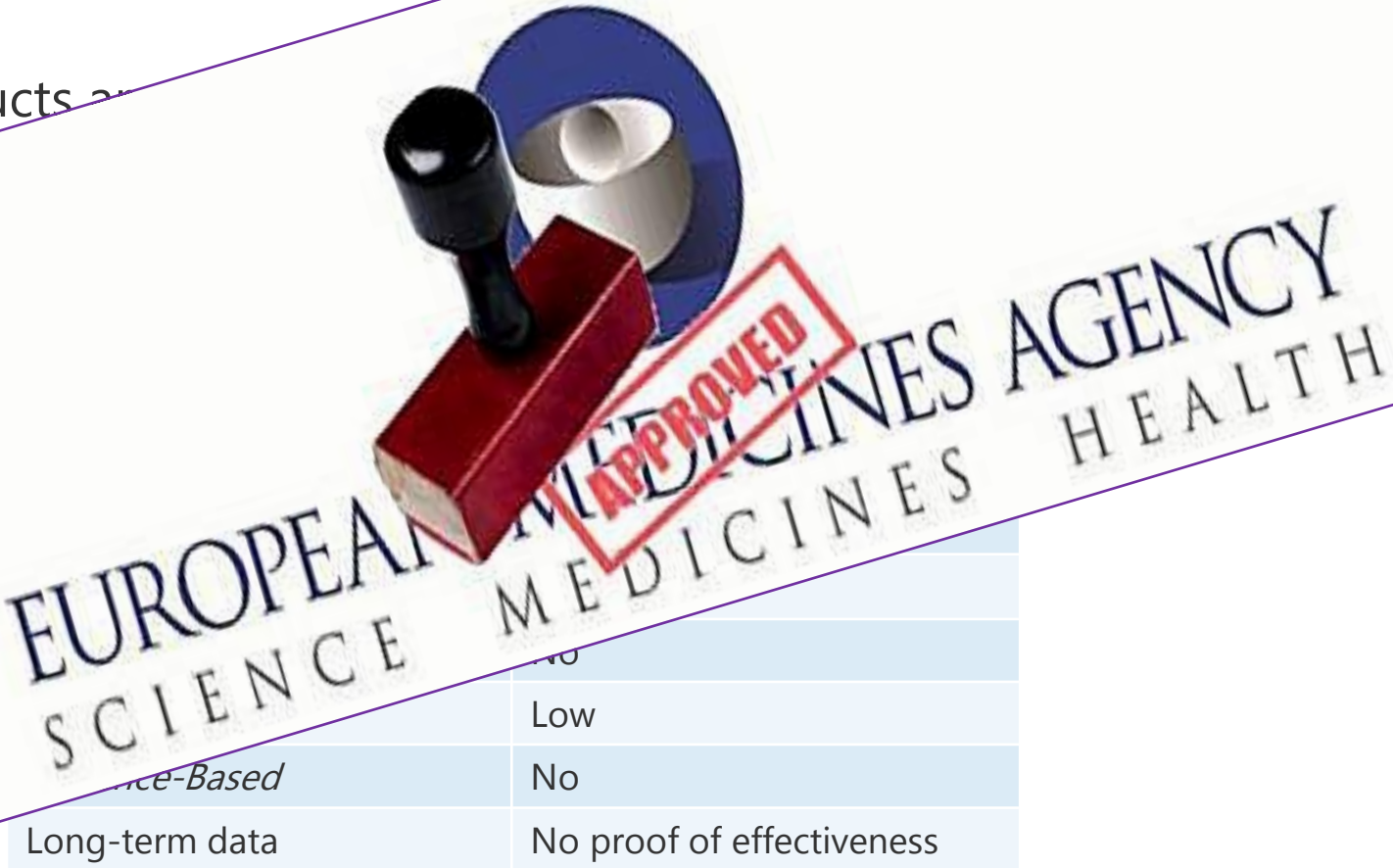
# Melatonin as a dietary supplement

- IR melatonin is frequently used as a dietary supplement; inexpensive and available (in the past) in the pharmacies



# Melatonin as a dietary supplement

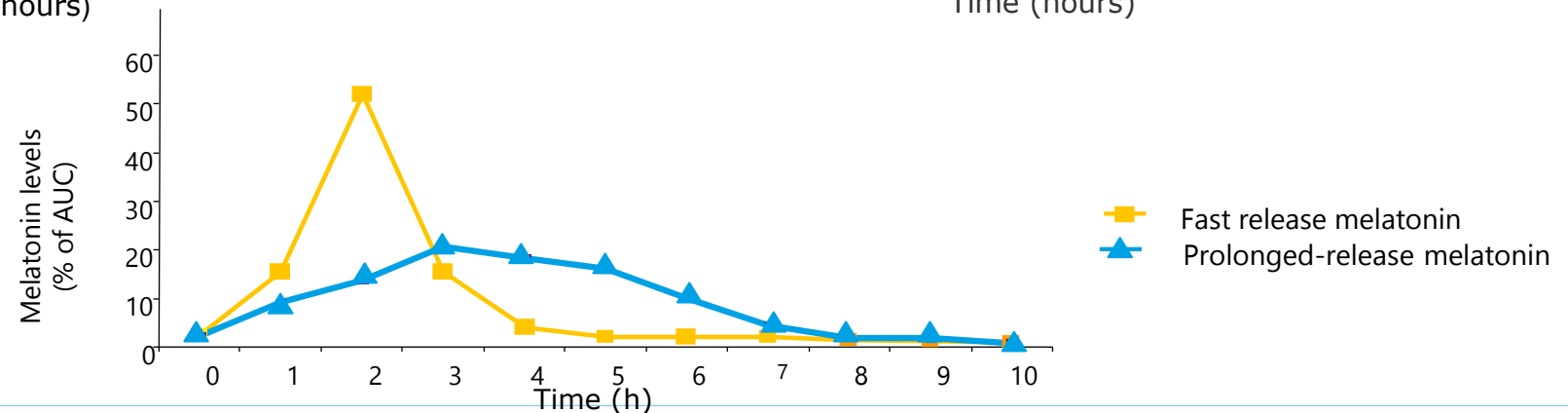
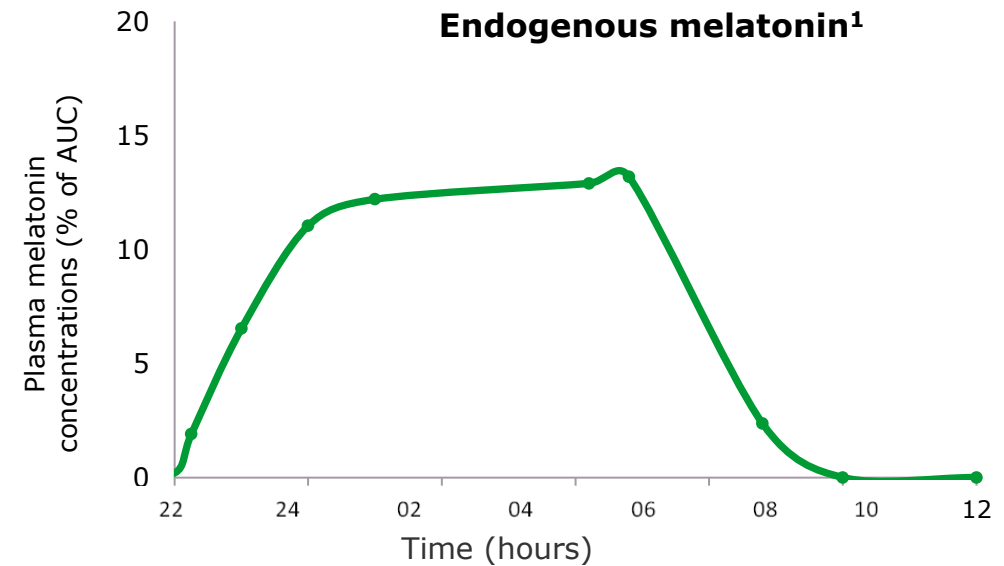
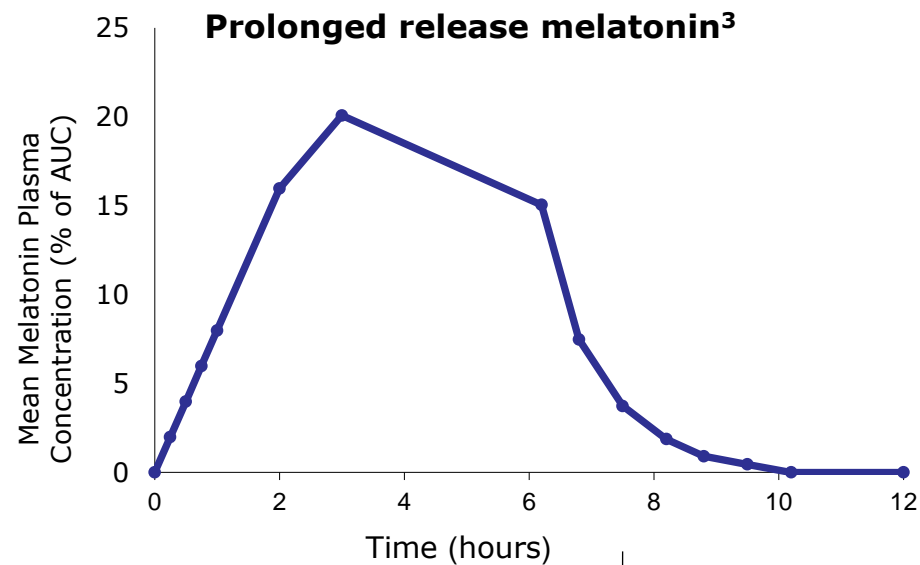
- IR melatonin is frequently used as a dietary supplement in pharmacies
- **However:** these products are not indicated
  - A recent study on their efficacy
  - Some products are not indicated



