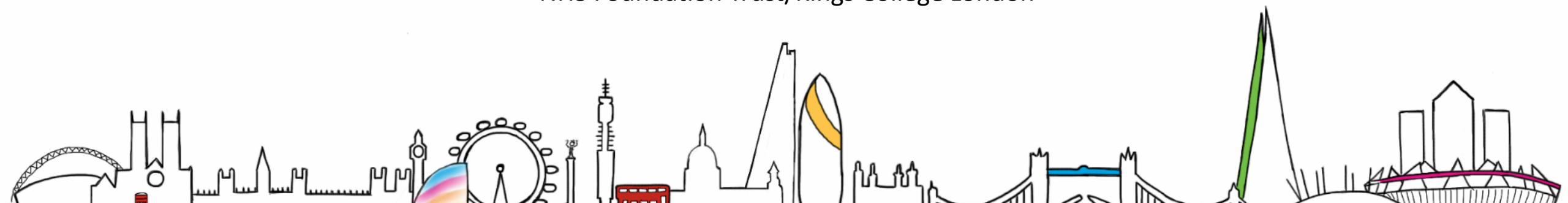


Sleep in Autism and other Neurodevelopmental Disorders

Focus on autism and other NDDs - Stockholm 2019

Handouts without images

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Topics

- Why bother to sleep
- What is normal sleep?
- Sleep in ASD and ADHD - Children and adults
- Non-pharmacological interventions
- Pharmacological interventions
- Novel non-pharmacological interventions

Why bother to sleep?

*‘Sleep is a criminal waste of time, inherited
from our cave days’*

Thomas Edison

'If sleep doesn't serve an absolutely vital function, then it is the greatest mistake the evolutionary process ever made'

Allan Rechtschaffen

Total Sleep Deprivation

- Rechtschaffen 1983
- Controlled (but cruel)
- Lost weight despite eating more
- After 33 days all sleep deprived rats dead

Sleep Deprivation - Humans v Rats

- Peter Trip-1960
 - 201 Hours –DJ
 - After 2 days hallucinate
 - Drugs to keep him awake after 140 hours
 - Then slept 13 hours 13 minutes
- Randy Gardner-1965
 - 11 nights
 - Blurred vision, slurred speech
 - Mild paranoia
 - Then slept 14 hours 40 minutes first night
 - (68% SWS 53% REM)

Sleep and Learning Basics

- ‘The price we pay for plasticity’
- Acute and cumulative effects
- Different sleep stages consolidate different aspects of memory
- Circadian and cellular changes in gene expression and white matter structure in brains

Brain imaging markers of sleep

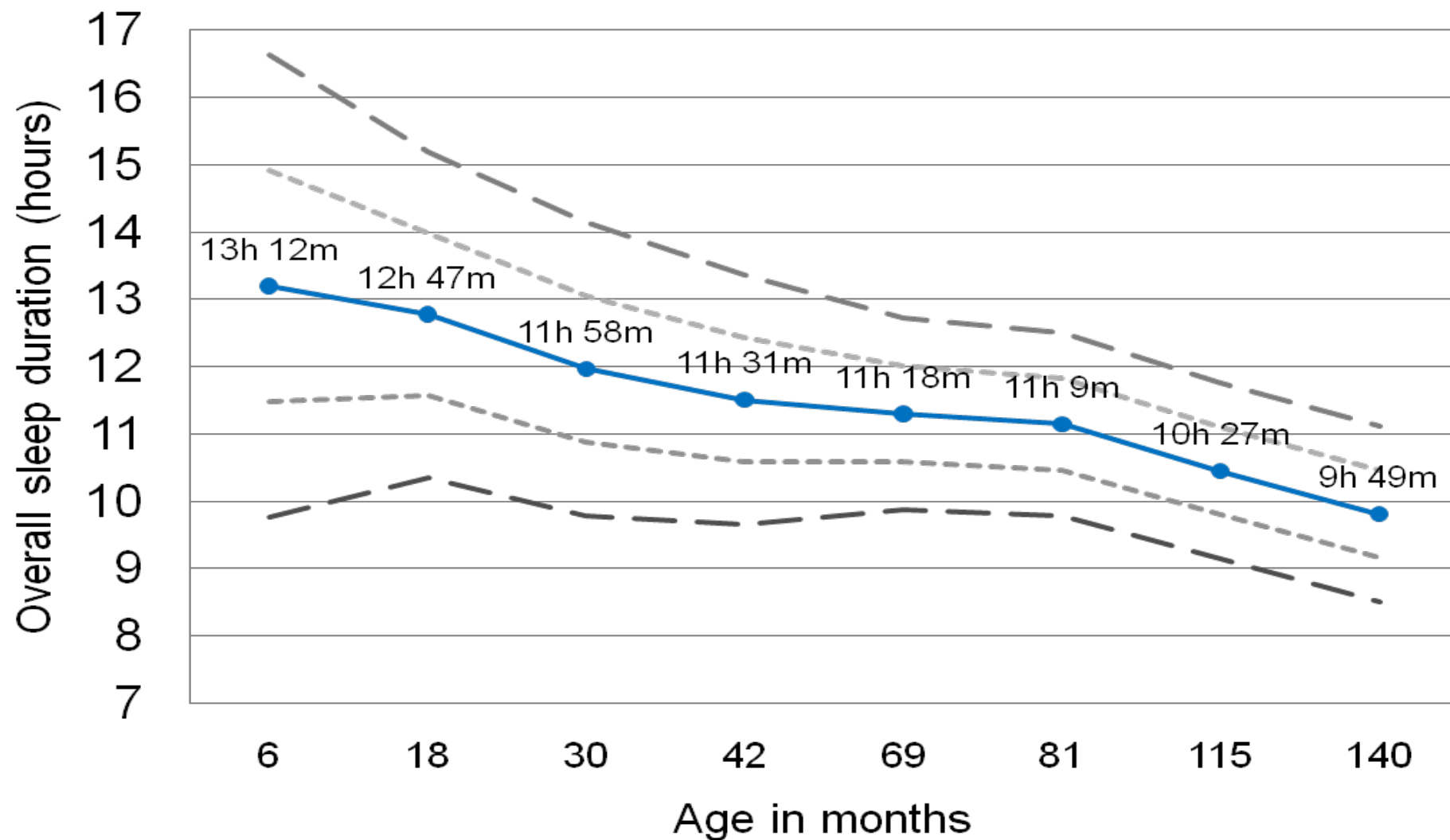
Not just little adults...

