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

# Management of insomnia in children with autism


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

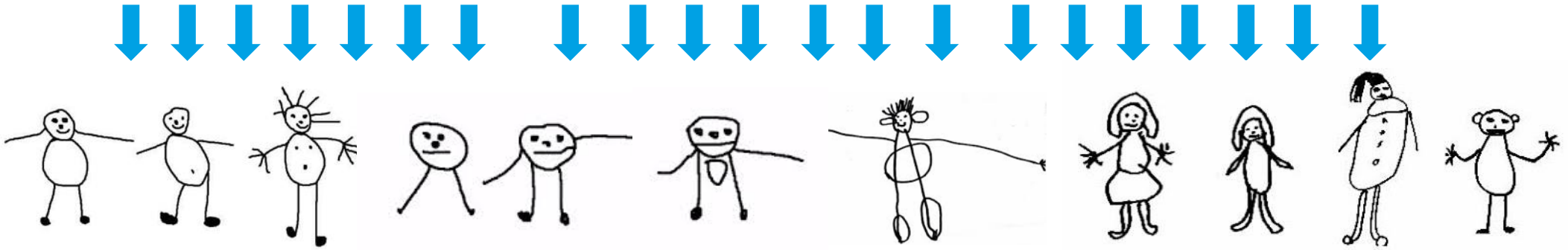
# Conflict of interest: Prof. CM Schröder

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, InfectoPharm |

**Importance of prevention, early detection, and diagnosis of sleep disturbances in children with ASD to improve not only sleep at night, but also daytime behavior and family quality of life**

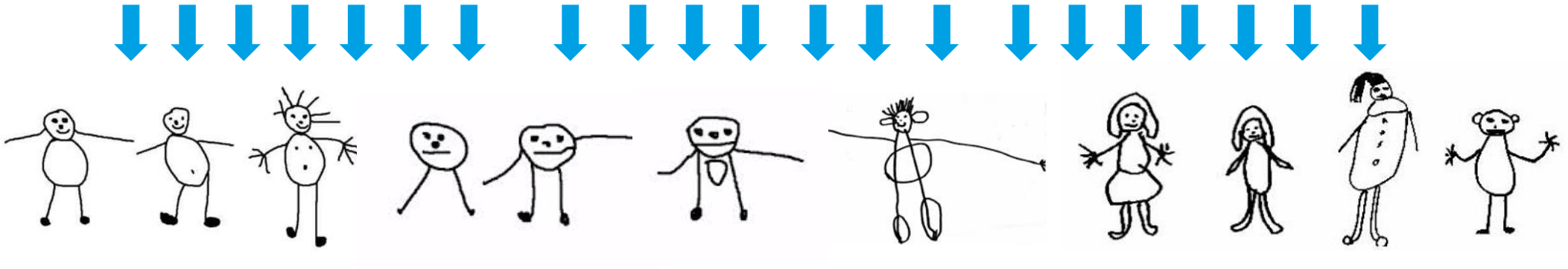
## Treating insomnia in ASD



1. Sleep hygiene and behavioural treatment
2. Pharmacological intervention

**Importance of prevention, early detection, and diagnosis of sleep disturbances in children with ASD to improve not only sleep at night, but also daytime behavior and family quality of life**

## Treating insomnia in ASD



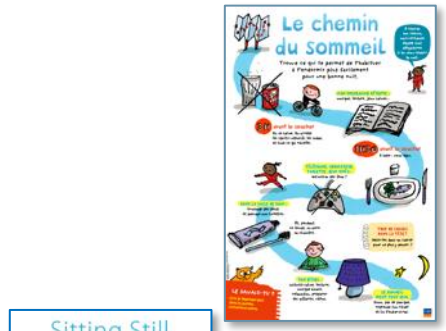
1. Sleep hygiene and behavioural treatment
2. Pharmacological intervention

# Behavioural interventions

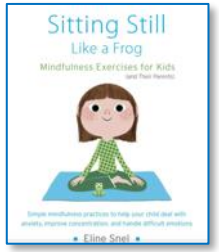

https://www.autismspeaks.org/tool-kit/atnair-p-strategies-improve-sleep-children-autism

# Behavioural interventions

1. Rituals and routines
2. Associations ‘bed-sleep’
3. Relaxation techniques
4. Positive reinforcement
5. *Bedtime fading*
6. Gradual extinction



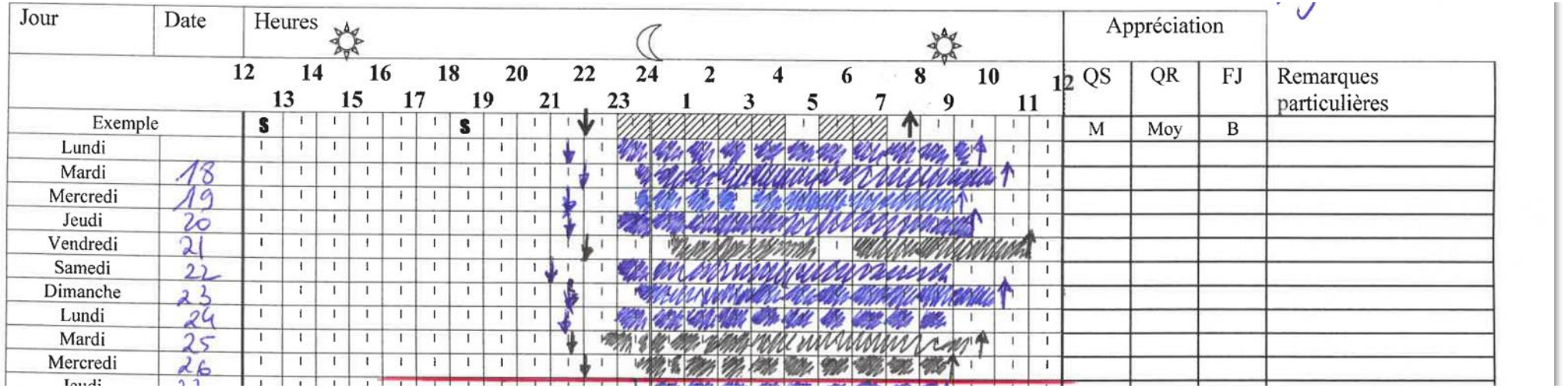







Malow B.A. et al. A Practice Pathway for the Identification, Evaluation, and Management of Insomnia in Children and Adolescents With Autism (2012) Pediatrics 130 Suppl 2:S106-242; Kleeman J. (2017) Sleep problems mounting in children, NHS, http://www.bbc.co.uk/news/health-39140836 (accessed on 12/05/2017); NICE Guidelines for sleep disturbances in children, https://www.nice.org.uk/advice/esuom2/ifp/chapter/about-melatonin (accessed: 16/05/2017); Gringras P. et al. Melatonin for sleep problems in children with neurodevelopmental disorders: randomised double masked placebo controlled trial (2012) BMJ 345:e6664.

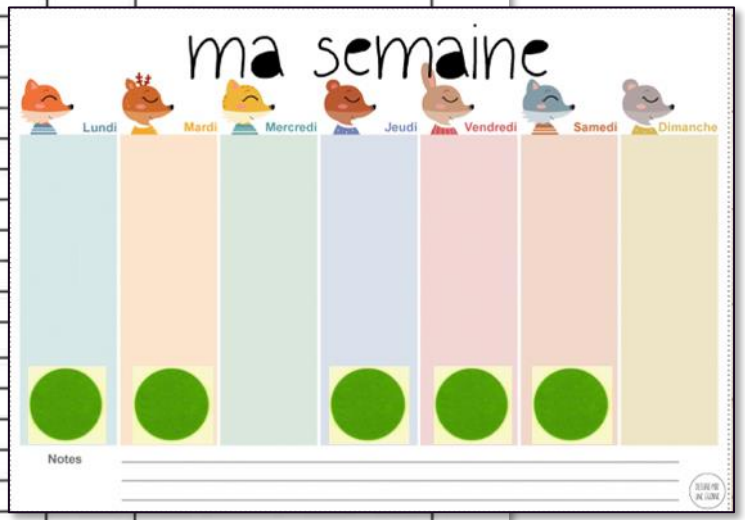
# Ex. behavioural intervention: *bedtime fading*



| Jour | Date | Heures | Appréciation | | | |
|---|---|---|---|---|---|---|
| | | 12 13 14 15 16 17 18 19 20 21 22 23 24 1 2 3 4 5 6 7 8 9 10 11 12 | QS | QR | FJ | Remarques particulières |
| Exemple | | S S | M | Moy | B | |
| Lundi | | | | | | |
| Mardi | 18 | | | | | |
| Mercredi | 19 | | | | | |
| Jeudi | 20 | | | | | |
| Vendredi | 21 | | | | | |
| Samedi | 22 | | | | | |
| Dimanche | 23 | | | | | |
| Lundi | 24 | | | | | |
| Mardi | 25 | | | | | |
| Mercredi | 26 | | | | | |

# Ex. behavioural intervention: *bedtime fading*

| Jour | Date | Heures | Appréciation | | | |
|---|---|---|---|---|---|---|
| | | 12 13 14 15 16 17 18 19 20 21 22 23 24 1 2 3 4 5 6 7 8 9 10 11 12 | QS | QR | FJ | Remarques particulières |
| Exemple | | S S | M | Moy | B | |
| Lundi | | | | | | |
| Mardi | 18 | | | | | |
| Mercredi | 19 | | | | | |
| Jeudi | 20 | | | | | |
| Vendredi | 21 | | | | | |
| Samedi | 22 | | | | | |
| Dimanche | 23 | | | | | |
| Lundi | 24 | | | | | |
| Mardi | 25 | | | | | |
| Mercredi | 26 | | | | | |
| Jeudi | 27 | | | | | |
| Vendredi | 28 | | | | | |
| Samedi | 29 | | | | | |
| Dimanche | 30 | | | | | |
| Lundi | 31 | | | | | |
| Mardi | 1 | | | | | |
| Mercredi | 2 | | | | | |
| Jeudi | 3 | | | | | |
| Vendredi | 4 | | | | | |
| Samedi | 5 | | | | | |
| Dimanche | 6 | | | | | |
| Lundi | 7 | | | | | |
| Mardi | 8 | | | | | |
| Mercredi | 9 | | | | | |
| Jeudi | 10 | | | | | |
| Vendredi | 11 | | | | | |
| Samedi | 12 | | | | | |
| Dimanche | 13 | | | | | |