Erland, L.A. and P.K. Saxena, Melatonin Natural Health Products and Supplements: Presence of Serotonin and Significant Variability of Melatonin Content. J Clin Sleep Med, 2017. 13(2): p. 275-281. Zisapel, N., Melatonin and Sleep. The Open Neuroendocrinology Journal, 2010. 3: p. 85-95. Gringras, P., et al., Melatonin for sleep problems in children with neurodevelopmental disorders: randomised double masked placebo controlled trial. Bmj, 2012. 345: Reiter RJ, Calvo JR, Karbownik M, Qi W, Tan DX. Melatonin and its relation to the immune system and inflammation. Ann N Y Acad Sci 2000; 917: 376-86. Johnson KP, Malow BA. Assessment and pharmacologic treatment of sleep disturbance in autism. Child Adolesc Psychiatr Clin N Am 2008; 17: 773-85.

# Pharmacokinetic profile

- Pediatric prolonged-release melatonin (Slenyto®) **mimics endogenous melatonin secretion profile**



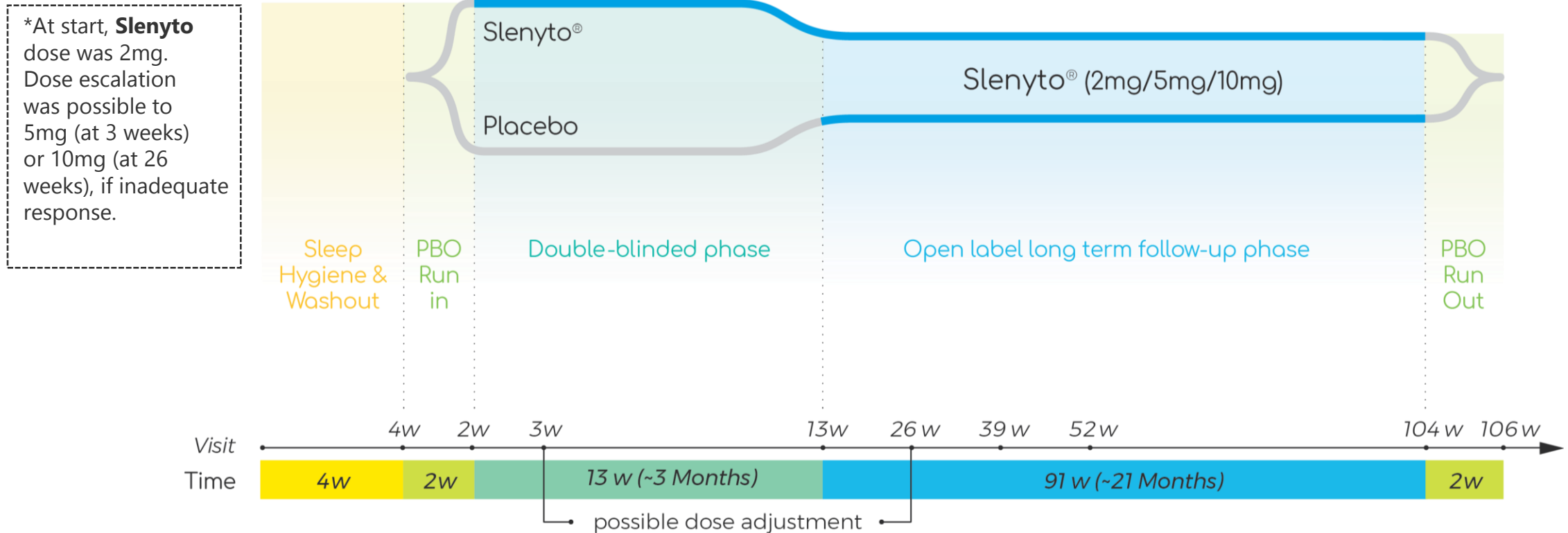
1. Adapted from Arendt J et al Immunoassay of 6-hydroxymelatonin sulfate in human plasma and urine: abolition of the urinary 24-hour rhythm with atenolol. J Clin Endocrinol Metab. 1985 Jun;60(6):1166-73.; 2. Slenyto EPAR April 2019 <https://www.ema.europa.eu/en/medicines/human/EPAR/slenyto>; 3. Circadin EPAR. Assessment report for Circadin. Procedure No. EMEA/H/C/695,200 ; <https://www.ema.europa.eu/en/medicines/human/EPAR/circadin>

# Slenyto<sup>®</sup> prolonged release melatonin for children with ASD

- **New paediatric formula** of prolonged release melatonin
- **Tablets properties:** 3mm coated minitablet (small, easy to swallow, tasteless and odourless)
- Corresponds to GMP, GLP, GCP standards



