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Sleep Issue

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night in infancy is a marker
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Editorial

Guest Editor, Dr Mark Lovell

This edition of The Bridge concentrates on sleep, a poignant reminder that I am editing this on a 6am train to London having shortened my own sleep cycle and feeling rather sleep deprived on this dark winter morning. Having looked at the original research and summaries, I can now thankfully say I am now wide awake and feel invigorated for the rest of the day (with a little help from the contents of my coffee mug).

Clinically, sleep is often presented to Paediatric and Child and Adolescent Mental Health settings, either as the primary issue or as a symptom or sign of another condition. Often where it is presented can be luck of the draw, and has no logic. It is therefore important that clinically we understand the interrelationships between sleep from a biological, psychological and social perspective. It can be affected within neurodevelopmental disorders such as ASD and ADHD, in Cerebral Palsy and cortical blindness, as part of ear, nose and throat conditions, epilepsy may alter it, as may pain and discomfort, it may be a symptom or sign of either low or high mood and may be affected in children that have been affected by traumatic experiences or even be genetically pre-programmed with differences in sleep patterns eg in Smith Magenis Syndrome. As the scientific literature expands, we are learning more and more about the reason we sleep and what happens when we don't sleep enough. Also we are learning what interventions work and for whom.

In today's society where data is literally being fed into our lives 24 hours a day and we are accessing stimulating electronic devices with backlights that reduce our naturally produced melatonin that helps us sleep, the importance of sufficient quality and quantity of sleep couldn't be more pertinent, particularly as we are understanding more about its effects.

There have been some fascinating research articles in ACAMH's journals CAMH and JCPP covering a diverse range of sleep-related topics. From neurological predictors of poor sleep in the future, sleep and links to behavioural problems, cognitive and language development, links to depression, adverse childhood experiences and a summary of the evidence base for pharmacological treatments for sleep disturbance. This edition of the bridge contains some summaries by the original authors as well as commissioned summaries by our science writer.

I hope that you enjoy reading this issue of The Bridge and perhaps you'll be interested in attending one of ACAMH's periodic events on sleep either in person or online.

Mark Lovell

ACAMH Lead for CPD and Training



Research highlights in this edition are prepared by Dr Jessica K Edwards. Jessica is a freelance editor and science writer, and started writing for 'The Bridge' in December 2017.



Sleepiness in adolescence is associated with criminal behaviour in adulthood

By Dr Jessica K Edwards

Poor sleep seems to be associated with antisocial and criminal behaviour, but the longitudinal nature of this relationship is unclear. A recent study conducted by Adrian Raine and Peter Venables tested two hypotheses: (1) that adolescent daytime sleepiness is associated with later adult criminal offending; and (2) that social adversity predisposes to sleepiness, which in turn predisposes to attention impairment and adult crime. To address their hypotheses, the researchers recruited >100 15-year-old boys and collected self-report sleepiness and self-report and teacher-report antisocial behaviour ratings, assessed attentional capacity (by autonomic orienting) and arousal (by electroencephalogram) at baseline and collected conviction records for crime when the boys reached 29 years-of-age. They found that sleepy adolescents were more likely to be antisocial during adolescence and 4.5 times more likely to commit a crime by 29 years-of-age.

Interestingly, self-report sleepiness predicted adult crime over objective measures of daytime sleepiness (based on electroencephalogram theta activity). Poor levels of daytime attention partly mediated this relationship between sleep and crime. Finally, social adversity predisposed boys to daytime sleepiness, which was associated with reduced attention, which in turn predisposed to adult crime. Sleep is an alterable risk factor for crime, and crime is a costly international public health problem. Consequently, the researchers explain that giving more attention to this neglected health risk factor for crime will have societal, clinical and educational benefits.

Referring to:

Raine, A. & Venables, P.H. (2017) Adolescent daytime sleepiness as a risk factor for adult crime. *J. Clin. Psychol. Psychiatr.* 58: 728-735. doi: 10.1111/jcpp.12693.

Study Implications

Clinical Practice:

The researchers recommend that a simple, self-report question on daytime sleepiness may be predictive of a future salient negative outcome (crime). Posing this question to children and adolescents during daytime therapy could, therefore, have some prognostic utility. The availability of brief but effective behavioural sleep intervention for adolescents provides an opportunity for prevention and intervention studies to reduce externalising behaviour problems in clinical and nonclinical adolescent samples.