Long réveil

Temps de sommeil ou sieste

Heure de coucher

Heure du lever

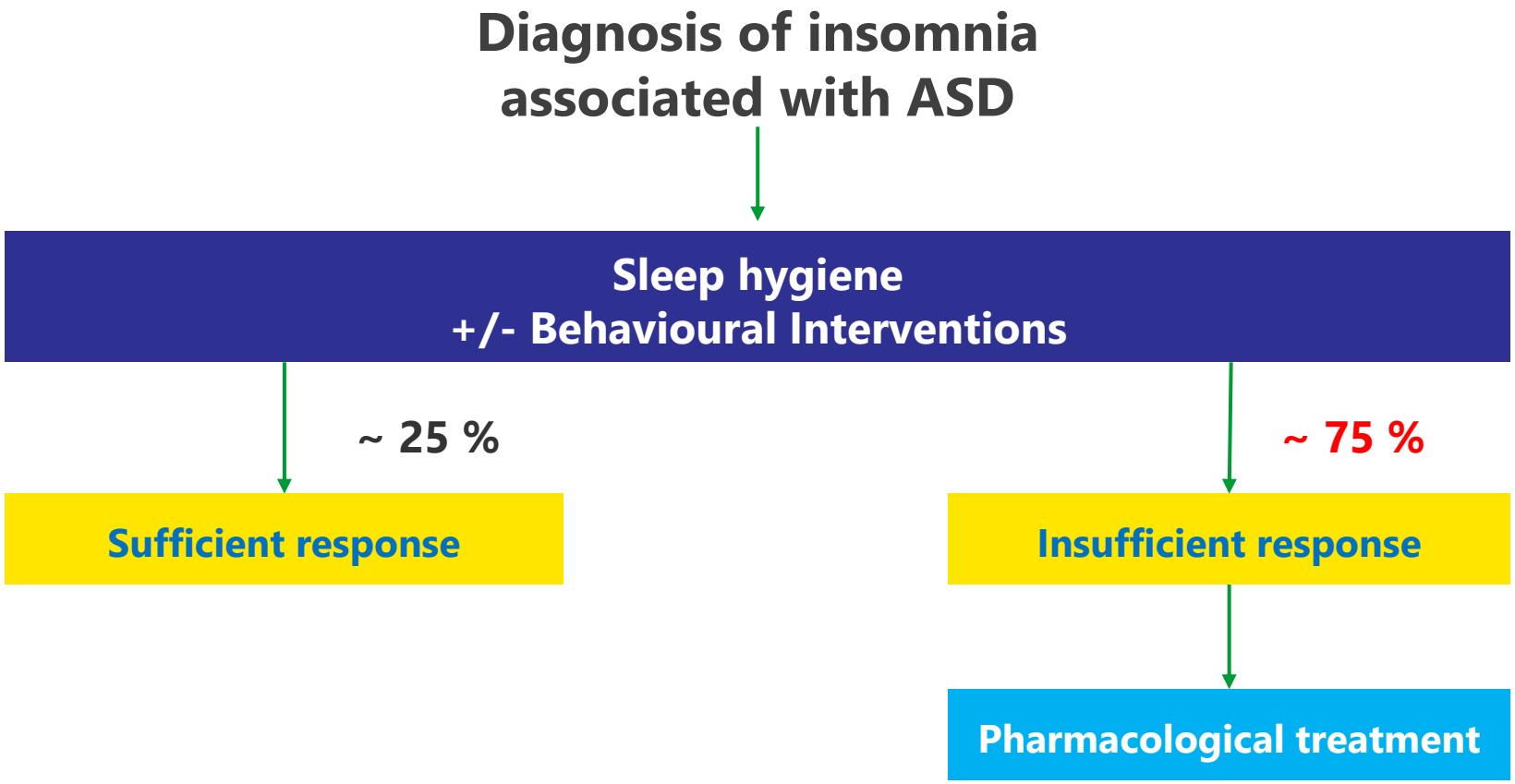
**S** = somnolence

**P** = pleurs

- QS = Qualité du sommeil
- QR = Qualité du réveil
- FJ = Forme de la journée

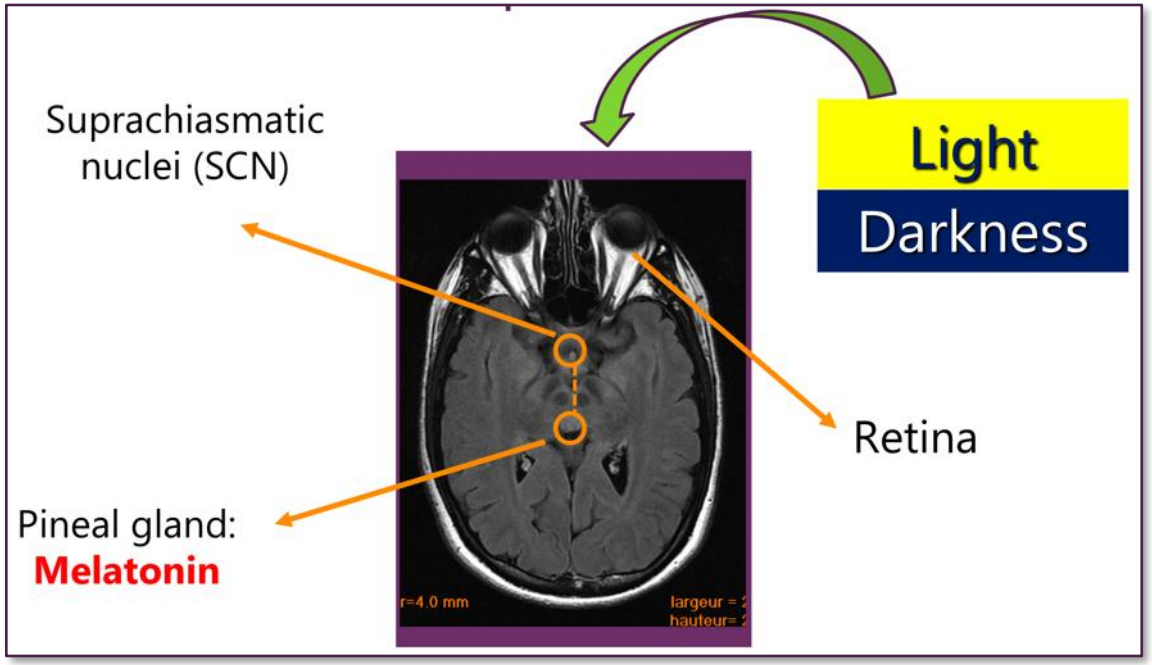
- TB = très bon
- B = bon
- Moy = moyen
- M = mauvais
- TM = Très mauvais

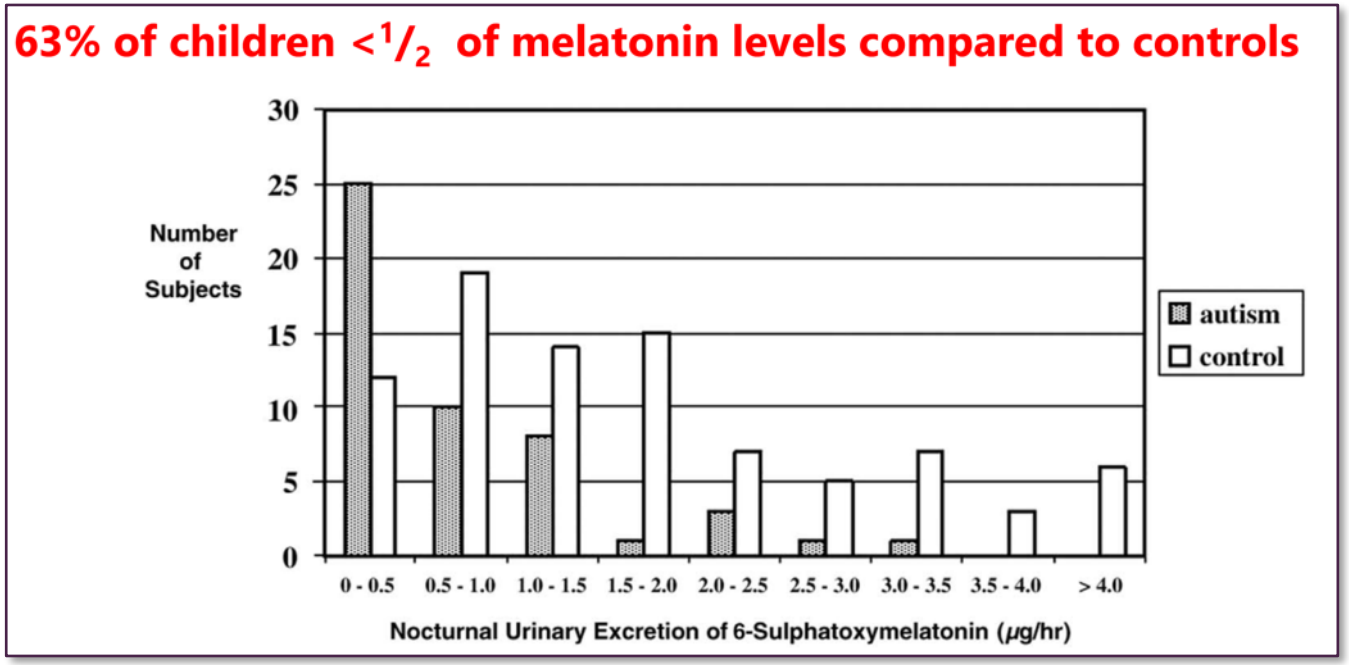
# Limitations of behavioural interventions