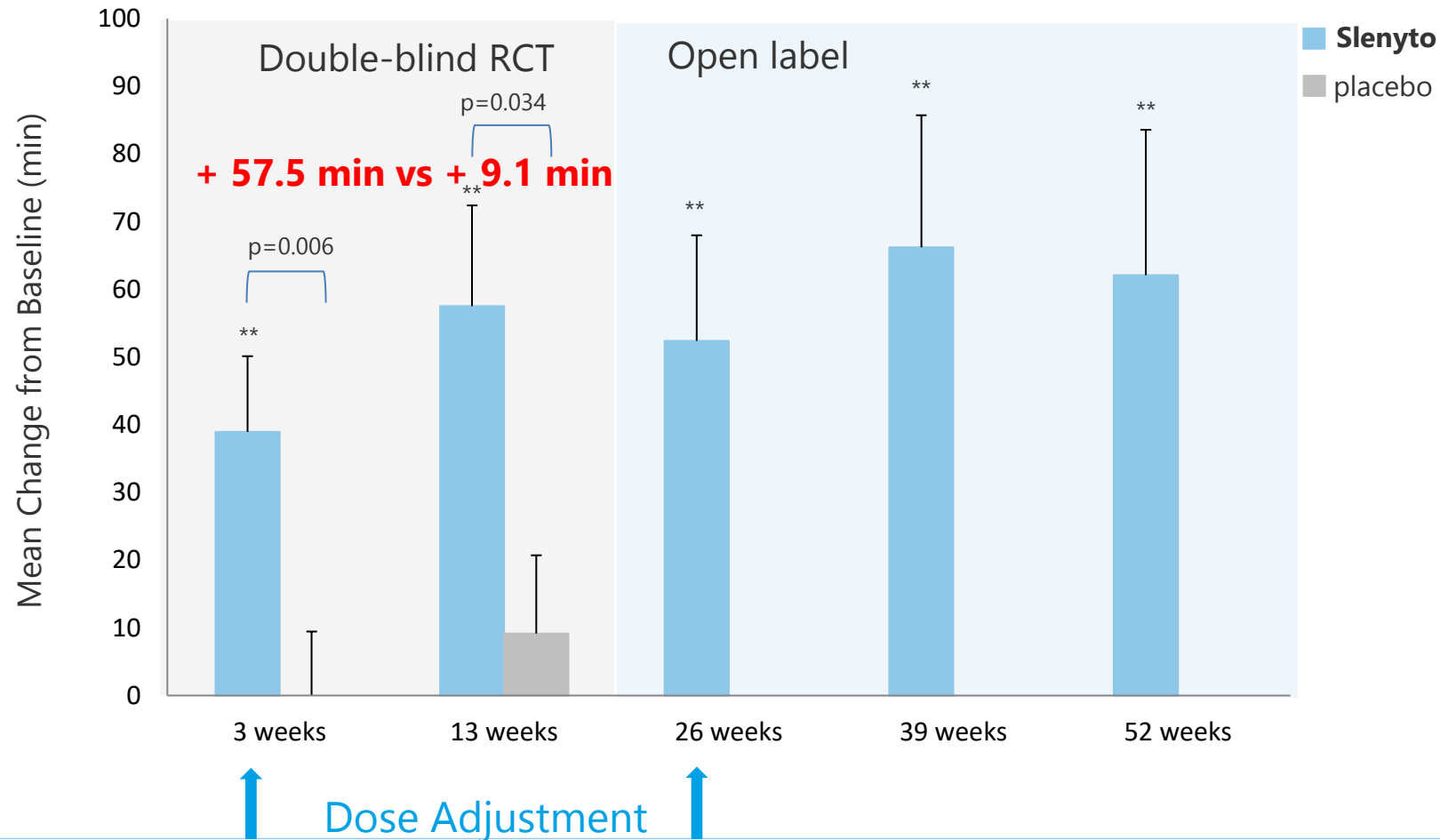
# PedPRM (Slenyto®) Phase III - clinical trial design



- 24 sites in EU (10) and US (14) under FDA-IND ; **n= 125 children & adolescents aged 2-17 years over 2 years**

# Slenyto<sup>®</sup> significantly improved **sleep duration**

## Total Sleep Time (TST)



**+48,8**  
minutes

↑ Improvement  
Based on double-blind  
RCT at 13 weeks

**+62**  
minutes

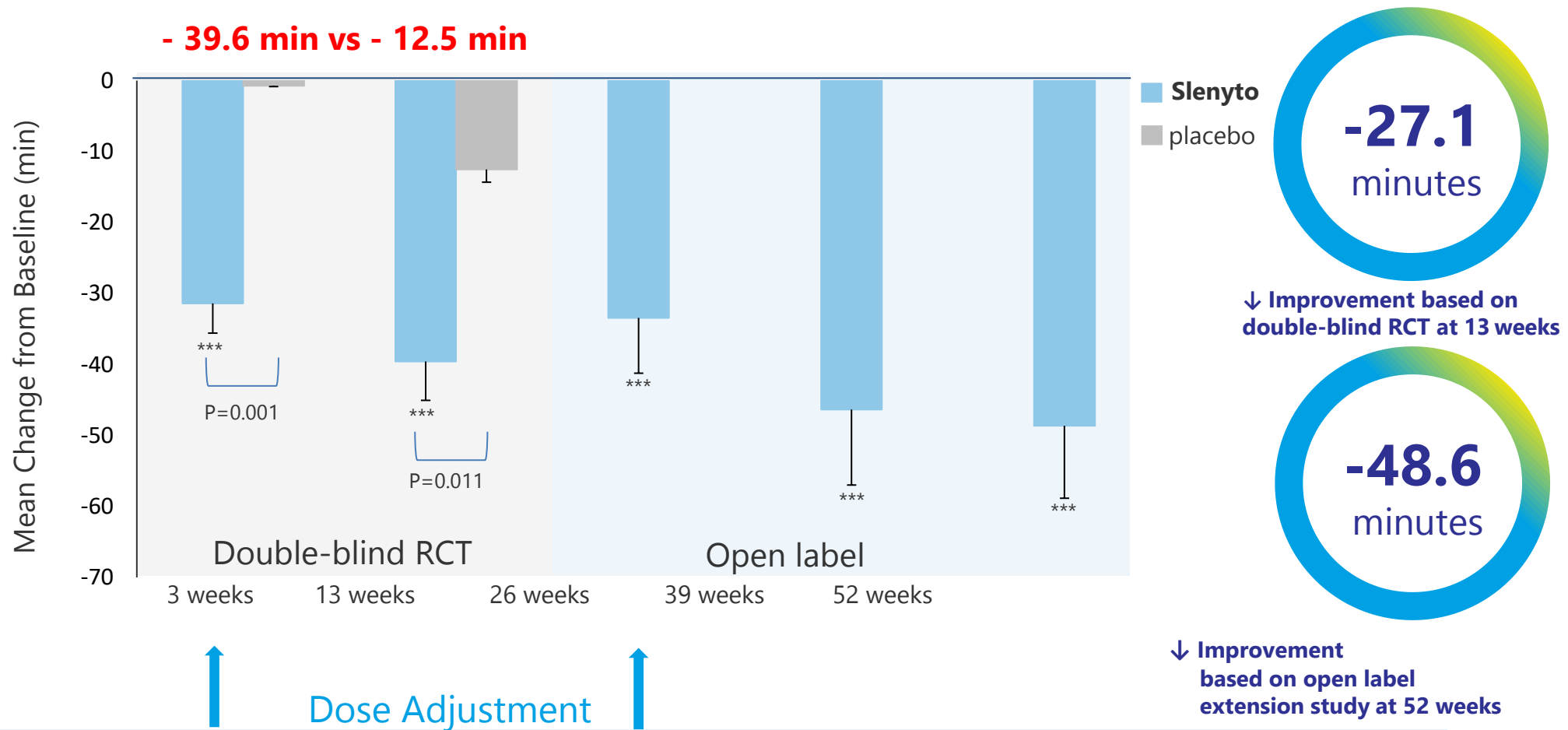
↑ Improvement  
Based on open label extension  
study at 52 weeks

$**p\leq 0.01$  vs BL



# Slenyto<sup>®</sup> significantly shortened **sleep onset**

## Sleep Latency



# Slenyto<sup>®</sup> significantly improved **uninterrupted sleep** duration

## Longest Sleep Duration



Gringras, P., et al., Efficacy and Safety of Pediatric Prolonged-Release Melatonin for Insomnia in Children With Autism Spectrum Disorder. J Am Acad Child Adolesc Psychiatry, 2017. 56(11): p. 948-957.e4 ; Maras, Schroder et al. Long-term Efficacy and Safety of Pediatric Prolonged-Release Melatonin for Insomnia in Children with Autism Spectrum Disorder. Journal of Child and Adolescent Psychopharmacology, 2018.