- By the age of 2 years the average child has spent 13 months sleeping
- Memory, behaviour and learning
- Growth, metabolism, immune function, injuries
- Different responses to medication, both efficacy and adverse effect

What is 'normal' sleep?

- And how does sleep differ in ADHD and ASD?

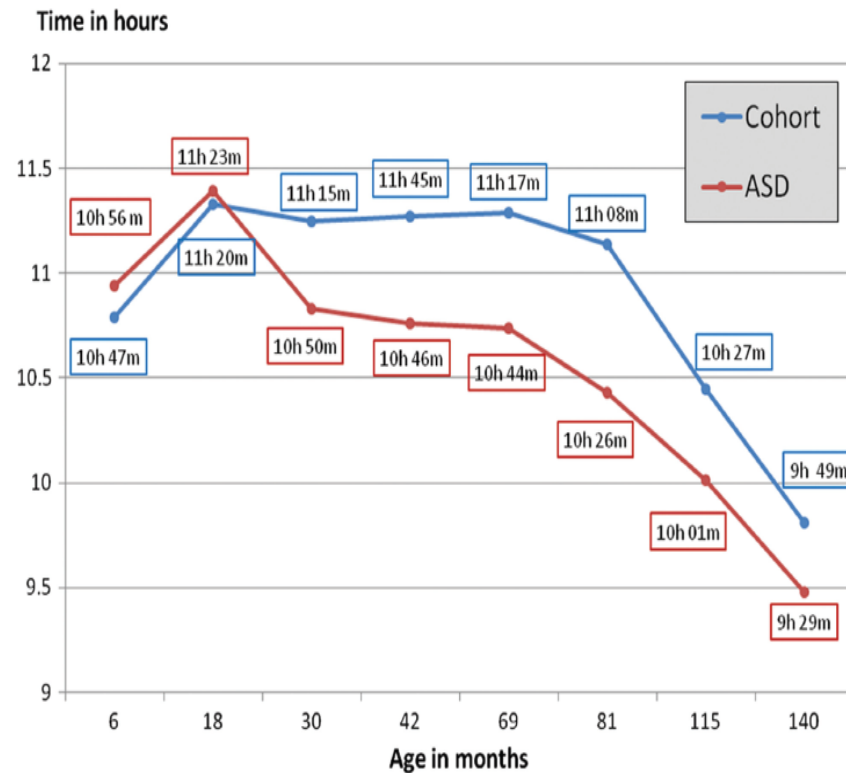
Total sleep duration amongst children (Mean \pm 1 and 2 Standard Deviations)



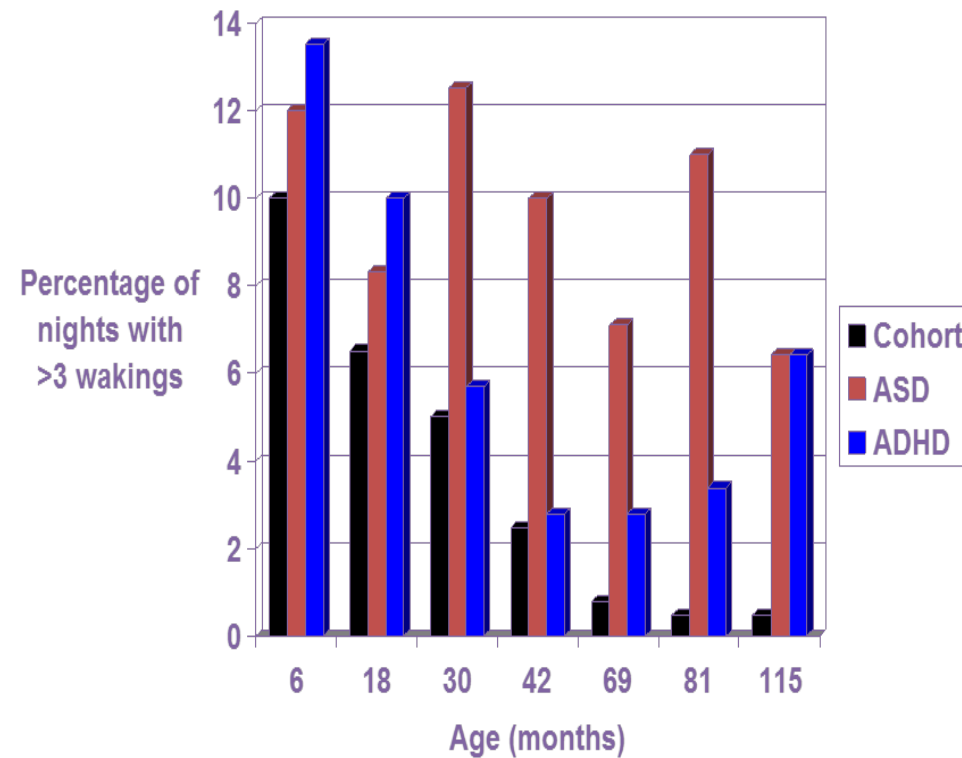
Blair PS, Humphreys JS, Gringras P, et al Childhood sleep duration. *Sleep*. 2012 Mar 1;35(3):353-60.