Service development/delivery:

The researchers note that daytime sleepiness and sleep measures are not currently incorporated into risk assessment tools to predict future dangerousness. They propose that including a question on daytime sleepiness in such instruments could ascertain whether this risk factor has utility in improving recidivism prediction. Future crime may be reduced by screening high-risk adolescents for sleep problems and providing them with sleep hygiene education to attenuate this risk factor.



Cortical hyperarousal in children may predict insomnia in adolescence

By Dr Jessica K Edwards

Cortical hyperarousal can be inferred from high-frequency (beta) electroencephalogram (EEG) activity during nonrapid eye movement (NREM) sleep. This hyperarousal is regarded as an underlying mechanism of insomnia persistence,¹ as cross-sectional studies have shown that increased beta EEG activity during NREM sleep is associated with insomnia.² Now, Julio Fernandez-Mendoza and colleagues have conducted the first developmental study to examine whether increased beta EEG activity in childhood precedes the onset of pathological insomnia symptoms in adolescence. The study included a case-control subsample of the Penn State Child Cohort, consisting of 45 children aged between 6 and 11 years. These children were monitored for low (15-25 Hz) and high (25-35 Hz) beta EEG activity during NREM sleep and were then followed 8 years later as adolescents. The data showed that childhood high-beta EEG activity during NREM sleep was associated with a threefold increased risk of developing insomnia symptoms in adolescence compared to normal sleeping controls. The researchers propose that cortical hyperarousal during NREM sleep may

thus be a pre-morbid neurophysiological sign of insomnia and an early treatment target in high-risk children.

Referring to:

Mendoza-Fernandez, J. Li, Y., Fang, J., Calhoun, S.L., Vgontzas, A.N., Liao, D. & Bixler, E.O. (2018,) Childhood high-frequency EEG activity during sleep is associated with incident insomnia symptoms in adolescence. *J Clin Psychol Psychiatr.* doi: 10.1111/jcpp.12945.

Further reading:

¹Bonnet, M.H. et al. (2010), Hyperarousal and insomnia: State of the science. *Sleep Med. Rev.* 14: 9-15. doi: 10.1016/j.smrv.2009.05.002.

²Riemann, D. et al. (2010), The hyperarousal model of insomnia: A review of the concept and its evidence. *Sleep Med. Rev.* 14: 19-31. doi: 10.1016/j.smrv.2009.04.002.

Glossary:

Nonrapid eye movement (NREM) sleep: a collection of three sleep stages during which there is little-to-no eye movement, dreaming is rare and the muscles are not paralyzed. Stage 1 of NREM sleep occurs in the beginning of sleep and the state is referred to as relaxed wakefulness. In stage 2, EEG recordings show short bursts of high-frequency brain activity, known as “sleep spindles”. Stage 3 is a deep sleep, known as slow-wave sleep.

Cortical hyperarousal: fast electroencephalographic (EEG)-defined cortical activity.

Study Implications

Clinical Practice:

Cortical hyperarousal may serve as an early preclinical marker to detect those at risk of insomnia and associated psychiatric disorders. Cortical hyperarousal may have a role in the increased risk for the development of depression associated with insomnia as early as adolescence or even childhood. As such, novel treatments to prevent insomnia and associated psychiatric morbidity should target cortical hyperarousal in high-risk children.

Recommendations for further science:

The researchers propose that large longitudinal cohorts with a developmental design are needed to replicate the study findings and confirm that cortical hyperarousal during NREM sleep can serve as a preclinical marker to detect those at risk of chronic insomnia phenotypes and associated psychiatric disorders. Such studies should combine multiple sources of data from the sleeping brain.

Future studies should also investigate the longitudinal association between sleep EEG activity in childhood and psychopathologic outcome in adolescence and early adulthood.



Time spent awake during the night in infancy is a marker for cognitive trajectories

By Dr Manuela Pisch

This article is a summary of the Original Article in the JCPP: Infant wake after sleep onset serves as a marker for different trajectories in cognitive development – by Pisch et al.