# Responders and dose split

76% response rate after dose adjustment (52 weeks Based on open label extension)

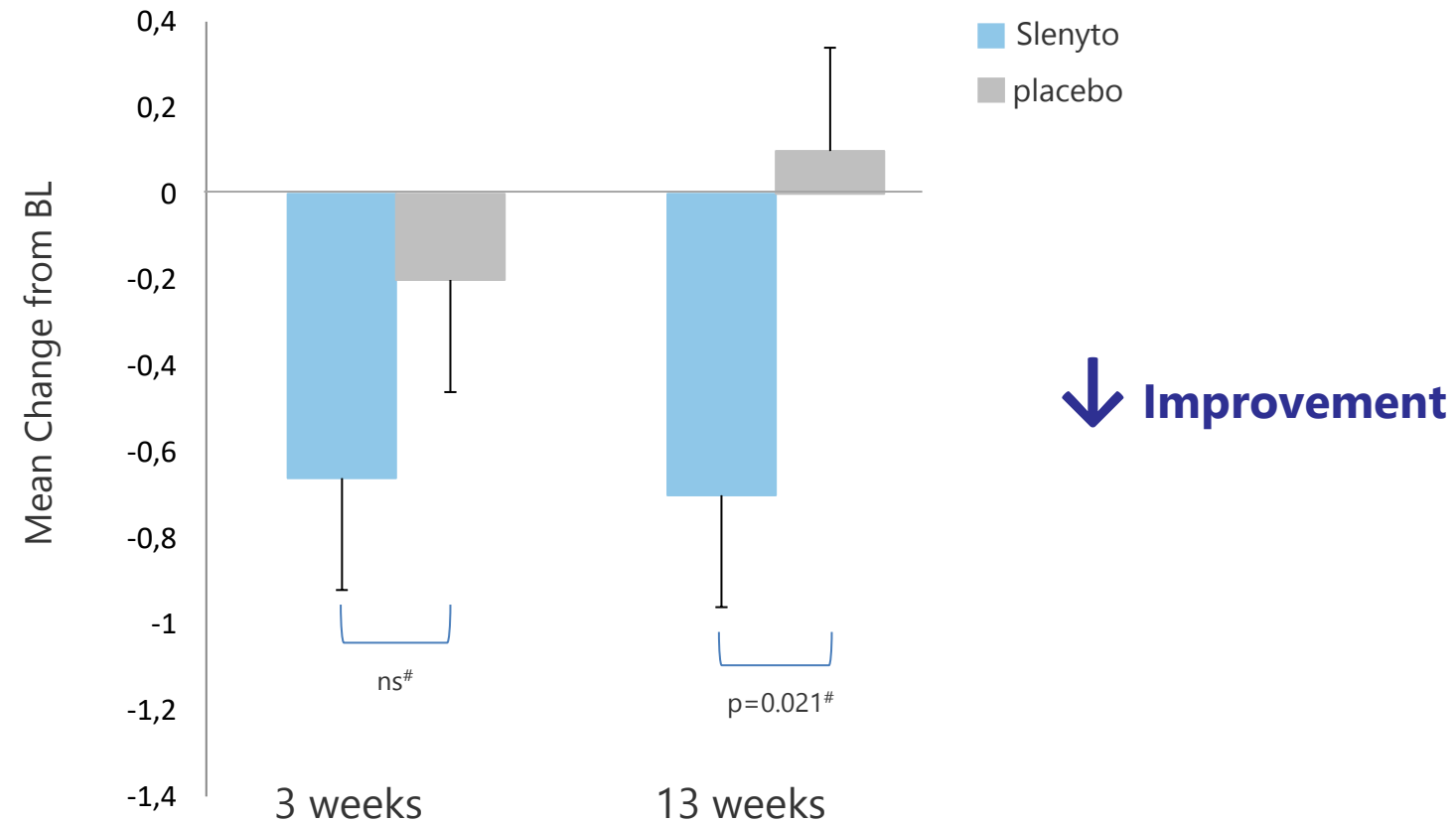


#Responder = overall improvement of 1 hour or more in TST, SL, or both.

\*Including patients that were randomized to received placebo in the 3 months DB period

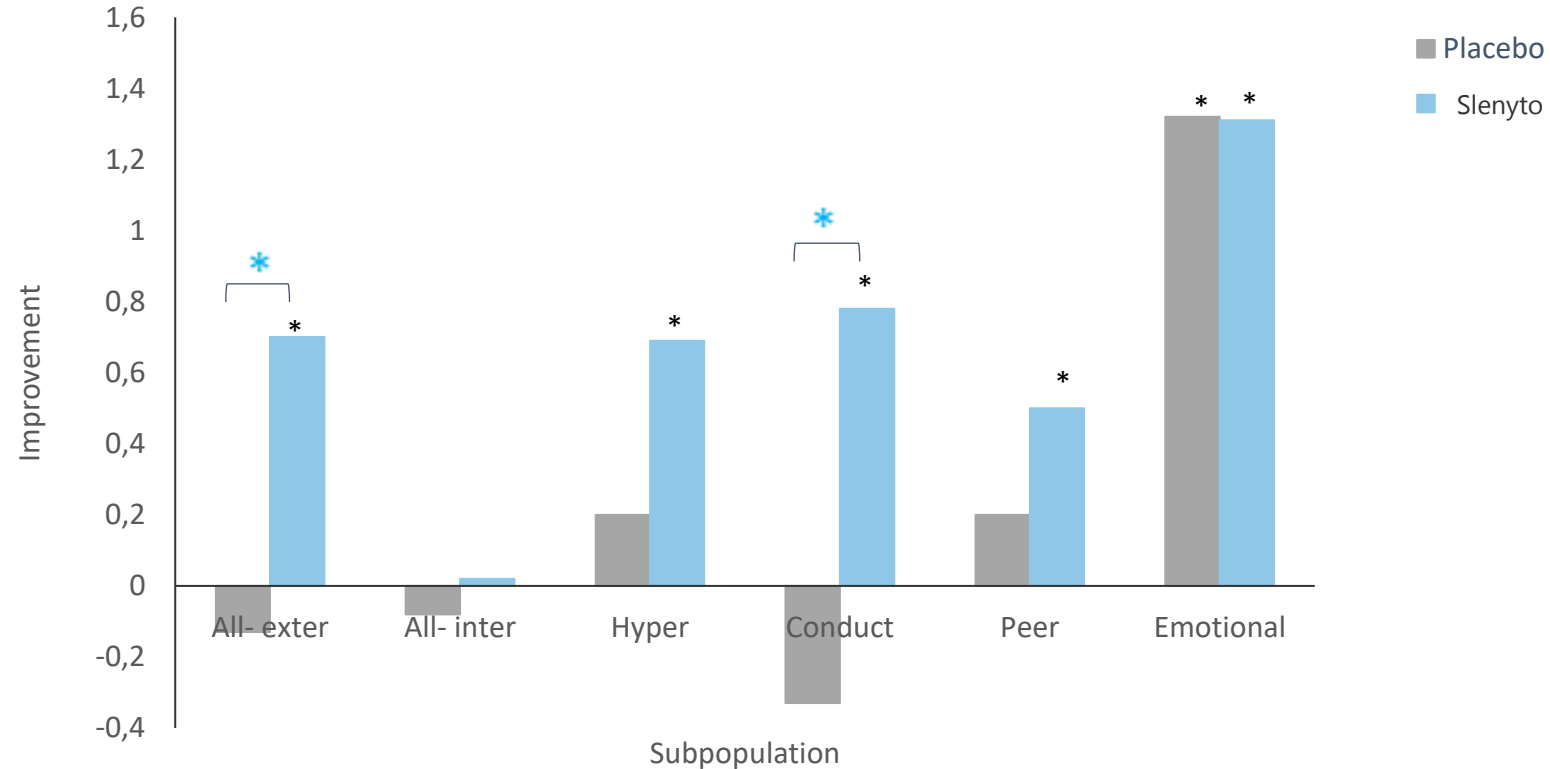
# Slenyto<sup>®</sup> improved **Externalizing Behavior (SDQ)**

Double blind period



#MMRM analysis

# Effect of treatment on respective behaviour in subpopulations



\* Significant vs. Placebo ( $p < 0.05$ )