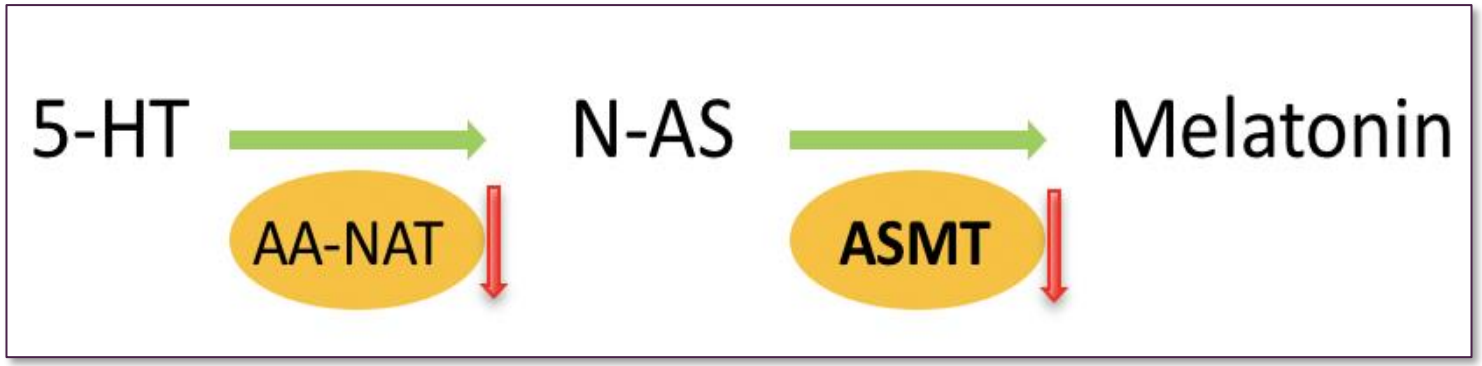


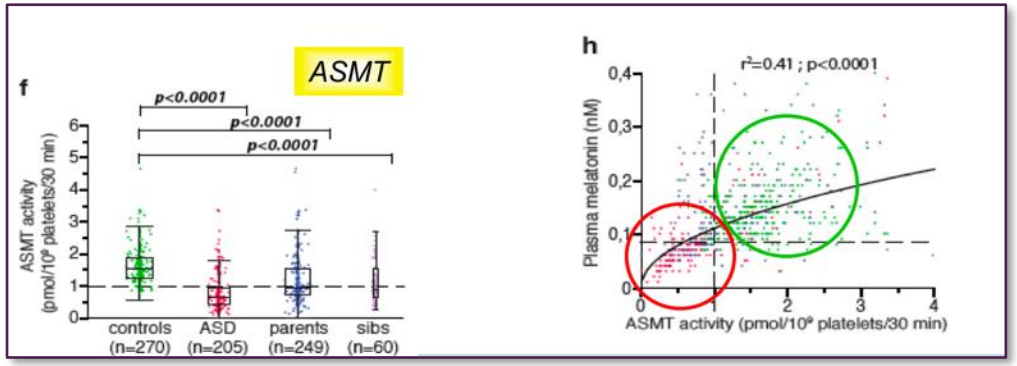

Malow B.A. et al. A Practice Pathway for the Identification, Evaluation, and Management of Insomnia in Children and Adolescents With Autism (2012) Pediatrics 130 Suppl 2:S106-242; Kleeman J. (2017) Sleep problems mounting in children, NHS, http://www.bbc.co.uk/news/health-39140836 (accessed on 12/05/2017); NICE Guidelines for sleep disturbances in children, https://www.nice.org.uk/advice/esuom2/ifp/chapter/about-melatonin (accessed: 16/05/2017); Gringras P. et al. Melatonin for sleep problems in children with neurodevelopmental disorders: randomised double masked placebo controlled trial (2012) BMJ 345:e6664.

# What causes insomnia in children with ASD?



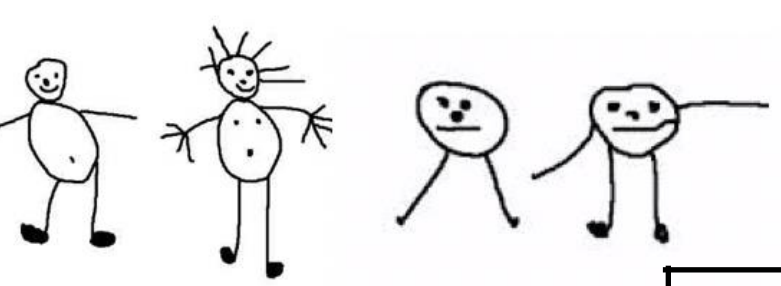




**Melatonin deficiency** is the main pathophysiological mechanism

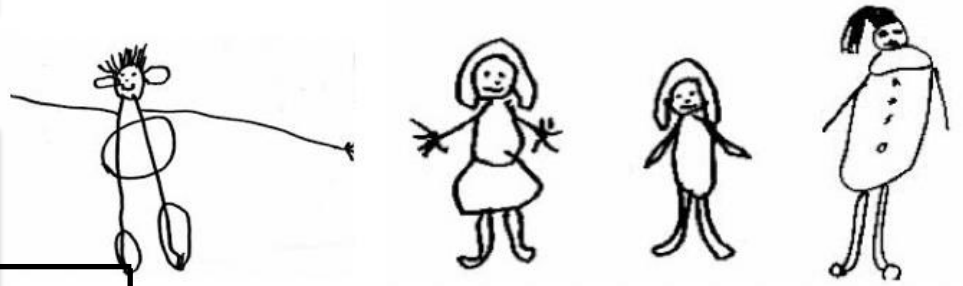
*Tordjman et al., 2005; Pagan et al., 2017*



**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

*If insufficient*

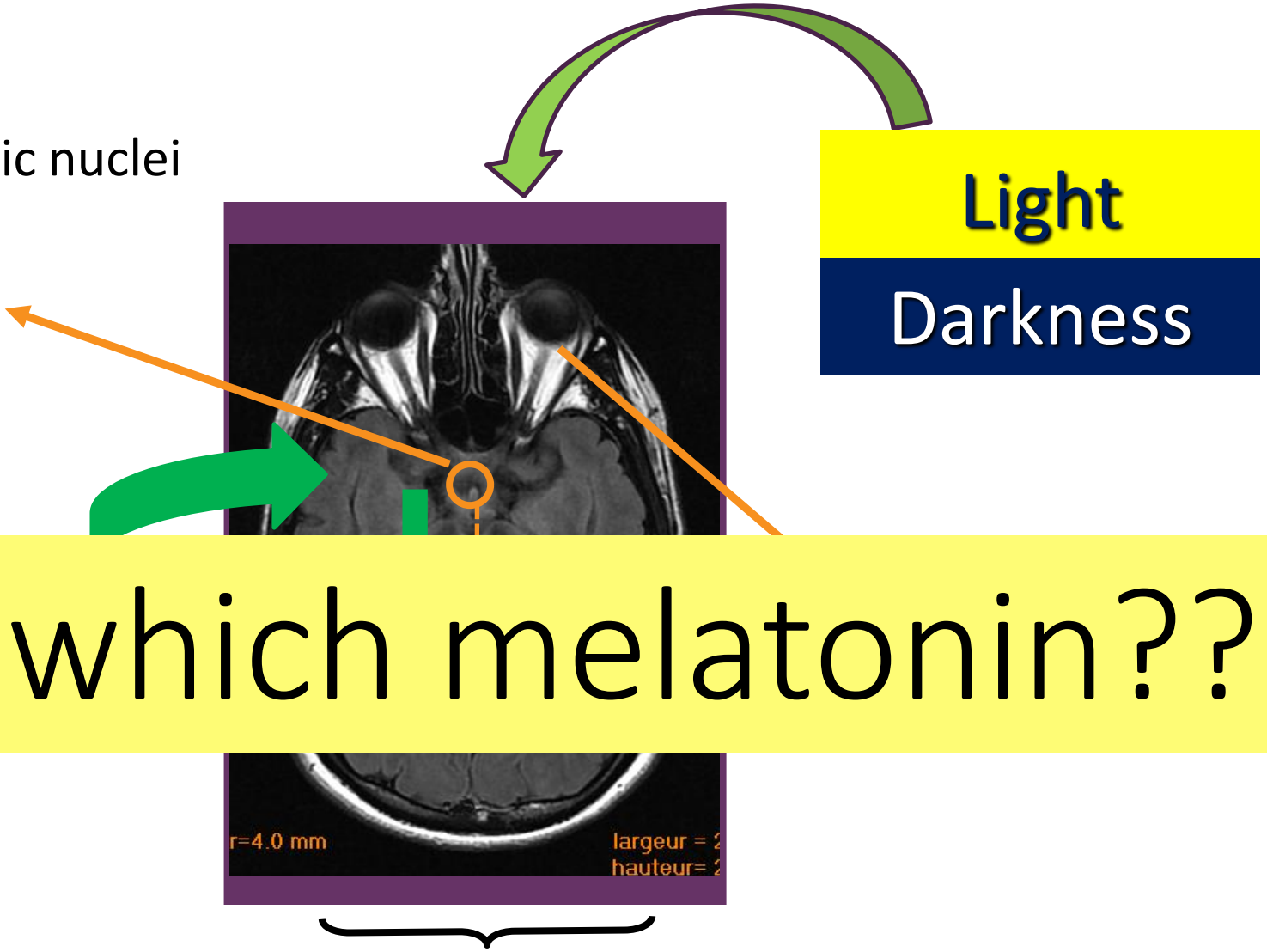
- Behavioural intervention
- Pharmacological treatment: Melatonin

*If insufficient*

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

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

# Melatonin treatment…




… but which melatonin???