ASD and ADHD- A problem of sleep duration and night wakings

Sleep duration ASD vs Controls

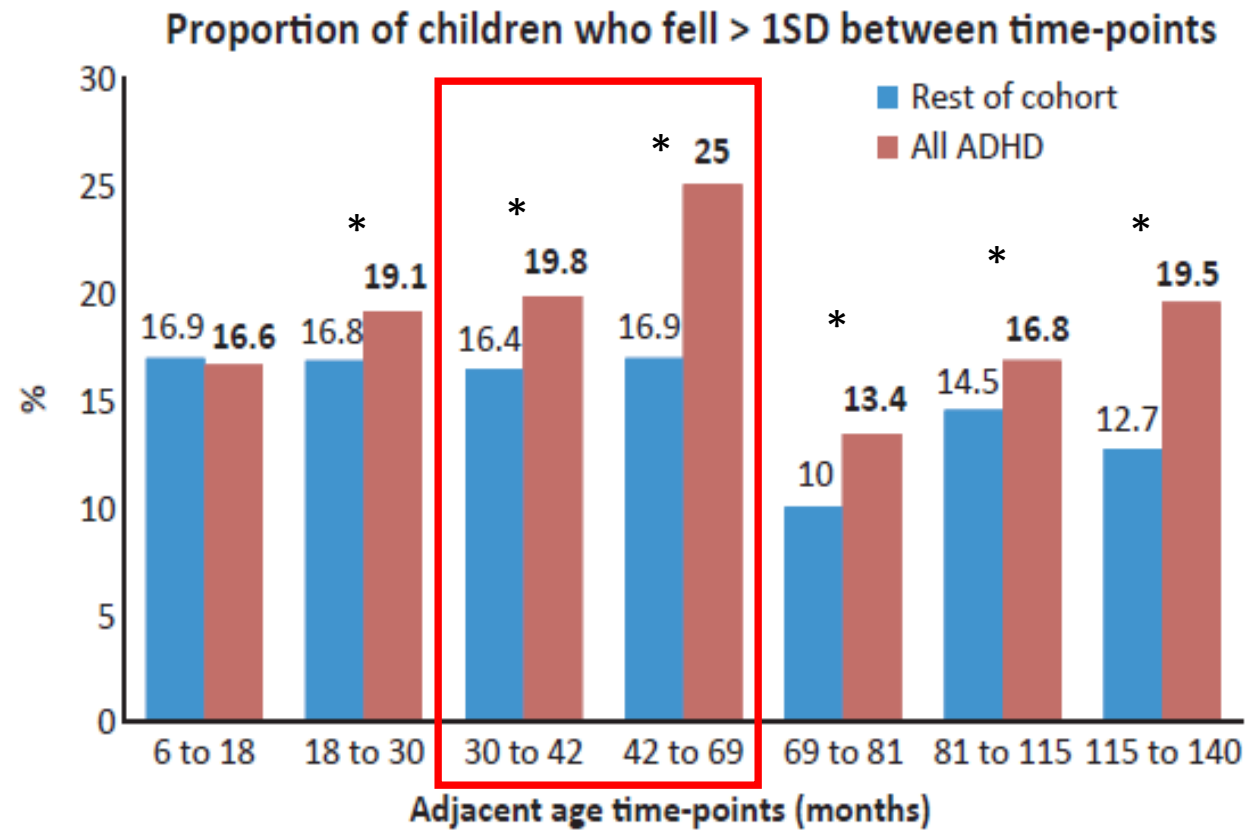


Waking at night ASD vs ADHD vs Control



Humphreys, J.S., et al., Sleep patterns in children with autistic spectrum disorders: a prospective cohort study. Arch Dis Child, 2014. 99(2): p. 114-8.

Early identification of ADHD and ASD



Scott N, Blair PS, Emond AM, Fleming PJ, Humphreys JS, Henderson J, Gringras P. *J Sleep Res.* 2012

Sleep in Adults with ASD

- Problems
 - Much less research than paediatrics
 - Often not adjusted for intellectual disability or comorbidities
 - Small number and subjective measures
- Conclusions
 - In Baker 36 adults with HFASD vs controls
 - HFASD have more general disturbances associated with sleep (PSQI)
 - Take a significantly longer time to fall asleep with resultant poorer SE%
 - Less refreshed upon waking compared to control group.
 - Only sleep diary variables were correlated with daytime sleepiness

Sleep physiology in adults with ASD

- 28 adolescents/young adults with autism spectrum disorders (ASD) and controls
- Questionnaires, actigraphy (four weeks), and salivary cortisol and melatonin (four days each).
- Compared to those with TD, adolescents/young adults with ASD had longer sleep latencies and more difficulty going to bed and falling asleep.
- No differences with cortisol or melatonin timing
- Insomnia in ASD is multifactorial and not solely related to physiological factors.

Treating Sleep Disorders in NDD

Goals of treatment?

1. Improve Sleep (Objective and Subjective)
 - a. Sleep latency
 - b. Total sleep time
 - c. Sleep efficiency
 - d. Sleep neurophysiology (spindles/slope/spectra)
2. Daytime alertness and learning
3. Daytime behaviour
4. Daytime quality of life and wellbeing

SleepSuite - child sleep-specific learning



Behavioural Interventions

Evidence for behavioural interventions

- All studies show extinction or graduated extinction works
- Evidence in children with learning difficulties that an information booklet can be as effective as therapy
- In most studies, across most conditions, behavioural input achieves an effect size of >0.6

- *Mindell JA. J Pediatr Psychol. 1999*
- *Kuhn BR, Elliott AJ. J Psychosomatic Res. 2003*
- *Weiss 2005 ACAP conference proceedings*
- *Montgomery 2004 Child neurology and disability*

Sensory interventions

Weighted Blankets in Autism

Champagne et al (2007). AOTA: <http://www.ot-innovations.com/content/view/33/63>

Olson LJ, Moulton HJ (2004). Physical and Occupational Therapy in Pediatrics, 24, Issue 2/3

Weighted Blanket N of 1 'Snuggledown'