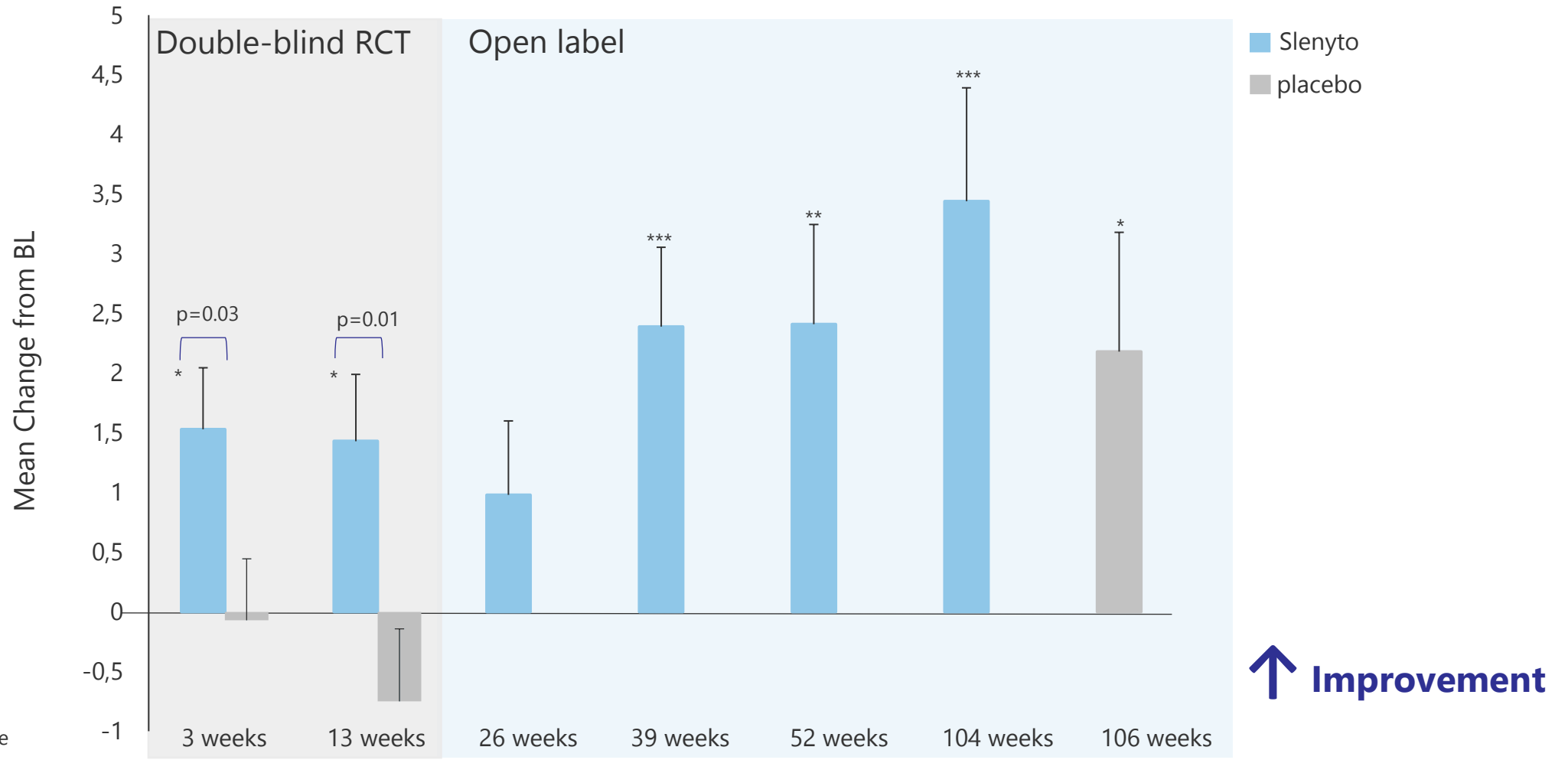
\* Significant vs. baseline ( $p < 0.05$ )

\* $p < 0.05$



# Slenyto<sup>®</sup> significantly improved parents' Quality of Life

## WHO-5



\*p≤0.05  
\*\* p≤0.01  
\*\*\*p≤0.001 vs baseline

# SAFETY - Adverse Events - 104 weeks

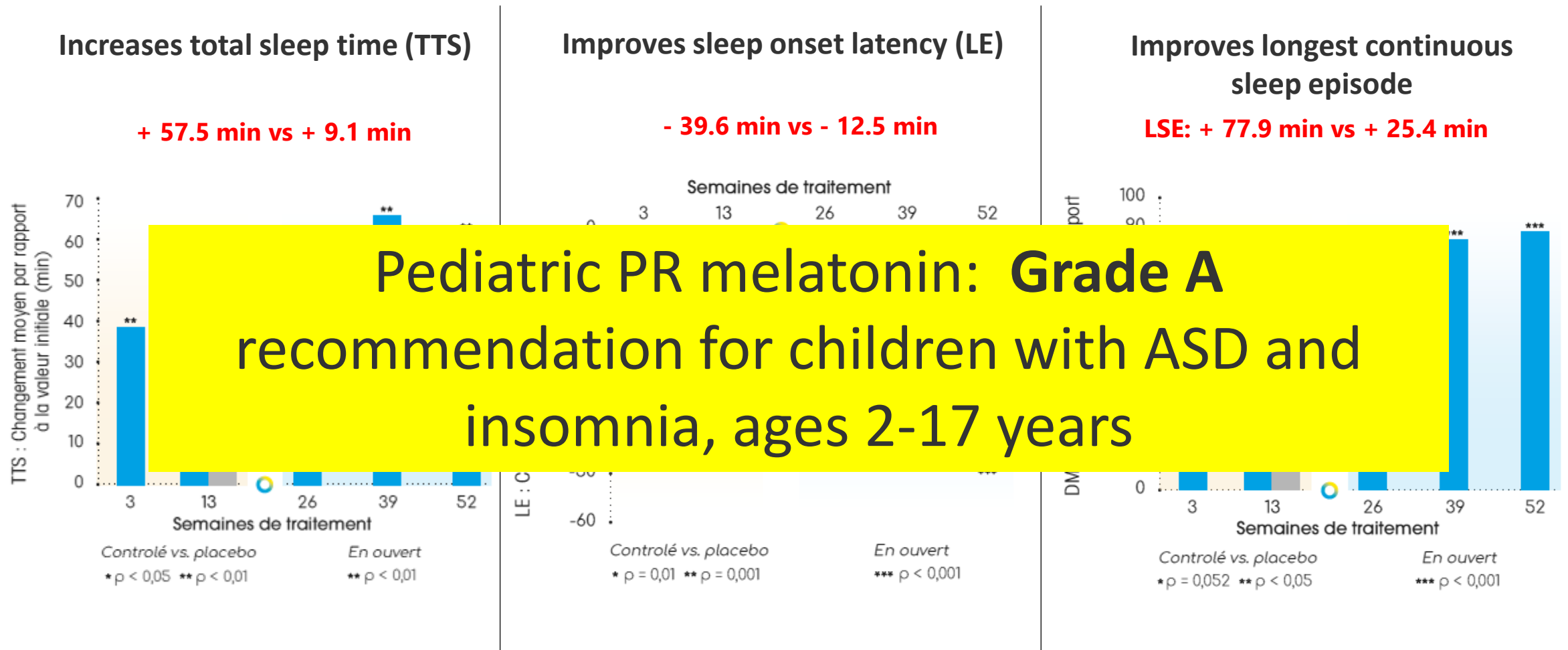
Most commonly reported treatment-emergent adverse events - up to 104 weeks

	Double-blind phase – 13 weeks				Open-label phase – 91 weeks	
	Slenyto		Placebo		Slenyto	
	Patients	Events	Patients	Events	Patients	Events
	(N=60)		(N=65)		(N=95)	
Number of patients with at least one TEAE	51 (85.0%)	208	50 (76.9%)	156	80 (84.2%)	524
Total number of Aes/week		<b>16</b>		<b>12</b>		<b>5.75</b>
Preferred term						
Somnolence	17 (28.3%)	18	8 (12.3%)	8	24 (25.3%)	31
Fatigue	15 (25.0%)	19	12 (18.5%)	13	25 (26.3%)	33
Upper respiratory tract infection	9 (15.0%)	9	7 (10.8%)	8	14 (14.7%)	24
Mood swings	10(16.7%)	10	11 (16.9%)	12	17 (17.9%)	24
Vomiting	8 (13.3%)	11	10 (15.4%)	10	20 (21.1%)	33
Agitation	11 (18.3%)	12	7 (10.8%)	8	8 (8.4%)	10
Headache	8 (13.3%)	8	4 (6.2%)	4	12 (12.6%)	12
Cough	7 (11.7%)	7	5 (7.7%)	5	16 (16.8%)	27
Dyspnoea	6 (10.0%)	6	4 (6.2%)	4	10 (10.5%)	10