The link between learning and memory is bi-directional. Not only do we need to sleep in order to consolidate previously learned information, but also, we need to sleep to perform better and prepare our brains for subsequent learning. Especially infants, who learn an astounding amount of new information every day and require high quality sleep. In our study, performed by researchers at the Birkbeck Babylab in London, we showed that infants who woke less during the night at an early age, performed better at a working memory task over time.

In detail, we wanted to understand how the quality and quantity of sleep experienced early in life might be a marker for trajectories in working memory performance over the first year of life. Working memory is an important component of learning and executive functioning as it requires maintaining and manipulating information for a short period of time. Most studies on sleep and learning in infancy only take a snapshot by looking at data collected at one point in time. This however, might be misleading, as some associations might only show over time. Also, aspects of sleep and learning might not show a linear trajectory and therefore associations found at one particular age could differ from the ones found at other ages.

We measured infant sleep variables as well as performance of working memory at 4, 6, 8, and 10 months in a group of 40 infants. Our aim was to group infants depending on their trajectories in working memory and compare the sleep variables of those groups. Working memory was measured using an eyetracking task, where infants had to link two specific sounds with two moving toys for several trials. After that familiarisation period, infants only heard the sounds one after the other. The eyetracking data revealed whether infants were then searching for the corresponding toy at the correct location. Interestingly, we found that one group of infants searched at the correct location at 4 months, but stopped to do so later-on, even though they spent a long time searching for the toy on the whole screen. Probably they had realised that the toy did not appear at the expected locations and hence expected it to appear elsewhere. The other group only started to search at the correct location at 8 months.

Sleep variables were measured using actigraphy. An actigraph is a watch, similar to a Fitbit, that infants wore around their ankles during the nights. This watch measured movement every 30 seconds and using an algorithm, translated the movement data into periods of sleep and periods of wakefulness. Parents also reported the amount of day sleep in a questionnaire. Former studies have shown that objective measures of infant night sleep, such as actigraphs, are more accurate than parental report. Possible explanations are that many infants don't signal every time when they wake during the night.

The infants in our study slept an average of 10 to 10.5 hours every night. Furthermore, the amount of time they spent in wakefulness decreased over developmental time, with 4-month-olds being awake for about 40 minutes with an average of 4 awakenings, while the 10-month-old infants were only awake for 25 minutes each night spread over an average of 2 awakenings. Day time sleep also decreased from 4.6 hours to 2.6 hours.

We then asked the question: Do the two groups with different trajectories in working memory performance also sleep differently? Or in other words, can sleep be a marker for different trajectories of working memory?

We found that the groups of infants who performed better at an earlier age in the working memory task, also spent less time awake during the night, especially at a very young age. The difference of time spent awake between the two groups was greatest at 4 months suggesting that particularly sleep variables early in life are related to working memory trajectories. Night and day sleep duration was comparable between the two groups. This was a bit surprising as sleep duration was found to be related to learning in older children such as teenagers. One possible explanation is that the importance of sleep duration increases over developmental time. Furthermore, infants usually sleep according to their individual needs as opposed to teenagers who are often sleep deprived. Finally, the number of awakenings was also unrelated to the working memory trajectories suggesting that only infants who have difficulties settling back to sleep are more likely to be in the group who performed worse at an earlier age.

In summary, this is – to our knowledge – the first study displaying that habitual night wake duration serves as a marker for trajectories in a working memory task in infants. Also, this study highlights the importance of longitudinal studies if we really want to understand associations of different determinants of development. A snapshot of just the 8-month-old infants of this study would have shown that more time spent awake during the night is associated with better working memory performance, as we would not have known that infants who apparently performed worse in the memory task had already taken a further step in searching the whole screen.

Dr Manuela Pisch studied psychology in Strasbourg, Heidelberg, and Cambridge. In 2015, she finished her Marie-Curie funded PhD on the association between infant sleep and cognitive development at the Centre for Brain and Cognitive Development in London. Currently, she is a post-doc at the Institute of Childhood and Great Ormond Street Hospital in London where she is involved in an epidemiological study looking at neuro-psychological outcomes of infants with early-onset epilepsy.