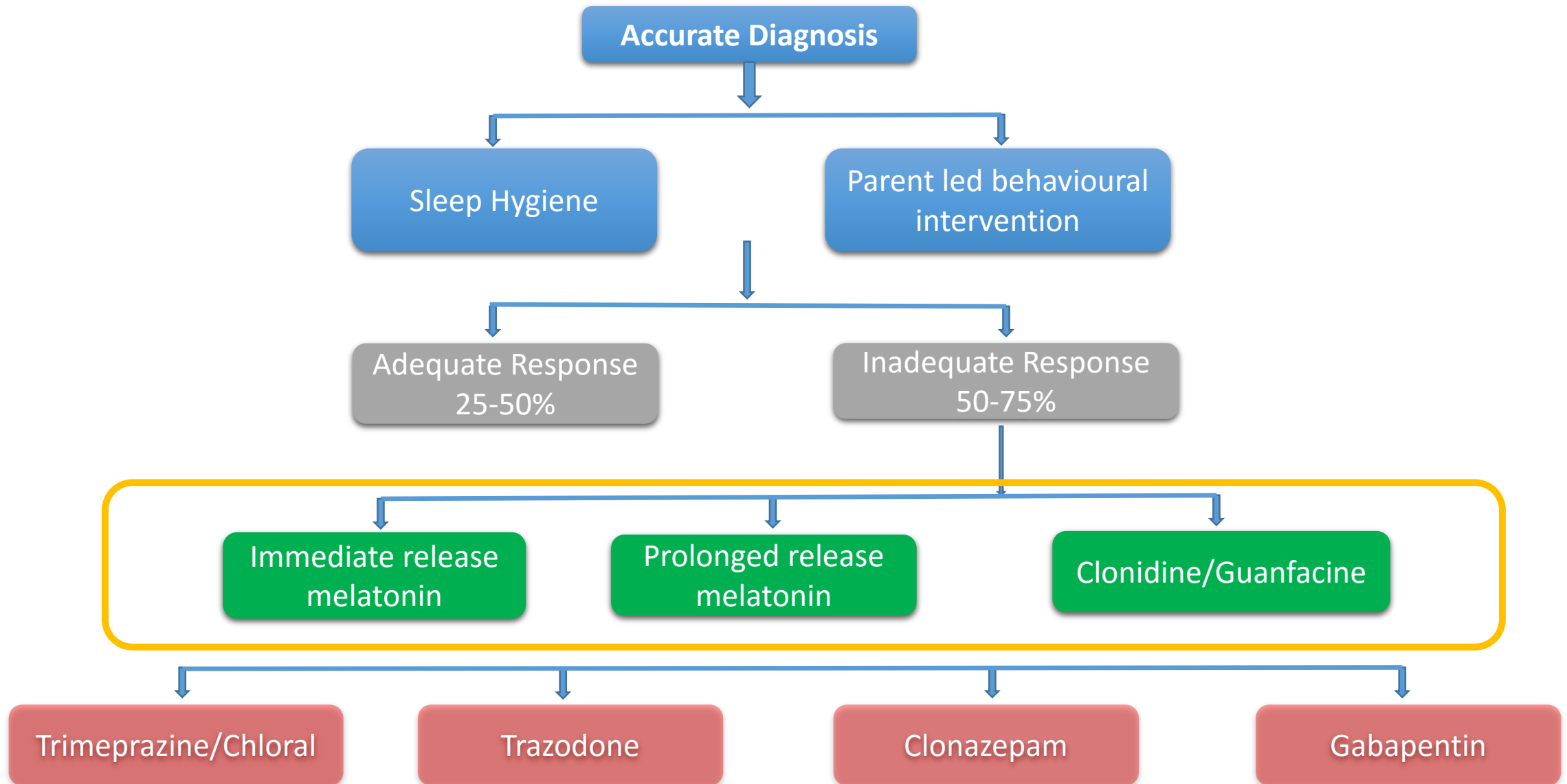
Results

- 67 children completed the trial
- No change in total sleep time, sleep latency, night wakings or sleep efficiency.
 - Based on objective actigraphy and subjective sleep diary measures
- Subjectively:
 - No group differences in sensory or child behaviours
 - Parents and children preferred the weighted blanket
 - Parents said sleep better and children calmer with weighted blankets

Gringras P et al, Pediatrics. 2014

Light (and melatonin)

Treatment pathways in children with sleep problems and ASD



The MENDS Study: IR melatonin vs. placebo

Results

- Adjusted difference in mean sleep latency between the melatonin and placebo groups was **-37.5** (-55.3 to -19.7) minutes ($p < 0.001$)
- Adjusted difference in mean total sleep time between the melatonin and placebo groups was **22.4** (0.5 to 44.3) minutes ($p = 0.04$; shorter than expected from the improvement in SL)
- Earlier waking times with melatonin than placebo 29.9 (13.6 to 46.3) minutes ($p < 0.001$) compatible with advance of the circadian clock
- No major safety concerns

RCT melatonin and Behavior in children with ASD

134 children (4-10y)

- 3mg controlled release
- Multifactorial CBT
 - Combined (n=35)
 - Melatonin (n=34)
 - CBT (n=33)
 - Placebo (n=32)

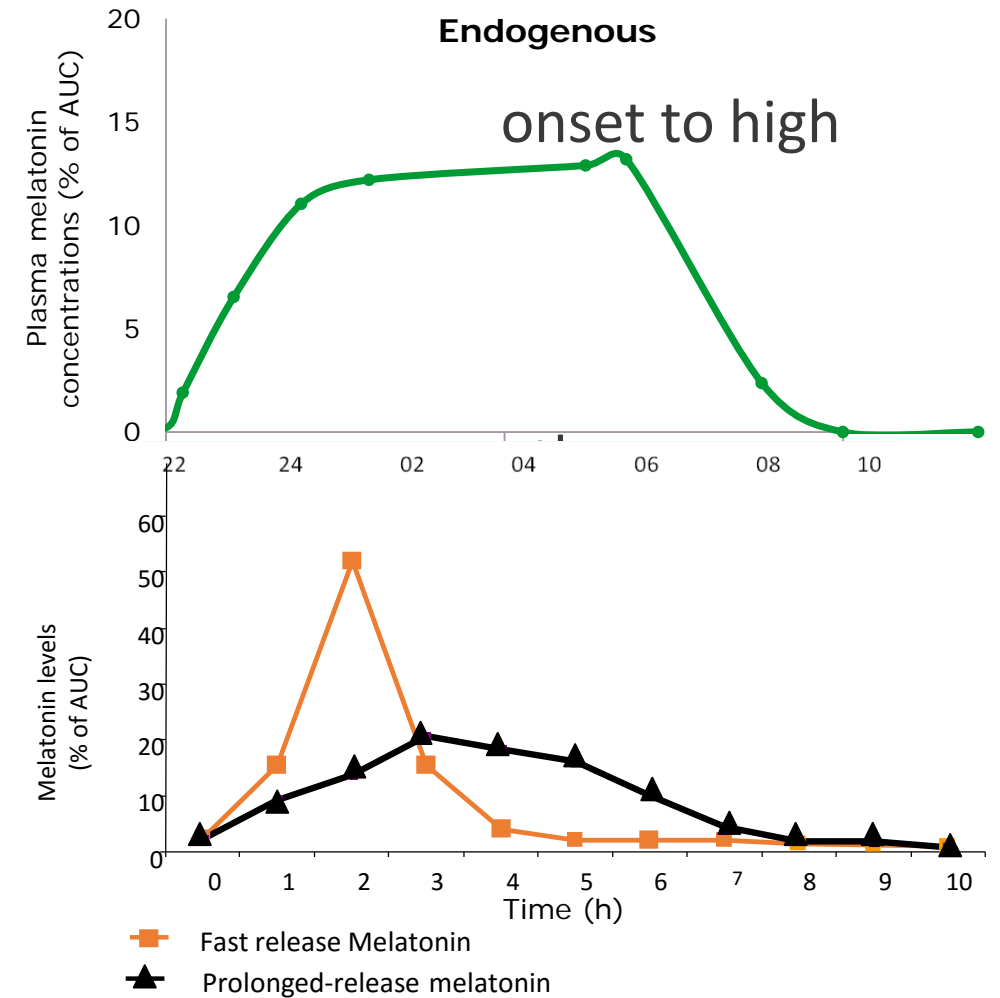
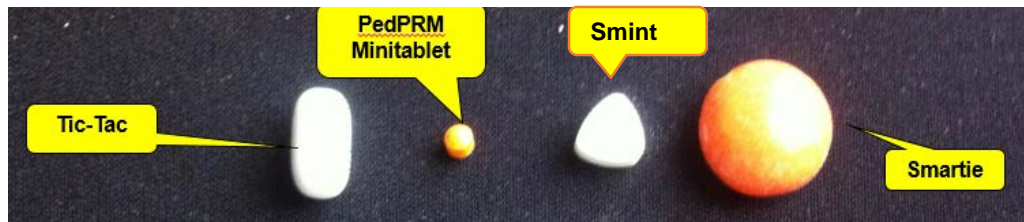
Combined > melatonin > CBT > placebo