# Long term safety -104 weeks

- Slenyto<sup>®</sup> is **well-tolerated in long term treatment**
- The mean **BMI** Z-score and minimum and maximum scores are considered **within the normal distribution**
- The mean **Tanner** SD scores and minimum and maximum scores were **within the normal distribution**
- No delay in pubertal development and growth was evident

# Efficacy of PedPR melatonin (2-10 mg) on insomnia in children with ASD



Gringras, P., et al., Efficacy and Safety of Pediatric Prolonged-Release Melatonin for Insomnia in Children With Autism Spectrum Disorder. *J Am Acad Child Adolesc Psychiatry*, 2017. 56(11): p. 948-957.e4.; Maras, A., et al., Long-Term Efficacy and Safety of Pediatric Prolonged-Release Melatonin for Insomnia in Children with Autism Spectrum Disorder. *J Child Adolesc Psychopharmacol*, 2018. doi: 10.1089/cap.2018.0020. Schroder CM, Malow B, Maras A, Melmed R, Findling R, Breddy J, Nir T, Shahmoon S, Zisapel N, Gringras P. Pediatric Prolonged-Release Melatonin for Sleep in Children with Autism Spectrum Disorder: Impact on Child Behavior and Caregiver's Quality of Life. *Journal of Autism and Developmental Disorders* 2019 Aug;49(8):3218-3230I. Malow B et al. 2020. Sleep, Growth, and Puberty After 2 Years of Prolonged-Release Melatonin in Children With Autism Spectrum Disorder, *J Am Acad Child Adolesc Psychiatry* 2020;

# Monitoring of sleep in children with ASD in primary care

## - *when time is short*

### Novel structured follow-up tool for insomnia – child's sleep

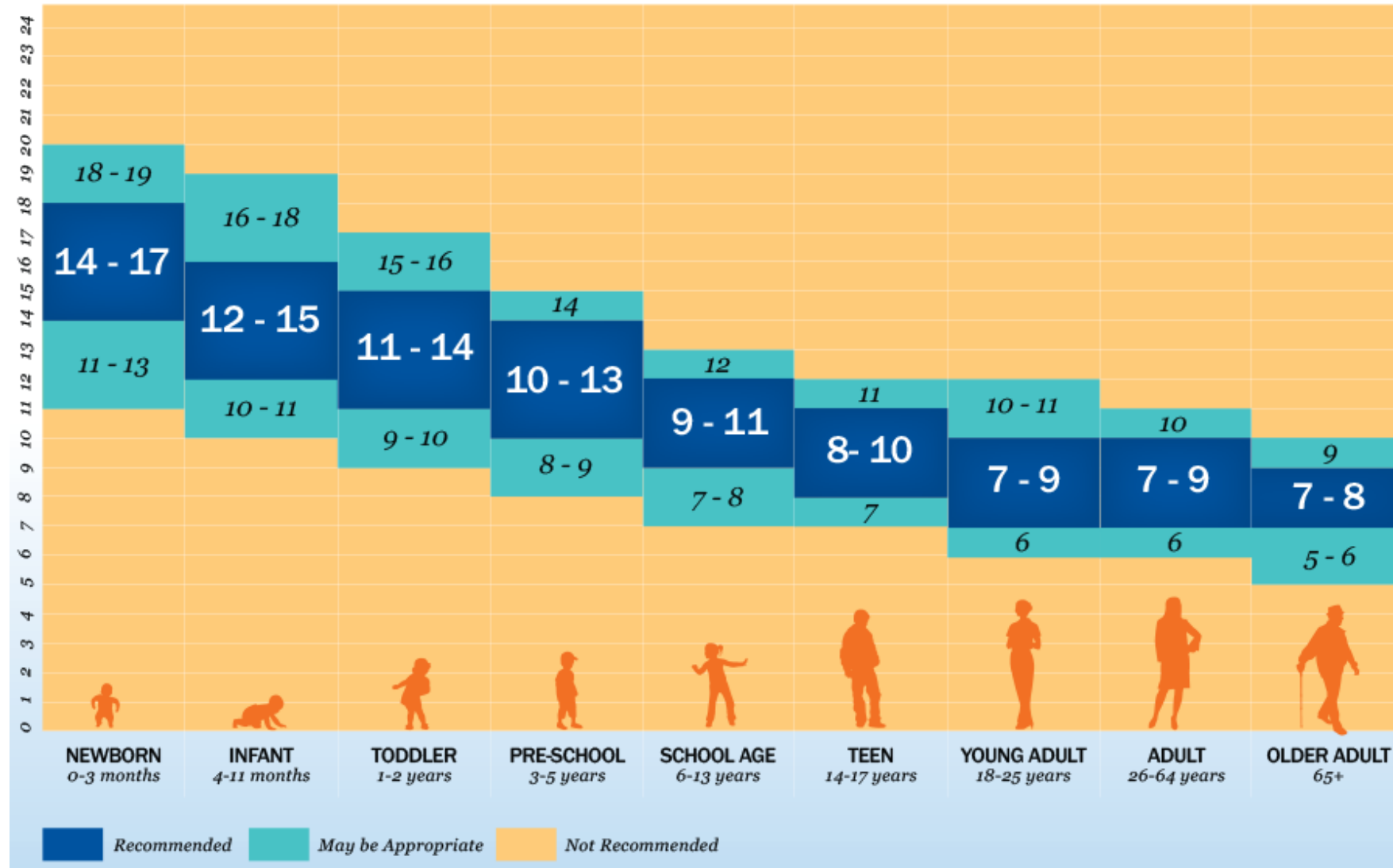
Date	Child's name	Age
Child's sleep*	<ol style="list-style-type: none"> <li>At what time does your child go to bed?</li> <li>How long does it take your child to fall asleep from lights off? ____ minutes</li> <li>After falling asleep <u>about</u> how many times does your child wake up at night (not counting final awakening)?</li> <li>In total, how long do these awakenings last approximately? ____ minutes</li> <li>What is approximately the longest episode of continuous sleep / uninterrupted sleep that your child has per night? ____ hours: minutes</li> <li>At what time does your child finally wake up for the day?</li> <li>How many hours of actual sleep does your child get during the night? ____ hours: minutes</li> <li>Does your child feel tired /rested upon awakening?</li> <li>In total how long does the child nap during the day? ____ minutes</li> </ol>	
Consideration	<ol style="list-style-type: none"> <li>Is the response to Q2 (SOL) &lt;30 minutes?</li> <li>Is the response to Q5 (LSE) &gt;6 hours?</li> <li>Is the response to Q7 (TST) acceptable sleep duration per age according to NSF, <math>\geq 8</math> (age 2-6) or <math>\geq 7</math> (age 6-18) hours?</li> </ol> <p>(If one of the above is No consider treatment/dose adjustment)</p>	<p>Yes/No</p> <p>Yes/No</p> <p>Yes/No</p>

# GOAL

- Time to fall asleep: < 30 minutes
- Longest episode of continuous sleep: > 6 hours
- Sleep duration within acceptable range for the age group of the child