# Which melatonine are we talking about?

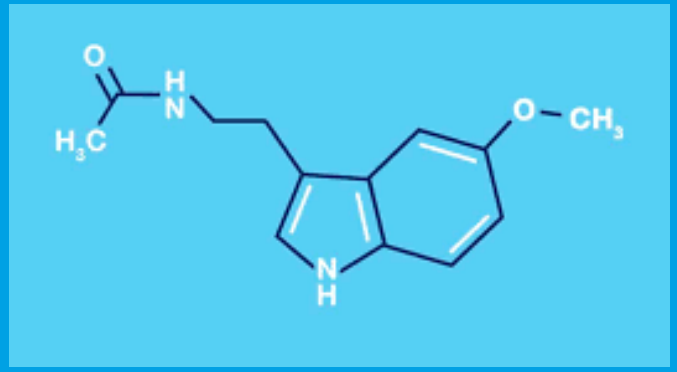
## Immediate release (IR) melatonin

- **Many studies in chronobiology / neurosciences**
- **Few studies in children … because available over the counter in many countries**

## Prolonged release (PR) melatonin

- **Less studies in chronobiology / neurosciences**
- **Very few studies in children with typical development**
- **Several studies in children with ASD or neurogenetic disorders**

# Melatonin treatment in children




**Efficacy studies in children's sleep disorders**
(**not** ASD or NDD)


1. Smits MG, Nagtegaal EE, van der Heijden J, Coenen AML, Kerkhof GA. Melatonin for chronic sleep onset insomnia in children: a randomized placebo-controlled trial. J Child Neurol. **2001**;16(2):86-92. https://doi.org/10.1177/088307380101600204 PMID:11292231

2. Ivanenko A, Crabtree VM, Tauman R, Gozal D. Melatonin in children and adolescents with insomnia: a retrospective study. Clin Pediatr (Phila). **2003**;42(1):51-58. https://doi.org/10.1177/000992280304200108 PMID:12635982

3. Smits MG, van Stel HF, van der Heijden K, Meijer AM, Coenen AML, Kerkhof GA. Melatonin improves health status and sleep in children with idiopathic chronic sleep-onset insomnia: a randomized placebo-controlled trial. J Am Acad Child Adolesc Psychiatry. **2003**;42(11):1286-1293. https://doi.org/10.1097/01.chi.0000085756.71002.86

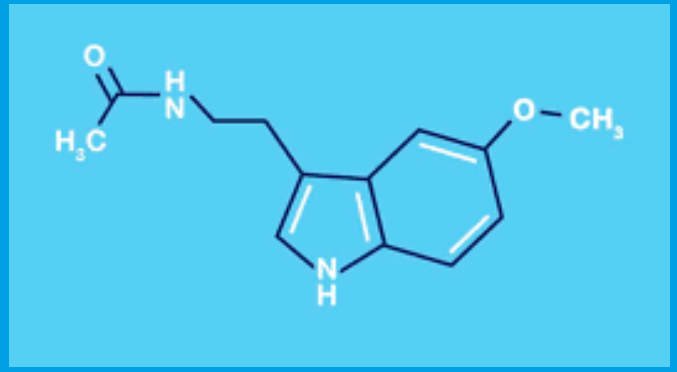
4. [van der Heijden KB, Smits MG, van Someren EJW, Boudewijn Gunning W. Prediction of melatonin efficacy by pretreatment dim light melatonin onset in children with idiopathic chronic sleep onset insomnia. J Sleep Res. **2005**;14(2):187-194. https://doi.org/10.1111/j.1365-2869.2005.00451.x PMID:15910516 ]

5. van Geijlswijk IM, van der Heijden KB, Egberts ACG, Korzilius HPLM, Smits MG. Dose finding of melatonin for chronic idiopathic childhood sleep onset insomnia: an RCT. Psychopharmacology (Berl). **2010**;212(3):379-391. https://doi.org/10.1007/s00213-010-1962-0 PMID:20668840

6. Eckerberg B, Lowden A, Nagai R, Åkerstedt T. Melatonin treatment effects on adolescent students' sleep timing and sleepiness in a placebo-controlled crossover study. Chronobiol Int. **2012**;29(9):1239-1248. https://doi.org/10.3109/07420528.2012.719962 PMID:23005039

7. van Maanen A, Meijer AM, Smits MG, van der Heijden KB, Oort FJ. Effects of melatonin and bright light treatment in childhood chronic sleep onset insomnia with late melatonin onset: a randomized controlled study. Sleep. **2017**;40(2). https://doi.org/10.1093/sleep/zsw038 PMID:28364493

# Melatonin treatment in children




**Efficacy studies in children's sleep disorders**
(**not** ASD or NDD)


1. Smits MG, Nagtegaal EE, van der Heijden J, Coenen AML, Kerkhof GA. Melatonin for chronic sleep onset insomnia in children: a randomized placebo-controlled trial. J Child Neurol. **2001**;16(2):86-92. https://doi.org/10.1177/088307380101600204 PMID:11292231

2. Ivanenko A, Crabtree VM, Tauman R, Gozal D. Melatonin in children and adolescents with insomnia: a retrospective study. Clin Pediatr (Phila). **2003**;42(1):51-58. https://doi.org/10.1177/000992280304200108 PMID:12635982

3. Smits MG, van Stel HF, van der Heijden K, Meijer AM, Coenen AML, Kerkhof GA. Melatonin improves health status and sleep in children with idiopathic chronic sleep-onset insomnia: a randomized placebo-controlled trial. J Am Acad Child Adolesc Psychiatry. **2003**;42(11):1286-1293. https://doi.org/10.1097/01.chi.0000085756.71002.86

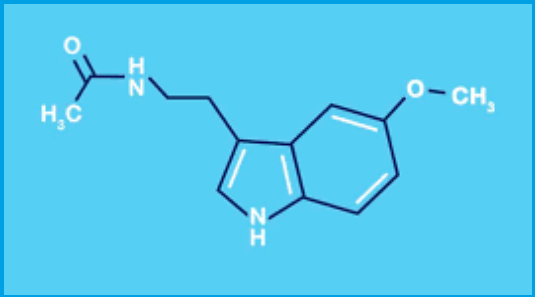
4. [van der Heijden KB, Smits MG, van Someren EJW, Boudewijn Gunning W. Prediction of melatonin efficacy by pretreatment dim light melatonin onset in children with idiopathic chronic sleep onset insomnia. J Sleep Res. **2005**;14(2):187-194. https://doi.org/10.1111/j.1365-2869.2005.00451.x PMID:15910516 ]

5. van Geijlswijk IM, van der Heijden KB, Egberts ACG, Korzilius HPLM, Smits MG. Dose finding of melatonin for chronic idiopathic childhood sleep onset insomnia: an RCT. Psychopharmacology (Berl). **2010**;212(3):379-391. https://doi.org/10.1007/s00213-010-1962-0 PMID:20668840

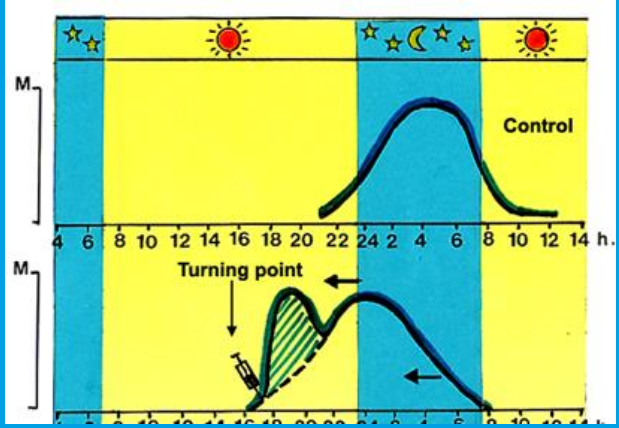
6. Eckerberg B, Lowden A, Nagai R, Åkerstedt T. Melatonin treatment effects on adolescent students' sleep timing and sleepiness in a placebo-controlled crossover study. Chronobiol Int. **2012**;29(9):1239-1248. https://doi.org/10.3109/07420528.2012.719962 PMID:23005039

7. van Maanen A, Meijer AM, Smits MG, van der Heijden KB, Oort FJ. Effects of melatonin and bright light treatment in childhood chronic sleep onset insomnia with late melatonin onset: a randomized controlled study. Sleep. **2017**;40(2). https://doi.org/10.1093/sleep/zsw038 PMID:28364493

# Melatonin treatment in children




## … with measured effect on DLMO





1. ***Smits MG, Nagtegaal EE, van der Heijden J, Coenen AML, Kerkhof GA. Melatonin for chronic sleep onset insomnia in children: a randomized placebo-controlled trial. J Child Neurol. 2001;16(2):86-92. https://doi.org/10.1177/088307380101600204 PMID:11292231***

2. Ivanenko A, Crabtree VM, Tauman R, Gozal D. Melatonin in children and adolescents with insomnia: a retrospective study. Clin Pediatr (Phila). **2003**;42(1):51-58. https://doi.org/10.1177/000992280304200108 PMID:12635982

3. ***Smits MG, van Stel HF, van der Heijden K, Meijer AM, Coenen AML, Kerkhof GA. Melatonin improves health status and sleep in children with idiopathic chronic sleep-onset insomnia: a randomized placebo-controlled trial. J Am Acad Child Adolesc Psychiatry. 2003;42(11):1286-1293. https://doi.org/10.1097/01.chi.0000085756.71002.86***

4. [van der Heijden KB, Smits MG, van Someren EJW, Boudewijn Gunning W. Prediction of melatonin efficacy by pretreatment dim light melatonin onset in children with idiopathic chronic sleep onset insomnia. J Sleep Res. **2005**;14(2):187-194. https://doi.org/10.1111/j.1365-2869.2005.00451.x PMID:15910516 ]

5. ***van Geijlswijk IM, van der Heijden KB, Egberts ACG, Korzilius HPLM, Smits MG. Dose finding of melatonin for chronic idiopathic childhood sleep onset insomnia: an RCT. Psychopharmacology (Berl). 2010;212(3):379-391. https://doi.org/10.1007/s00213-010-1962-0 PMID:20668840***

6. Eckerberg B, Lowden A, Nagai R, Åkerstedt T. Melatonin treatment effects on adolescent students' sleep timing and sleepiness in a placebo-controlled crossover study. Chronobiol Int. **2012**;29(9):1239-1248. https://doi.org/10.3109/07420528.2012.719962 PMID:23005039

7. ***van Maanen A, Meijer AM, Smits MG, van der Heijden KB, Oort FJ. Effects of melatonin and bright light treatment in childhood chronic sleep onset insomnia with late melatonin onset: a randomized controlled study. Sleep. 2017;40(2). https://doi.org/10.1093/sleep/zsw038 PMID:28364493***

# Logic of prescription of IR versus PR melatonin

## Immediate release (IR) melatonin

- **Many studies in chronobiology / neurosciences**
- **Few studies in children … because available over the counter in many countries**

- **Chronohypnotic / Chronobiotic effect**
- Inhibition of the wake signal coming from the biological clock (SCN)
- Induction of a phase advance of sleep
  - Decrease of sleep onset latency
  - Possible induction of an early morning awakening