Mean % change from baseline	Combined	Melatonin	CBT	Placebo
Sleep onset latency	60.75	44.33	22.54	-0.02
Total sleep time	22.01	17.31	9.31	0.07
Sleep efficiency	20	15.46	11.26	1.12

Immediate-Release vs. Prolonged-Release Melatonin pharmacokinetic profile

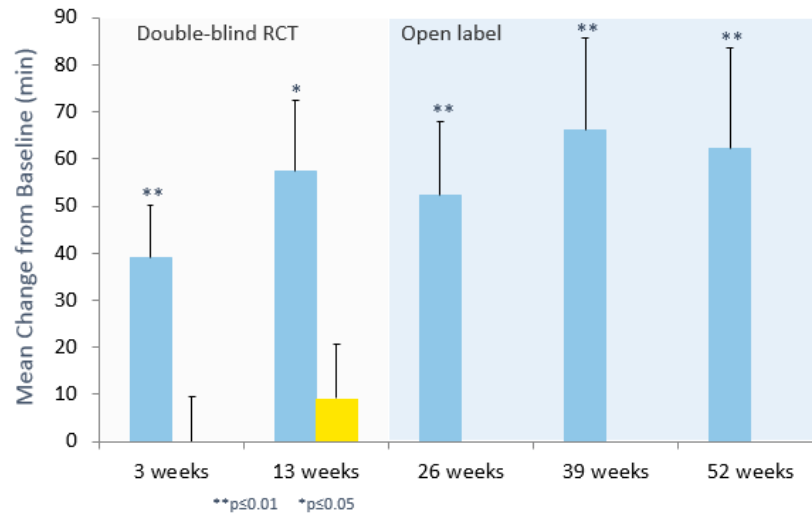
Immediate Release melatonin (IRM) has a rapid levels and rapid decline

Prolonged Release melatonin (PRM) mimics endogenous profile of melatonin

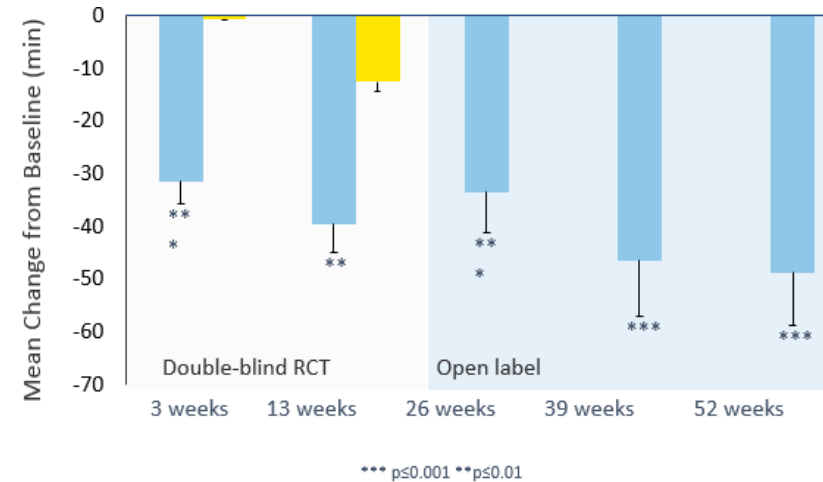


Impact of PR Melatonin on Child's Sleep

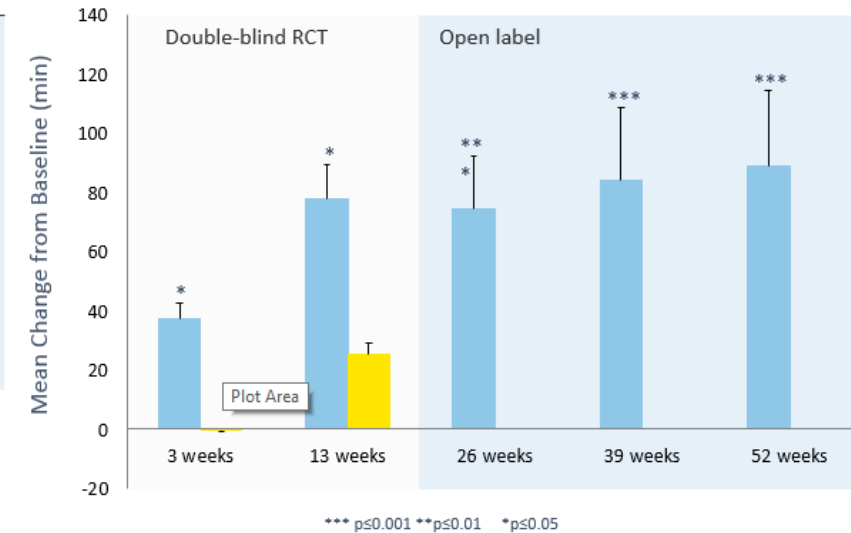
Total Sleep Time (NNT 4.7)



Sleep Latency (NNT 3.2)