# National Sleep Foundation's sleep duration recommendations

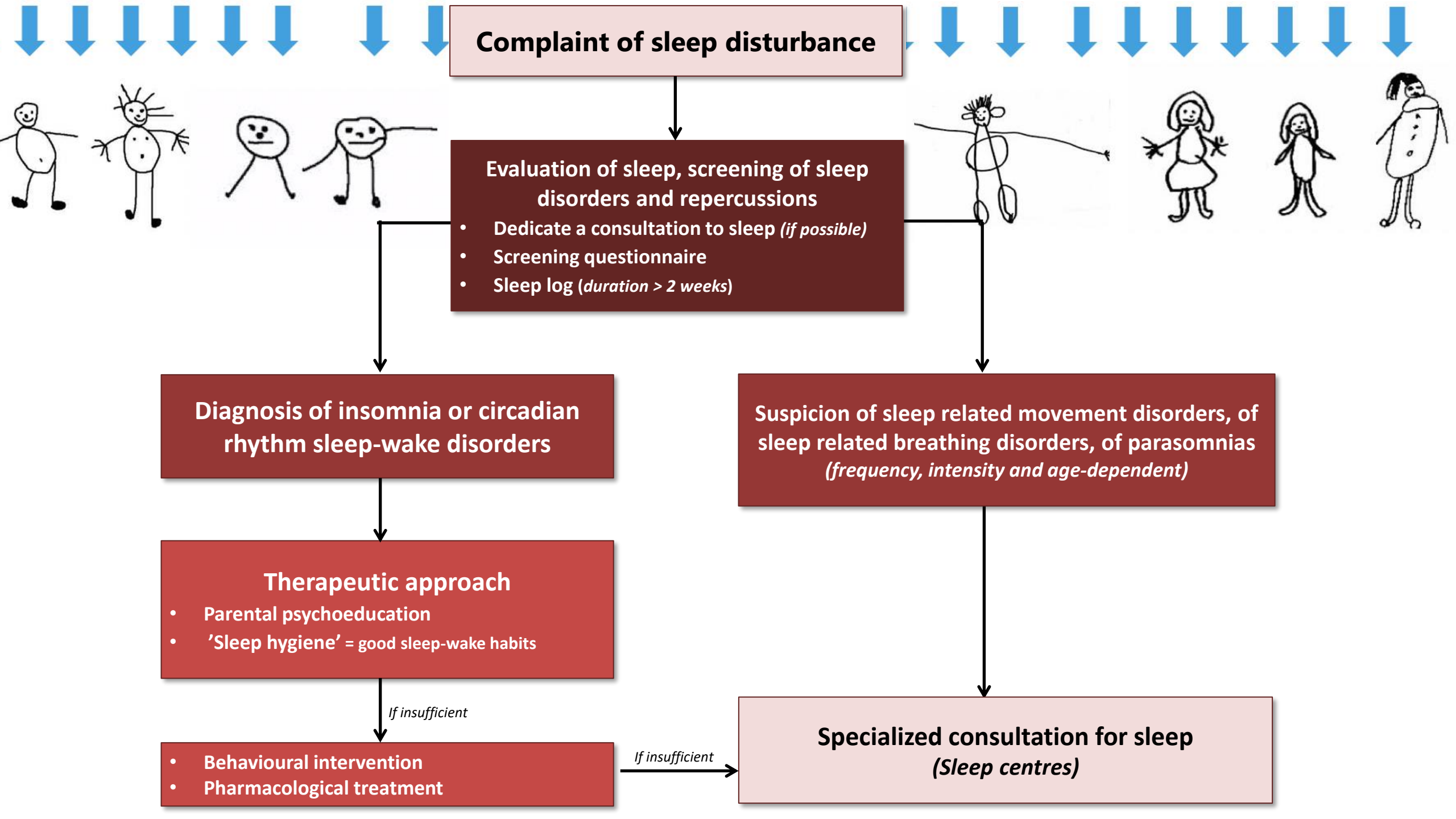


# Monitoring of sleep in children with ASD in primary care

## - *when time is short*

### Novel structured follow-up tool for insomnia – child's behavior and parent's satisfaction

Date	Child's name					Age
Child's behaviors	1. Have you noticed a change in your child's behavior after they had a good night's sleep? Please list the most important behaviors below • <i>ex: strong irritability</i>					
	2. How would you rate this behavior in the last month or since the last visit?					
	Score→ Behavior↓	1	2	3	4	5
	<i>irritability</i>	Markedly deteriorated	Deteriorated	Not changed	improved	Markedly improved
	_____	Markedly deteriorated	Deteriorated	Not changed	improved	Markedly improved
	_____	Markedly deteriorated	Deteriorated	Not changed	improved	Markedly improved
Parent's satisfaction	11. Are you satisfied with your child's sleep? (average over the last month)					
	Completely Dissatisfied (1)	Mostly Dissatisfied (2)	Neither Satisfied nor Dissatisfied (3)	Mostly Satisfied (4)	Completely Satisfied (5)	



# Clinical cases

# Case Study I - Lothar - Boy, age 2 years

Diagnosis: Typical ASD with developmental delay, allergies

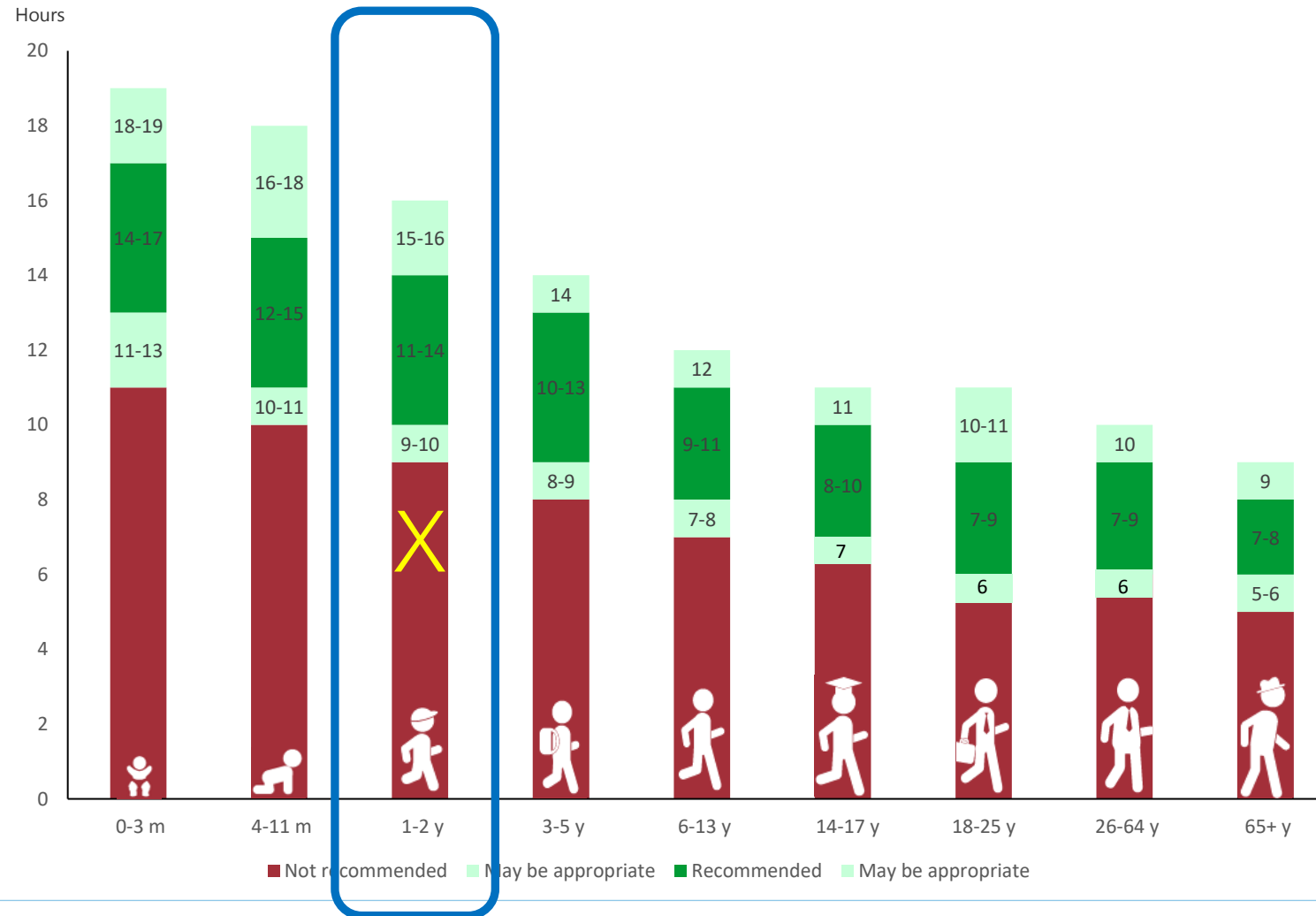
Sleep problem: sleep onset latency 90-120 minutes, 3-4 awakenings per night, duration: 5-40 minutes each, **total sleep time: 6.5 hours**

Daytime repercussion: Severe hyperactivity, several tantrums and social withdrawal

Family perspective: parents tired and stressed; father on sick leave for major depression



# National Sleep Foundation's sleep duration recommendations:



National Sleep Foundation 2015; Hirshkowitz M, Whiton K, Albert SM, Alessi C, Bruni O, DonCarlos L, Hazen N, Herman J, Adams Hillard PJ, Katz ES, Kheirandish-Gozal L, Neubauer DN, O'Donnell AE, Ohayon M, Peever J, Rawding R, Sachdeva RC, Setters B, Vitiello MV, Ware JC. National Sleep Foundation's updated sleep duration recommendations: final report. Sleep Health. 2015; 1:233-243.