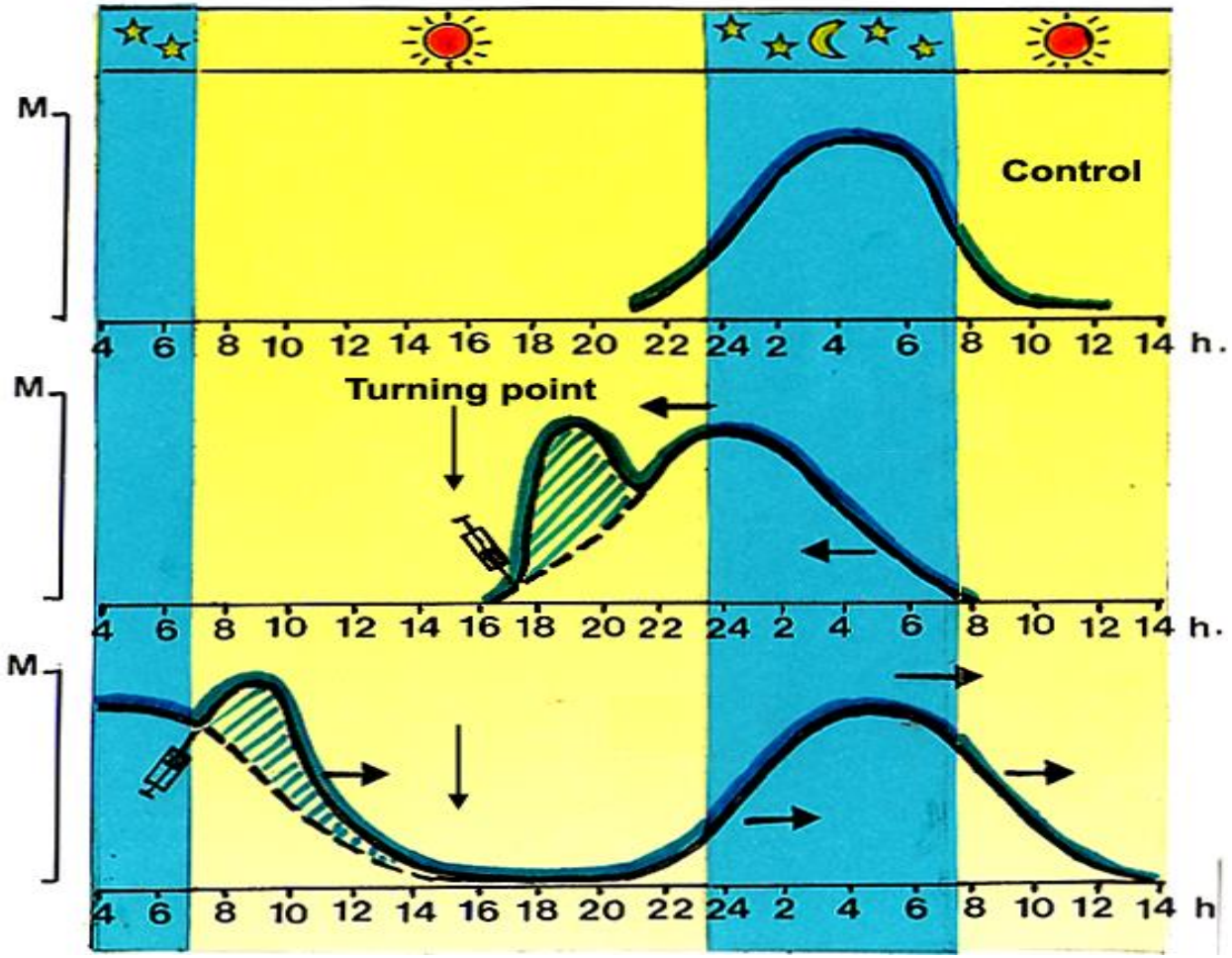
- **Soporific effect**
- Can induce sleep when homestatic sleep pressure is insufficient

## Prolonged release (PR) melatonin

- **Less studies in chronobiology / neurosciences**
- **Very few studies in children with typical development**
- **Several studies in children with ASD or neurogenetic disorders**

# Chronobiotic effect of IR melatonin

Modifies the position of endogenous melatonin secretion (advance or delay) dependent on time of administration




**Induces a phase advance** when given in the afternoon / early evening

May induce a phase delay when given in the morning

**Effect already at small doses:**
**0.5 – 2 mg of IR melatonin**

*Claustrat et al., 2009, 2020; Mundey et al., 2005*

# IR melatonin in ASD

*Gringras et al., the MENDS study, British Medical Journal 2012*

| | Melatonin | | | | Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | No of children | Baseline | Week 12 | Change | No of children | Baseline | Week 12 | Change | Adjusted difference |
| **Sleep diary** | | | | | | | | | |
| Total sleep (min) | 51 | 530.8 (64.8) | 571.3 (72.0) | 40.5 (71.8) | 59 | 545.5 (66.0) | 558.0 (68.9) | 12.5 (52.5) | 22.4 (0.5 to 44.3)* |
| Sleep onset latency (min) | 54 | 102.0 (72.6) | 54.8 (51.9) | −47.2 (64.4) | 59 | 102.1 (57.7) | 92.4 (63.0) | −9.7 (49.6) | −37.5 (−55.3 to −19.7)† |
| **Actigraphy** | | | | | | | | | |
| Total sleep (min) | 30 | 434.2 (72.3) | 449.9 (73.8) | 15.7 (63.6) | 29 | 412.3 (83.2) | 420.6 (82.9) | 8.3 (52.1) | 13.3 (−15.5 to 42.2) |
| Sleep onset latency (min) | 24 | 126.8 (71.5) | 68.4 (41.0) | −58.3 (53.7) | 25 | 107.8 (54.9) | 104.1 (59.5) | −3.71 (47.4) | −45.3 (−68.3 to −21.9)† |
| Sleep efficiency‡ (%) | 30 | 65.4 (11.3) | 70.23 (11.3) | 4.8 (9.8) | 28 | 63.3 (12.3) | 64.83 (11.7) | 1.56 (9.5) | 4.03 (−0.6 to 8.7) |

*P<0.05.

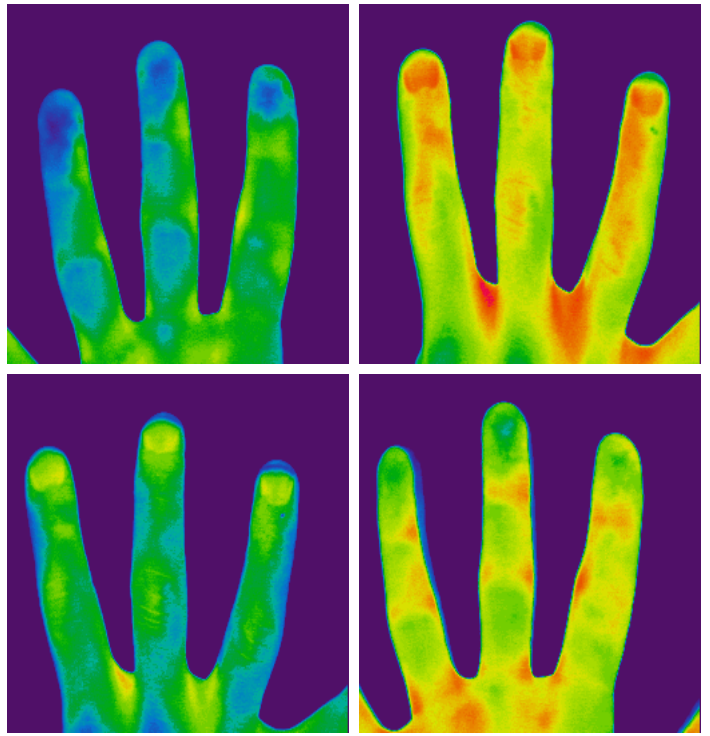
†P<0.001.

| | Melatonin (n=51) | | | Placebo (n=59) | | | Adjusted difference (95% CI) |
|---|---|---|---|---|---|---|---|
| | Baseline | Week 12 | Change | Baseline | Week 12 | Change | |
| No of wakes | 0.9 (1.3) | 0.8 (1.2) | −0.1 (−0.4 to 0.1) | 0.7 (1.6) | 0.6 (1.5) | −0.1 (−0.3 to 0.1) | 0.0 (−0.3 to 0.3) |
| Total duration of nightly wakes (min) | 24.5 (32.7) | 16.8 (26.3) | −7.7 (−15.5 to 0.2) | 11.0 (17.4) | 9.7 (22.3) | −1.3 (−8.6 to 6.0) | 2.8 (−6.2 to 11.7) |
| Wake up time (min from midnight) | 443.1 (59.1) | 426.4 (66.2) | −16.7 (−103.3 to 70.0) | 453.9 (54.6) | 464.8 (57.3) | 10.9 (−77.1 to 98.9) | −29.9 (−46.3 to −13.6)* |

*P<0.001.

# Soporific effect of melatonin: peripheral vasodilatation

Topohgraphical temperature analysis with infrared thermometry




Kräuchi K, Cajochen C, Pache M, Flammer J, Wirz-Justice A. Thermoregulatory effects of melatonin in relation to sleepiness. *Chronobiol Int*. 2006;23(1-2):475-484.