Longest sleep duration



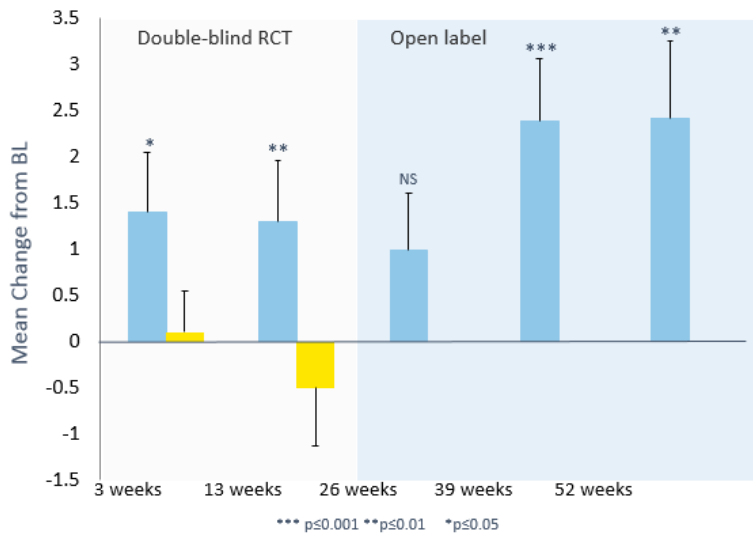
■ Ped PRM
■ placebo

Gringras P et al
J Am Acad Child Adolesc Psychiatry. 2017

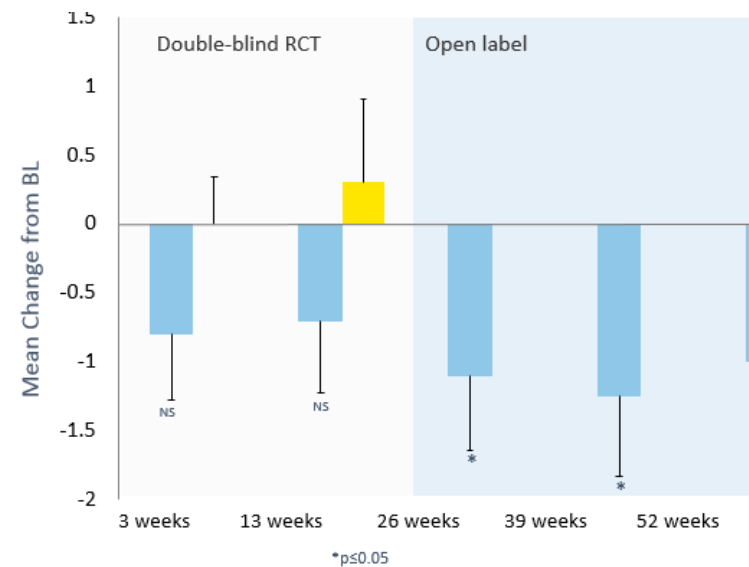
Maras, Schroder, Malow, Findling, Breddy, Nir, Zisapel, Gringras. J Child Adolesc Psychopharmacol. 2018

Secondary outcomes

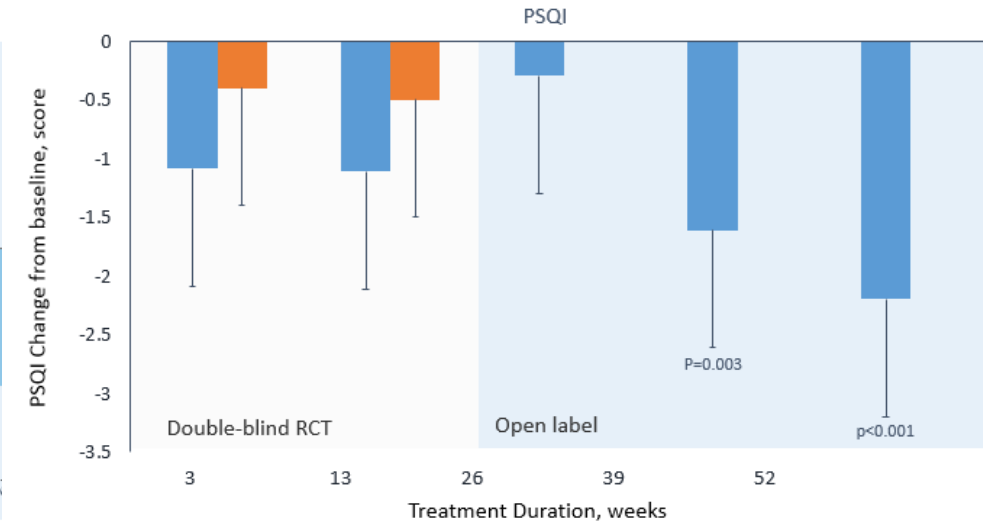
WHO-5 (12 months)



ESS (12 months)



PSQI- Parents Sleep Quality



Gringras P et al
J Am Acad Child Adolesc Psychiatry. 2017

Maras, Schroder, Malow, Findling, Breddy, Nir, Zisapel, Gringras. J Child Adolesc Psychopharmacol. 2018

Pharmacological Treatment in Adults with ASD

- Small studies eg 6 adults
- Melatonin appears to be effective in reducing sleep onset latency
- 'Probably effective in improving nocturnal awakenings and total sleep time in adults with autism'
- Remained effective for the 6-month period of administration.
- Melatonin was well tolerated in all patients and no side effects were noted during the therapy.

Galli-Carminatia G et al. Melatonin in the treatment of chronic sleep disorders in adults with autism: a retrospective study Swiss Med Wkly 2009

Melatonin and ADHD

- 105 children ADHD and sleep onset insomnia
- RCT 5 mg
- Reduction in sleep latency (~30 minutes)
- Small increase in total sleep time(~20 minutes)

*Van der heijden J Am Acad Ch Adolesc 2007
Weiss et al. 2006.*

Sleep and ADHD medications

- **Methylphenidate/Lisdexamphetamine**
 - Adds 30 minutes to sleep latency (Remarkably consistent across preparations)
- **Atomoxetine**
 - Adds 12 minutes to sleep latency
- **Clonidine/Guanfacine** (evening vs morning)-
probably improves in low dose

Clonidine

- *No RCT trials in children with ASD*
- UK- 'second-line' after melatonin
- Useful for sleep fragmentation
- Titrate dose carefully as high doses suppress REM sleep
- Tolerance can develop rapidly and consider role of 'cycling' with breaks on and off