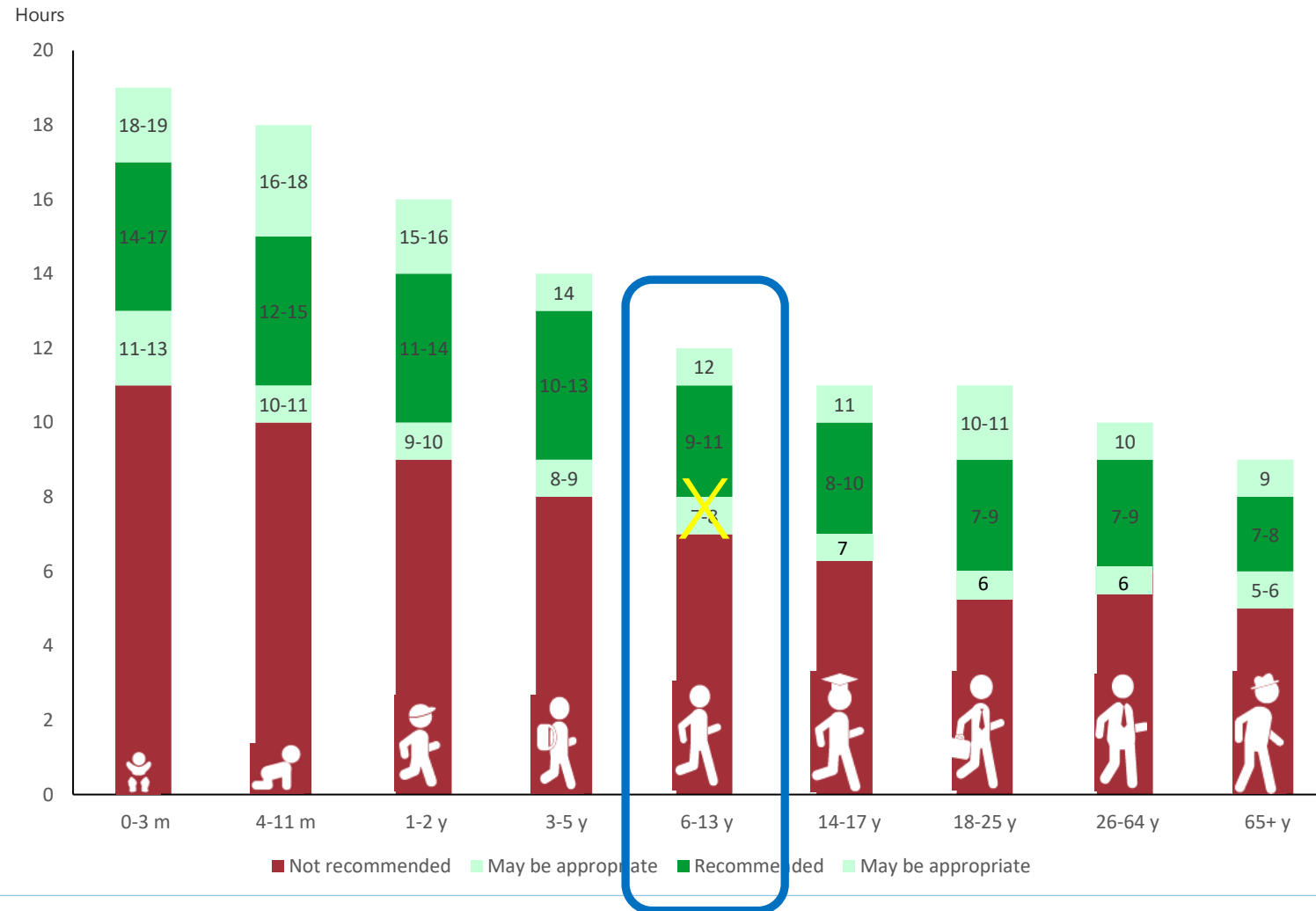
# Comparison I- Lothar - Boy, age 2 years

	Prior to treatment	IR melatonin 2 mg	Slenyto® 2 mg	
<b>SOL</b>	90-120 min	10-45 min	10-35 min	<b>&gt; 1hr improvement, better than IR</b>
<b>LSE and night awakenings</b>	<2 hours, 4-5 night awakenings, 5-40 min each	2.5 hours, 3-4 night awakenings, 5-20 min each	>6 hours, 1-2 short awakenings for 5 min	<b>LSE &gt; 6 hours, extremely improved</b>
<b>TST</b>	6.5 hrs	7 hrs 30 min	9 hrs 45 min	<b>+3 hrs 15 min per night, appropriate for his age</b>
<b>Behaviour</b>	Severe hyperactivity several tantrums and social withdrawal		Calmer, speech emerges, much less crying	<b>Significant improvement!</b>
<b>Parents</b>	Tired and stressed			<b>Highly satisfied</b>

# Case Study II- Nathan- Boy, age 8 years

- Diagnosis: high functioning ASD
  - Sleep problem: sleep onset latency 120 minutes, parents suspect awakenings, TST~8.5 hours
  - Daytime repercussion: hard to wake him up in the morning, tired, irritability, attention deficits, anxiety, has emotional difficulties (cries a lot), unstable mood
  - Family perspectives: emotional burden on the mother
-

# National Sleep Foundation's sleep duration recommendations:



# Comparison II - Nathan- Boy, age 8 years

	Prior to treatment	IR melatonin 2 mg	Circadin® 2 mg	Slenyto® 2 mg	
<b>SOL</b>	120 min	15-30 min	15-30 min	15-20 min	<b>&gt;1.5hr improvement, SL&lt;30min</b>
<b>LSE and night Awakenings</b>	5-6 times, 10-50 min each, co sleeping	2-3x/week , increased duration: several hours, LSE decreased	Less awakenings, irregularly LSE<6 hours	LSE 10.45 hours, no awakenings	<b>LSE &gt; 6 hours extremely improved</b>
<b>TST</b>	8.5 hrs	NA	NA	10.45 hrs	<b>+2.15 hrs per night, appropriate for age</b>
<b>Behavior</b>	Tired, irritability, attention deficits, anxiety, emotional difficulties (cries a lot), unstable mood	No significant improvement	More stable mood, less emotional	Decrease in fatigue during the day, mood more stable, cries much less	<b>Significant improvement!</b>
<b>Parents</b>	Exhausted			<b>Highly satisfied</b>	

# Modalities of pediatric appropriate PR melatonin prescription in children with ASD and insomnia

## *... a case studies*

### **Annals of Clinical Case Reports**

Case Series  
Published: 02 May, 2022



## **Pediatric Appropriate Prolonged-Release Melatonin Minitablet for Insomnia in Children and Adolescents with Autism Spectrum Disorder**

*Schroder C<sup>1,2\*</sup>, Bioulac S<sup>3</sup> and Hill CM<sup>4</sup>*



# Daily practice in treating insomnia in ASD



- **Even severe insomnia in children with ASD is not a fatality... even if associated with other neurodevelopmental disorders (ADHD, epilepsy, genetic syndroms)**
- If sleep hygiene and behavioural treatment fails or is insufficient, pediatric prolonged release melatonin (Slenyto®) is the first line treatment with the highest scientific evidence to date:
  - The **effects of Slenyto® are pronounced** and **maintained** over the **long term**
  - Slenyto® has a **positive safety profile and is well-tolerated** in this population; compliance with Slenyto® is high
  - No effect on sexual maturation and growth, lack of withdrawal and rebound effects
- **Progressive titration and individual dose adjustment, independent of age and weight, is the key to treatment success**



# Insomnia in children and adolescents with ASD - From science to clinical practice

## From research to practice



THANK YOU FOR YOUR ATTENTION