# Logic of prescription of IR versus PR melatonin

## Immediate release (IR) melatonin

- **Many studies in chronobiology / neurosciences**
- **Few studies in children … because available over the counter in many countries**

- **Chronohypnotic / Chronobiotic effect**
- Inhibition of the wake signal coming from the biological clock (SCN)
- Induction of a phase advance of sleep
  - Decrease of sleep onset latency
  - Possible induction of an early morning awakening

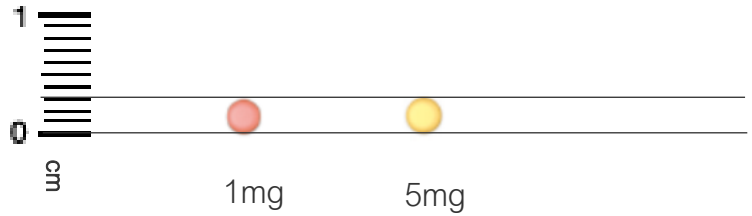
- **Soporific effect**
- Can induce sleep when homestatic sleep pressure is insufficient

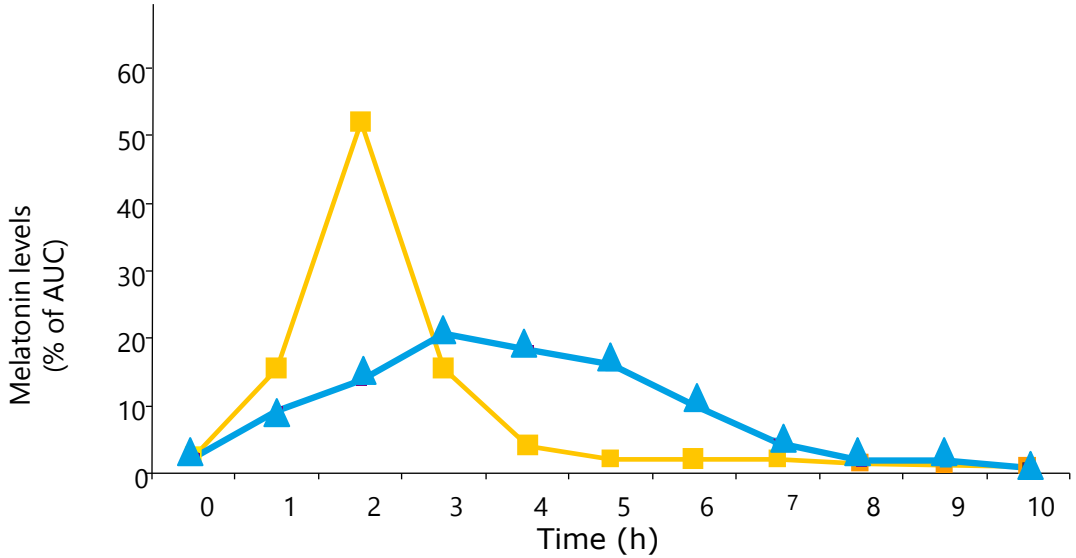
## Prolonged release (PR) melatonin

- **Less studies in chronobiology / neurosciences**
- **Very few studies in children with typical development**
- **Several studies in children with ASD or neurogenetic disorders**

- **Substitution**
- of an insufficient endogenous melatonin secretion
- = mimics the endogenous secretion

# Slenyto® prolonged release melatonin for children with ASD


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.; Zisapel, N., Melatonin and Sleep. The Open Neuroendocrinology Journal, 2010. 3: p. 85-95.;; Slenyto EPAR_April 2019 https://www.ema.europa.eu/en/medicines/human/EPAR/slenytp

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

**Increases total sleep time (TTS)**

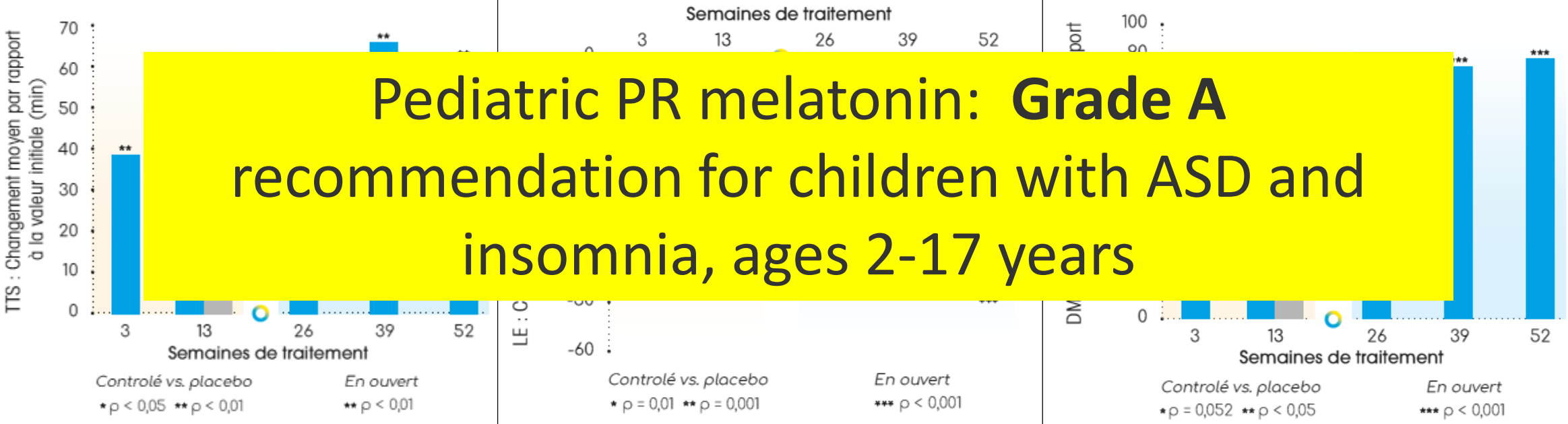
**+ 57.5 min vs + 9.1 min**

**Improves sleep onset latency (LE)**

**- 39.6 min vs - 12.5 min**

**Improves longest continuous sleep episode**

**LSE: + 77.9 min vs + 25.4 min**




Pediatric PR melatonin: **Grade A** recommendation for children with ASD and insomnia, ages 2-17 years

*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;*

# Prescription of IR versus PR melatonin

## Immediate release (IR) melatonin

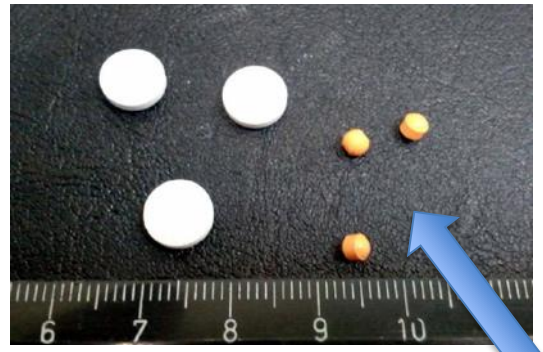
- Chronohypnotic / Chronobiotic effect
- Soporific effect

- OTC in many countries
- **beware** of heterogeneity of quality of the product and dosage:
  - up to 70% of dietary complements did not contain the dosage indicated on the box (variation of −83% to +478% of indicated doses)
- **Preparation in pharmacy** (as a liquid, as caps), **0.5-2mg**
- - 4-6 h before bedtime for a maximum effect on phase advance (=chronobiotic effect)
- at bedtime for combined chronobiotic and soporific effect

*Erland LAE, Saxena PK. Melatonin natural health products and supplements: presence of serotonin and significant variability of melatonin content. J Clin Sleep Med.* ***2017****;13(2):275-281.*

## Prolonged release (PR) melatonin

- Substitution





Elderly (>55 years) with insomnia


Children with ASD ages 2-18 years

**2 or 5 or 10 mg**

# Best validated pharmacological treatment for insomnia in children with ASD

## Immediate release (IR) melatonin

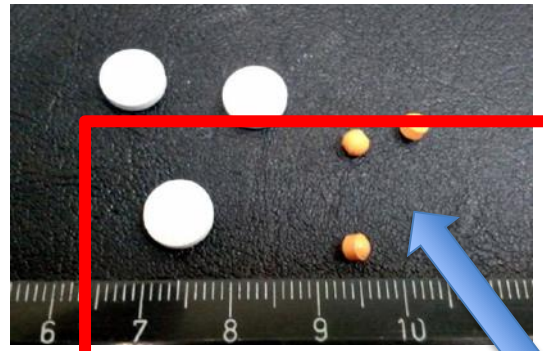
- Chronohypnotic / Chronobiotic effect
- Soporific effect

- OTC in many countries
- **beware** of heteregogeneity of quality of the product and dosage:
  - ➢ up to 70% of dietary complements did not contain the dosage indicated on the box (variation of −83% to +478% of indicated doses)
- **Preparation in pharmacy** (as a liquid, as caps), **0.5-2mg**
- - 4-6 h before bedtime for a maximum effect on phase advance (=chronobiotic effect)
- at bedtime for combined chronobiotic and soporific effect

*Erland LAE, Saxena PK. Melatonin natural health products and supplements: presence of serotonin and significant variability of melatonin content. J Clin Sleep Med. **2017**;13(2):275-281.*

## Prolonged release (PR) melatonin

- Substitution



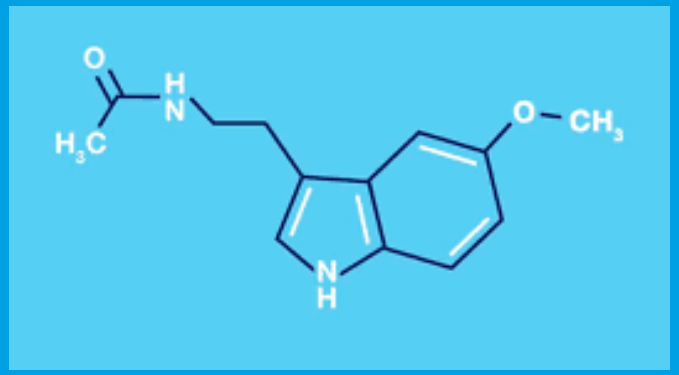




Elderly (>55 years) with insomnia


Children with ASD ages 2-18 years
**2 or 5 or 10 mg**

# Melatonin treatment in children




## Studies on safety


1. van Geijlswijk IM, Mol RH, Egberts TCG, Smits MG. Evaluation of sleep, puberty and mental health in children with long-term melatonin treatment for chronic idiopathic childhood sleep onset insomnia. *Psychopharmacology* (Berl). **2011**;216(1):111-120. https://doi.org/10.1007/s00213-011-2202-y PMID:21340475

2. Erland LAE, Saxena PK. Melatonin natural health products and supplements: presence of serotonin and significant variability of melatonin content. *J Clin Sleep Med*. **2017**;13(2):275-281. https://doi.org/10.5664/jcsm.6462 PMID:27855744