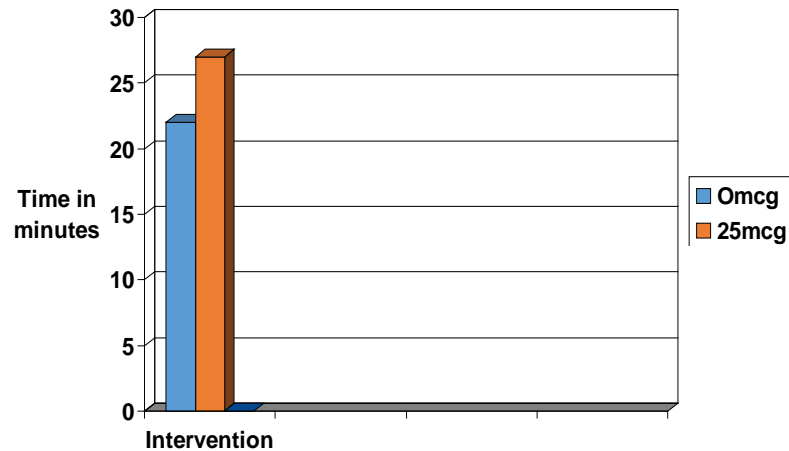
Clonidine Actigraphy Outcomes

Pre and Post **Clonidine**

25mcg 6 yrs boy (n=1)

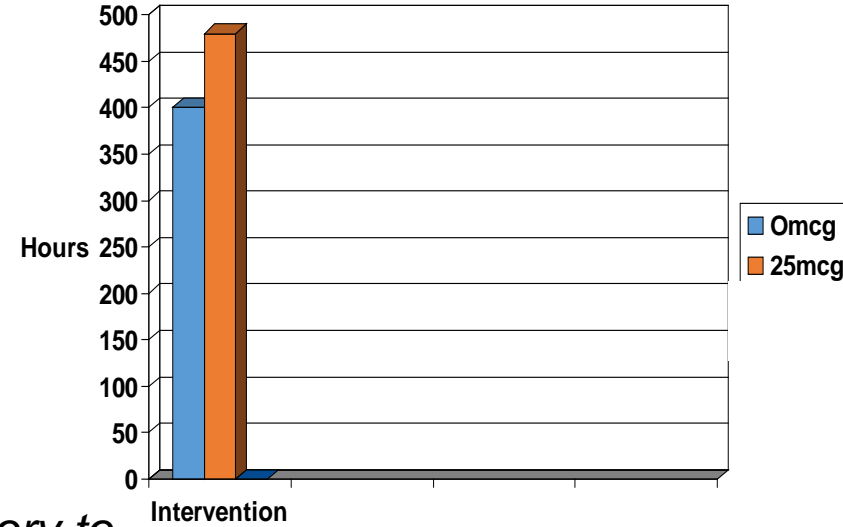
Agenesis of corpus callosum and autism (refractory to melatonin and chloral)

Sleep Latency



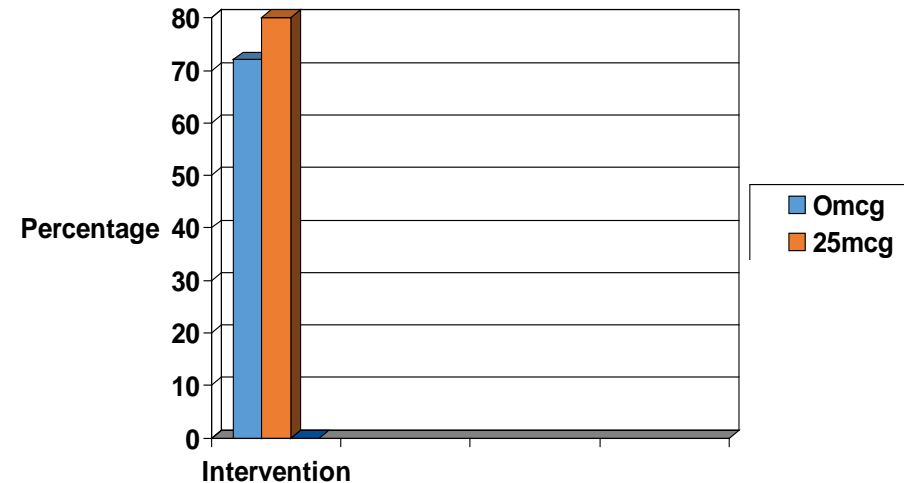
Total Sleep Time

(80 minutes longer)



Sleep Efficiency

(8% increase)



Safe space – an adjunct to behavioural
and medication approaches

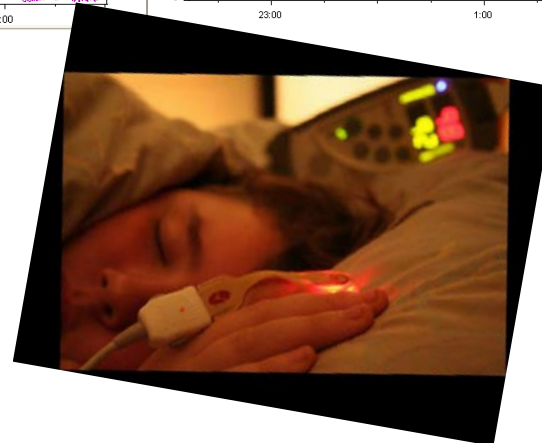
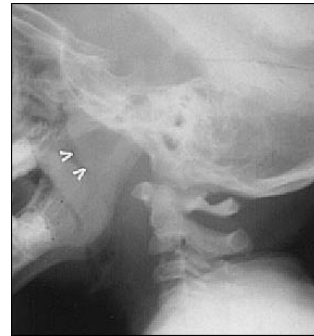
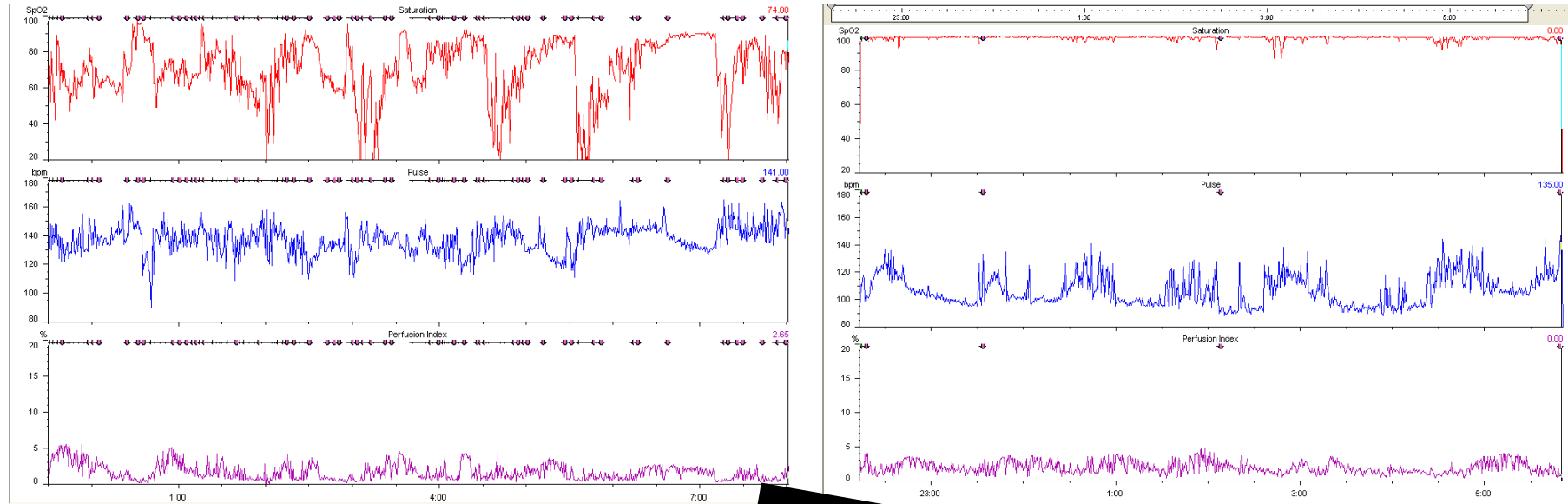
What does sleep-disordered breathing do?

- Intermittent hypoxia
 - Animal studies Functional deficits to hippocampus and prefrontal cortex
- Sleep Disruption
 - Animal studies inhibition of hippocampal long-term potentiation and neurogenesis

Effect of Sleep-Disordered Breathing on Parent-Reported Attention, Hyperactivity/Impulsivity, and Other Externalizing behaviours

Beebe DW. Sleep 2006;29(9):1115-1134

Pre and Post Adenotonsillectomy for Obstructive Sleep Apnoea Syndrome



Could it be sleep apnoea?

- **GASP** Does your child ever :
- **G** gasp or choke
- **A** stop breathing
- **S** snore loudly
- **P** sweat at night?

Non-pharmacological sleep interventions

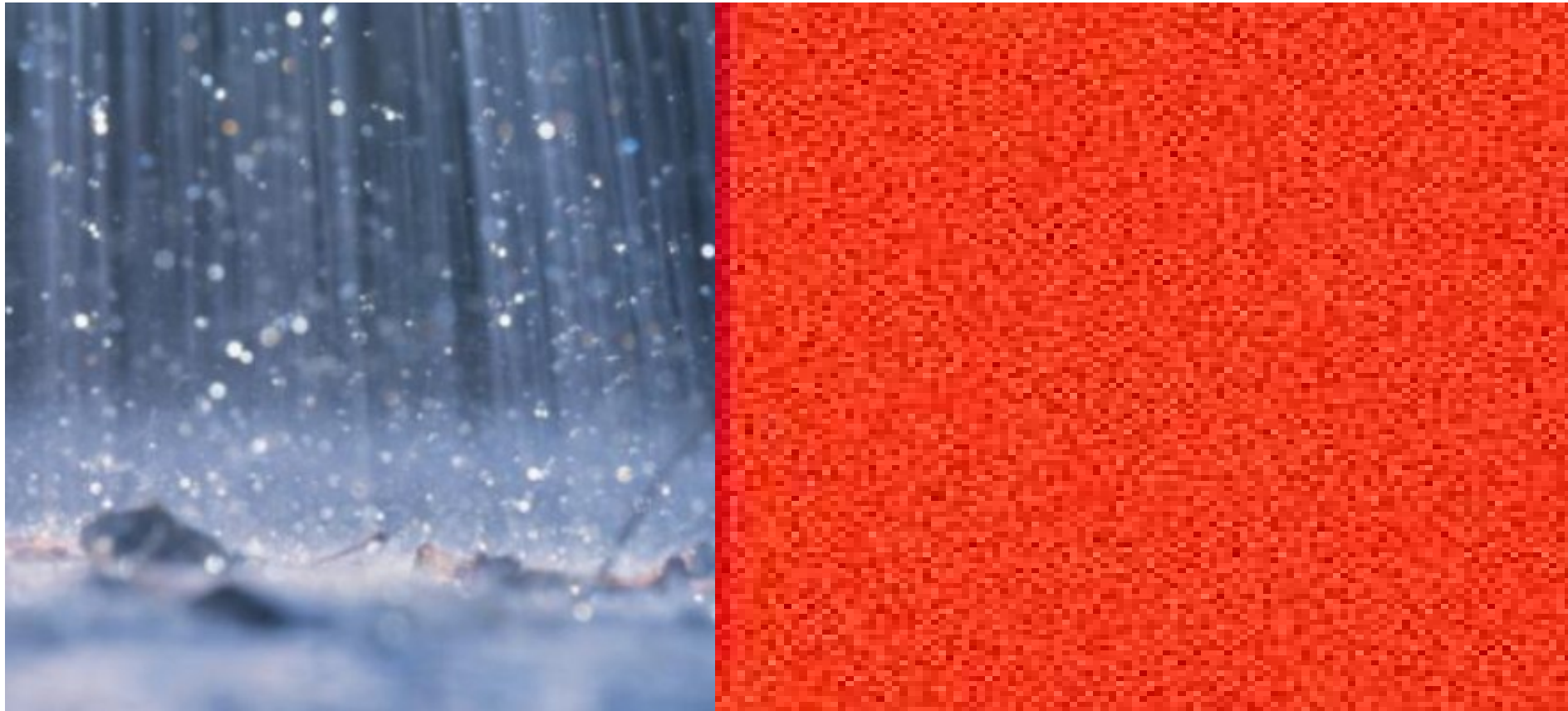
Sweat a little

- 11 subjects~12 years
- Control
 - Activity as usual
- Moderate
 - 65–70% of HR max for 30 min straight.
- Intense
 - 85–90% HR max to exhaustion
- Outcome:

Sleep Latency, Efficiency, and percent SWS improved but only after intense.



Rhythms of the night



*Auditory Closed-Loop Stimulation of the Sleep
Slow Oscillation Enhances Memory Ngo et al
2013*

The future

- We need to harmonise core outcome sets/measures
- We need more RCT of medications in common use
- More longitudinal follow-up/adult studies
- Explore more non-pharmacological sleep interventions

The End

Any Questions?

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