3. Zwart TC, Smits MG, Egberts TCG, Rademaker CMA, van Geijlswijk IM. Long-term melatonin therapy for adolescents and young adults with chronic sleep onset insomnia and late melatonin onset: evaluation of sleep quality, chronotype, and lifestyle factors compared to age-related randomly selected population cohorts. *Healthcare* (Basel). **2018**;6(1):E23. https://doi.org/10.3390/healthcare6010023 PMID:29498667

4. Donagh MS, Holmes R, Hsu F. Pharmacologic treatments for sleep disorders in children: a systematic review. *J Child Neurol*. **2019**;34(5):237-247. https://doi.org/10.1177/0883073818821030 PMID:30674203

5. Boafo[illegible]Greenham S, Alenezi S, et al. Could long-term administration of melatonin to prepubertal chil[illegible] affect timing of puberty? A clinician's perspective. *Nat Sci Sleep*. **2019**;11:1-10. ht[illegible]//doi.org/10.2147/NSS.S181365 PMID:30774488

6. [illegible]aras, A., et al., Long-Term Efficacy and Safety of Pediatric Prolonged-Release Melatonin for Insomnia [illegible] Children with Autism Spectrum Disorder. J Child Adolesc Psychopharmacol, 2018. doi: [illegible]10.1089/cap.2018.0020

Malow BA, Findling RL, Schroder CM, Maras A, Breddy J, Nir T, Zisapel N, Gringras P. Sleep, growth, and puberty after 2 years of prolonged-release melatonin in children with autism spectrum disorder. J Am Acad Child Adolesc Psychiatry. **2021**;60(20):252-261.e3. https://doi.org/10.1016/j.jaac.2019.12.007 PMID:31982581

# 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** | | **16** | | **12** | | **5.75** |
| **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 |

https://www.ema.europa.eu/en/documents/product-information/slenyto-epar-product-information_en.pdf; Maras A., Schroder C. 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. Vol. 28, No. 10 669-710

# Long term safety -104 weeks

- Slenyto® 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

https://www.ema.europa.eu/en/documents/assessment-report/slenyto-epar-public-assessment-report_en.pdf; Malow, B. A., Findling, R. L., Schroder, C. M., Maras, A., Breddy, J., Nir, T., ... & Gringras, P. (2020). Sleep, growth, and puberty after two years of prolonged-release melatonin in children with autism spectrum disorder. Journal of the American Academy of Child & Adolescent Psychiatry.

# Daily practice in treating insomnia in children with ASD

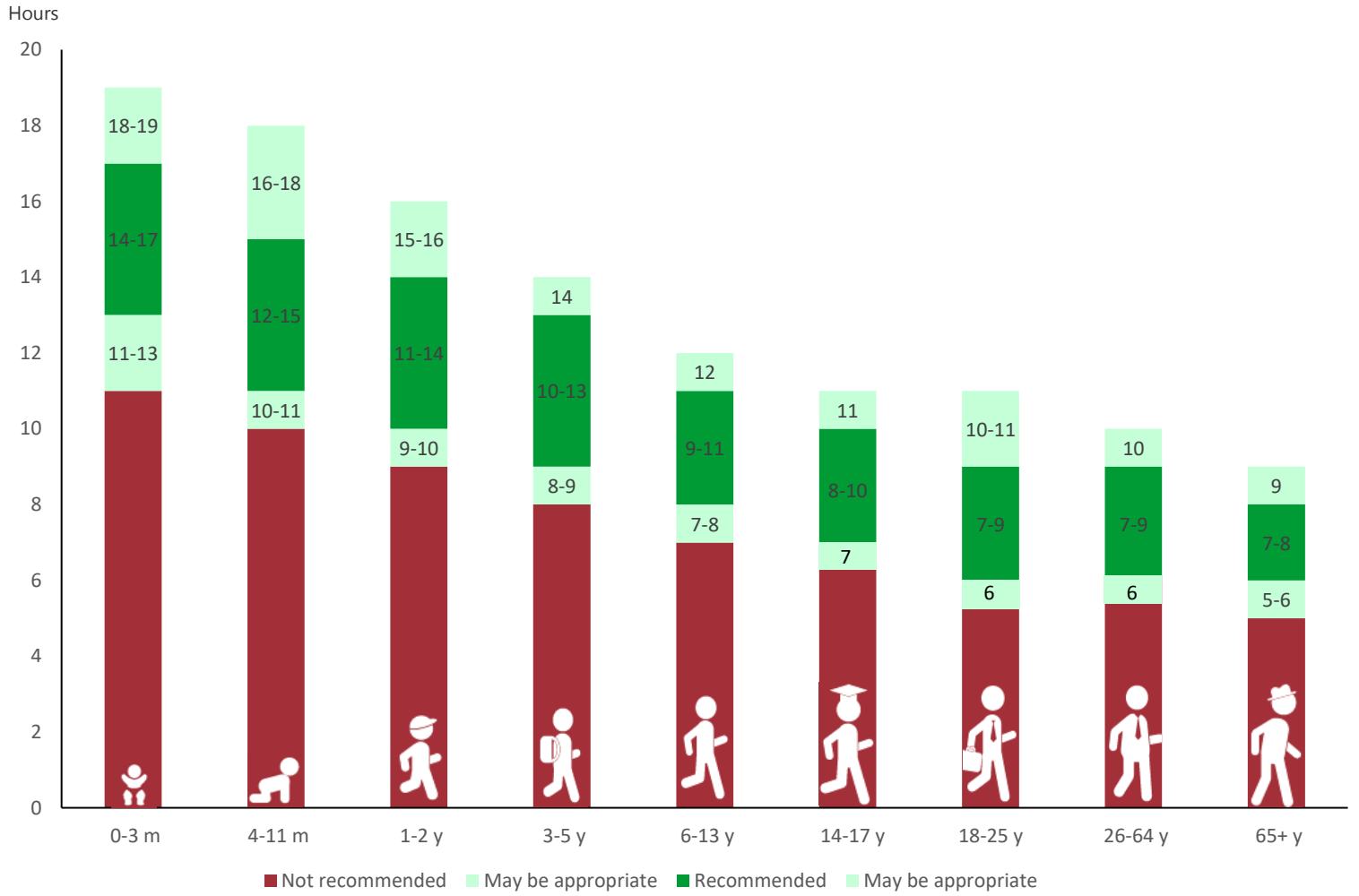
# Treatment goals

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

- Decreased child related problem behavior (…)

- Parents' satisfaction

# 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.

# Treatment goals

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

- Decreased child related problem behavior (…)

- Parents' satisfaction

**Treatment Evaluation:**

**1. Sleep measurements:**
SL >30 minutes and/or longest continues sleep period<6 Hours

**2. Daytime**: fatigue, irritability, attention deficits, externalizing behavior,

**3. Parent satisfaction**

Treatment initiation Slenyto **2mg** (2X1mg)

Evaluate the effect within 2-4 weeks of treatment*

Adequate improvement in any of the parameters?

Yes

No

Increase the dose to Slenyto **5 mg**

Evaluate the effect within 2-4 weeks*

Adequate improvement in any of the parameters?

Yes

No

Have any of the parameters evaluated deteriorated from the dose escalation?

No

Yes

Continue treatment with the same dose and evaluate regularly at least every 6 months

Increase the dose to Slenyto **10 mg** (2X5mg)

Down titration

Evaluate the effect within 2-4 weeks*

Adequate improvement in any of the parameters?

Take a closer look!

Yes

No

Have any of the parameters evaluated deteriorated from the dose escalation?

No

Yes

Treatment discontinuation

**That deviates from the product summary that recommends:**

**The patient should be monitored at regular intervals (at least every 6 months) to check that Slenyto is still the most appropriate treatment.**
**After at least 3 months of treatment, the physician should evaluate the treatment effect and consider stopping treatment if no clinically relevant treatment effect is seen. If a lower treatment effect is seen after titration to a higher dose, the prescriber should first consider a down-titration to a lower dose before deciding on a complete discontinuation of treatment**

*significant improvements appear within the first week of treatment (Malow, 2012)


# at dose down titration

In case that after dose increase any of the parameters evaluated deteriorated from the dose escalation

Decrease the dose to previous level

Evaluate the effect within 2-4 weeks*

Improvement in any of the parameters?

Yes

Continue treatment with the same dose and evaluate regularly at least every 6 months

No

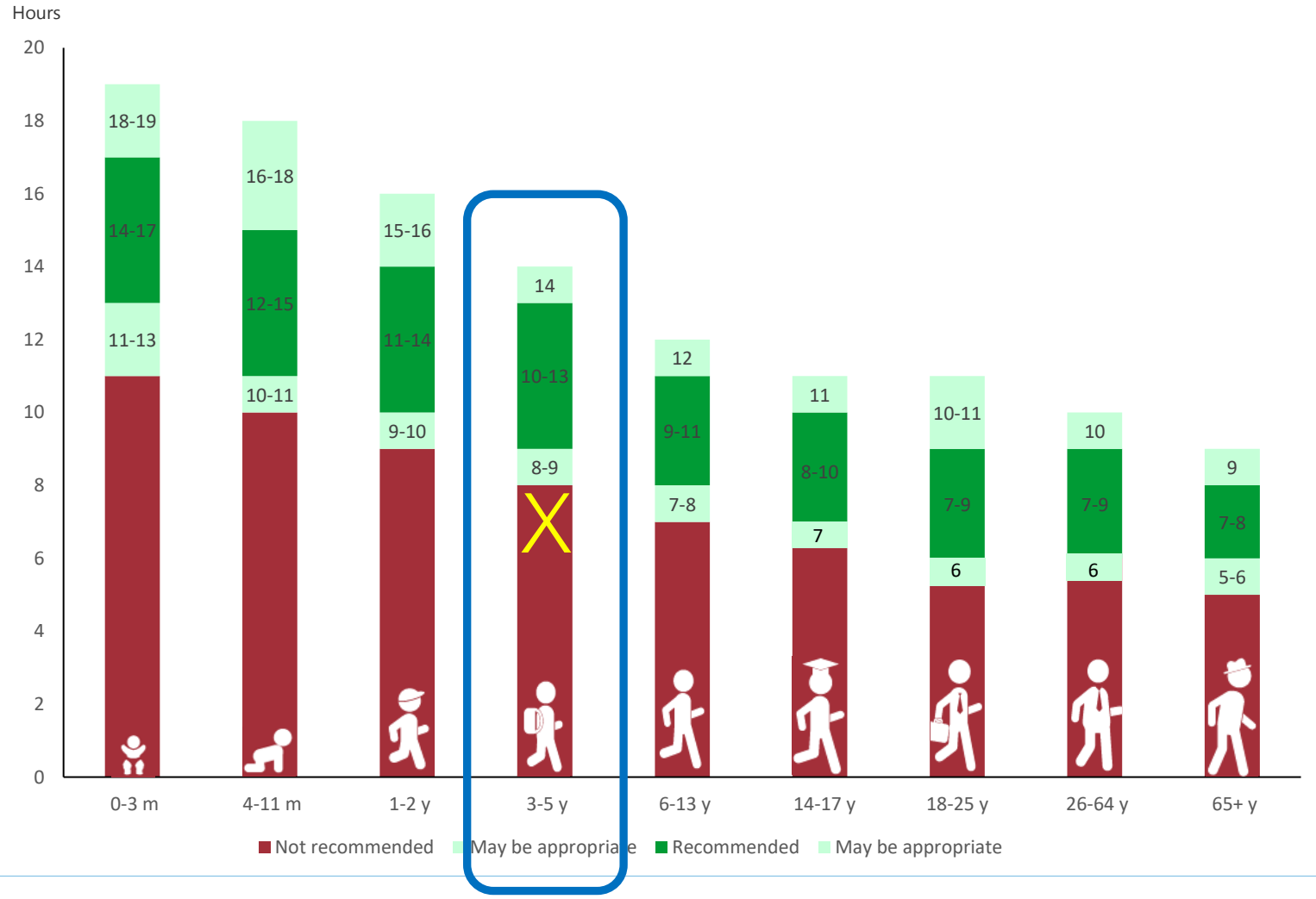
Treatment discontinuation

# Clinical cases

# Case study III- Myriam - Girl, age 5 years

- Diagnosis: ASD associated with a genetic syndrome (SHANK3), comorbid ADHD
- Sleep problem: sleep onset latency 60-90 minutes, 5-6 awakenings per night, duration: 10-60 minutes each, **total sleep time: <7 hours**
- Daytime repercussions: major motor hyperactivity (can't sit down even for 5 minutes), severe irritability with frequent, auto- and hetero-aggressive behavior (biting)
- Family perspectives: parents are exhausted (father : daytime sleepiness with several near-accidents at the wheel; mother: depressive symptomatology)

# National Sleep Foundation's sleep duration recommendations:




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, ello MV, Ware JC. National Sleep Foundation's updated sleep duration recommendations: final report. Sleep Health. 2015; 1:233-243.

# Case study III- Myriam, 5 years

## Initial treatment :

- **Sleep hygiene & behavioural interventions -** inefficient
- Prescription through pediatrician: **IR melatonin** 1mg, repeated up to 3x per night (on bedtime + nocturnal awakening before 3 am)
    - Paradoxical effect - near total insomnie; mother stops treatment after 3 nights

# Case study III- Myriam - Girl, age 5 years

## Switch to Slenyto® 2mg

Slenyto® initiated at 2 mg  at 19h for bedtime at 20h

- Sleep diary
- Phone appointment after 2 weeks

# Case study III- Myriam - Girl, age 5 years

- **Baseline:**
  - SOL: 60-90 minutes
  - Nocturnal awakenings: 5-6 per night, duration: 10-60 minutes each
  - TST<7 hrs
- **Slenyto® 2 mg**:
  - SOL: 30-45 minutes
  - Nocturnal awakenings: reduced (3 on average, spread out through the night, still joins the parents in their bed after the first awakening)
  - TST ~ 8h30 – 9h
  - Slightly improved hyperactivity during the day

**Parents very satisfied and relieved – should we maintain at 2 mg?**

# **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*** | 1. At what time does your child go to bed?<br>2. How long does it take your child to fall asleep from lights off? _____ **minutes**<br>3. After falling asleep about how many times does your child wake up at night (not counting final awakening)?<br>4. In total, how long do these awakenings last approximately? _____ **minutes**<br>5. What is approximately the longest episode of continuous sleep / uninterrupted sleep that your child has per night? ____ **hours: minutes**<br>6. At what time does your child finally wake up for the day?<br>7. How many hours of actual sleep does your child get during the night? ____ **hours: minutes**<br>8. Does your child feel tired /rested upon awakening?<br>9. In total how long does the child nap during the day? _____ **minutes** | |
| **Consideration** | 10. Is the response to Q2 (SOL) **<30** minutes?<br>11. Is the response to Q5 (LSE) >6 hours?<br>12. Is the response to Q7 (TST) acceptable sleep duration per age according to NSF, ≥ 8 (age 2-6) or ≥7 (age 6-18) hours?<br>*(If one of the above is No consider treatment/dose adjustment)* | Yes/No<br>Yes/No<br>Yes/No |

**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

Banaschewski T, Bruni O, Fuentes J, Hill CM, Hvolby A, Posserud MB, Schroder CM. Practice Tools for screening and monitoring insomnia in children and adolescents with autism spectrum disorders. JADD, 2021; Bruni, Ottaviano et al., Journal of Sleep Research 1996

# **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<br>• *ex: strong irritability*_____<br>2. How would you rate this behavior in the last month or since the last visit? | | | | |
| Score→<br>Behavior↓ | 1 | 2 | 3 | 4 | 5 |
| *irritability* | 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) | |

Banaschewski T, Bruni O, Fuentes J, Hill CM, Hvolby A, Posserud MB, Schroder CM. Practice Tools for screening and monitoring insomnia in children and adolescents with autism spectrum disorders. JADD, 2021; Bruni, Ottaviano et al., Journal of Sleep Research 1996

# Case study III- Myriam - treatment results - sleep

## Increase of Slenyto® to 5mg and clinical appointment 2 weeks later

- **Slenyto® 2 mg**:
  - SOL: 30-45 minutes
  - Nocturnal awakenings: reduced (3 on average, spread out through the night, still joins the parents in their bed after the first awakening)
  - TST: ~ 8h30 – 9h
- **Slenyto® 5mg**:
  - SOL: 15-30 minutes
  - Nocturnal awakenings: single awakening, short duration
  - TST: 10h30

# Case study III- Myriam - treatment results - behaviour

- **Baseline**:

  Behaviour:

  - Auto/heteroaggressive (bites)
  - Severe irritability with frequent tantrums
  - Major motor hyperactivity (can't sit for > 5 min)

  Parental perspective:
  parents exhausted (father: excessive daytime sleepiness, mother depressed)

- **Slenyto® 5mg:**

  Behaviour:

  - Auto/heteroaggressive behaviour stopped
  - Cries less, less tantrums
  - Hyperactivity improved (even if still present)

  The school described a significant improvement of her behaviour : she is calmer, and could sit during group activities for almost 30 min

  Parental perspective:
  Radical satisfaction: disappearance of daytime sleepiness (father), decrease of fatigue, less irritability, mother feels very relieved; both parents very thankful

# Comparison III - Myriam - Girl, age 5 years

| | Before treatment | Slenyto® 5 mg | |
|---|---|---|---|
| **SOL** | 60-90 min | 15-30 min | **Improvement >1hr** |
| **LSE and night awakenings** | 5-6 x, 10-60 min each time, *co-sleeping* | 1 x short | **Continuous sleep very improved** |
| **TST** | 7 hrs | 10.5 hrs | **+3.5 hrs per night** |
| **Behaviour** | Attention<5min, tantrums, irritability, auto/heteroaggressive | Attention~30 min, less tantrums, no aggressive behavoour | **Significant improvement** |
| **Parents** | Exhausted | **Very satisfied** | |

# Case study IV- Thomas - Boy, age 6 years

- Diagnosis: ASD, epilepsy, associated with a genetic syndrome (de novo mutation SYNGAP1); epilepsy is well treated and stable under lamotrigine
- Sleep problem: sleep onset latency 90-120 minutes, nocturnal awakening after 3h30 am with severe tantrums; **total sleep time:  approx. 6h30 hours**
- Daytime repercussions: restlessness, irritability, excessive daytime sleepiness if no activity (car)
- Family perspectives: parents are exhausted (father : anger issues; mother: depressive symptomatology; little brother: defiant behaviour)

# Case study IV- Thomas - Boy, age 6 years

Treatment:

- **Sleep hygiene and behavioural treatment (screen use) and IR melatonin at 1 mg, then increase to 2 mg**
  - Decrease of SOL: 45-60 min
  - Persistence of early morning awakening (3h30 am), now sometimes even earlier
- **Hydroxyzine**
  - Progressive increase up to 20 mg (= 1 mg/kg/day)
  - No effect
  - Side effect: increase of excessive daytime sleepiness
- **Slenyto®: introduction at 2 mg, increase to 5 mg**
  - Good effect on SOL (30 min), and TST, but morning awakening still at 4 am with tantrums (even though less common)

**Good partial effect of Slenyto® - should we maintain at 5 mg?**

# Comparison IV- Thomas - Boy, age 6 years

| | Before treatment | Melatonin IR | Slenyto® 2 then 5 mg | Slenyto® 10 mg | |
|---|---|---|---|---|---|
| **SOL** | 90- 120 min | 45-60 min | 30 min | 15 min | **>1.5hr** |
| **LSE and night awakenings** | Early morning awakening at 3h30 am with tantrum | Sometimes even earlier awakening (phase advance!) | Early morning awakening at 4h30 am (better) | Wakes up at 6h00 | **Better sleep continuity** |
| **TST** | Approx. 6 hours 30 min | Approx. 7 hours +/- 30 min | 9 hours | 10 hours 30minutes | **Almost 4 hr (correcting early morning awakening)** |
| **Behaviour** | Restlessness, irritability | | Less restless,<br>Less tantrums | | **Improvement** |
| **Parents** | Severe repercussions on family life | | Better sleep & less behavioural problems; but parents still tired because of early morning awakening | Parents highly satisfied | **Very satisfied** |

# 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[1,2]*, Bioulac S[3] and Hill CM[4]*

# Management of insomnia in children with 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

# Management of insomnia in children with autism


THANK YOU FOR YOUR ATTENTION