Day-time naps promote vocabulary growth in early childhood

By Dr Jessica K Edwards

Cross-sectional studies have indicated that daytime napping enhances cognitive processes, including word learning, in early childhood.^{1,2} Now, Klára Horváth and Kim Plunkett at the University of Oxford have investigated the longitudinal relationship between sleep and cognitive development, specifically vocabulary development in a cohort of 246 infants and toddlers. The researchers monitored day-time and night-time sleeping patterns using a uniquely designed sleep diary (Sleep and Naps Oxford Research Inventory; SNORI³) and made vocabulary assessments at baseline and on up to eight follow-up occasions. They then used the sleep measures as predictors in a multilevel growth curve analysis of vocabulary development. The data showed that the length of night-time sleep was negatively associated with expressive vocabulary growth. In addition, good quality, un-fragmented night-time sleep was associated with larger predicted receptive vocabulary. Interestingly, the number of daytime naps was positively associated with both predicted expressive and receptive vocabulary growth. The researchers conclude that napping is at least as important, if not more so, than night-time sleep when it comes to vocabulary learning in early childhood. Of note, the number of naps seemed to be more important than the total length of the daytime sleep. The authors thus propose that young children may benefit from more distinct periods of daytime sleep to provide opportunities to consolidate newly learnt words.

Referring to:

Horváth, K. & Plunkett, K. (2016), Frequent daytime naps predict vocabulary growth in early childhood. *J Child Psychol Psychiatr.* 57: 1008-1017. doi: 10.1111/jcpp.12583.

Study Implications

Lead author Klára Horváth indicates the key implications from the study data:

Clinical practice:

“Child practitioners should regularly check children’s sleep, as if necessary, early intervention (e.g. improving sleep hygiene) may prevent later hindered cognitive development. The sleep diary (SNORI) developed for this study can be used to obtain information of children’s sleep patterns and is freely available from the Oxford BabyLab website. If practitioners identify slow language development, it is worth looking at children’s sleep alongside usual investigations.”

Schools/educational practice:

“Parents and nurseries should be advised to promote daytime sleeping. Children should be given the opportunity to have more periods of daytime sleep, should they need it.”

Recommendations for further science:

“Future research should clarify whether improving sleep in children with language delay or in atypically developing children may result in better cognitive development.”

Further reading:

¹Horváth, K. et al. (2016), A daytime nap facilitates generalization of word meanings in young toddlers. *Sleep* 39: 203-207. doi: 10.5665/sleep.5348.

²Horváth, K. et al. (2015), Napping facilitates word learning in early lexical development. *J Sleep Res.* 24:503-509. doi: 10.1111/jsr.12306.

³<https://www.psy.ox.ac.uk/research/oxford-babylab>

Glossary:

Receptive vocabulary: words that a person can comprehend and respond to, even if the person cannot produce those words.

Expressive vocabulary: words that a person can express or produce in either speaking or writing.

Sleep problems in preschoolers predict depression and anxiety severity

By Dr Jessica K Edwards

The bidirectional links between sleep problems and psychopathology in children have been well-reviewed,¹ but few investigations have been performed in young samples and those with early-onset psychopathology. Researchers at Washington University have now examined three specific, but commonly observed aspects of sleep behaviours in preschool children (aged 3-6 years): (1) prolonged sleep onset latency (SOL), (2) refusal to sleep alone, and (3) night-time awakenings. The prospective, longitudinal study used data from 292 preschoolers with or at risk of depression, enrolled in the Preschool Depression Study.² Here, the researchers assessed whether any of the three sleep problems could predict anxiety or depression across the next 6 years of childhood via parent-report of psychiatric symptoms and sleep problems using the Preschool-Age Psychiatric Assessment. They found that parent-reported prolonged SOL and refusal to sleep alone were significant, independent predictors of major depressive disorder and anxiety severity, but not of attention deficit hyperactivity disorder severity over time. These sleep difficulties predicted depression and severity of anxiety even after controlling for family income-to-needs ratio and maternal internalising psychopathology. Finally, the researchers showed that parent-reported prolonged SOL and refusal to sleep alone also predicted anxiety severity in a separate cohort of 81 healthy preschoolers. As sleep problems are relatively common in young children, the researchers suggest a need to distinguish between developmental norms and early markers of psychopathology to decrease the likelihood that severe depression and anxiety symptoms continue over time.



Study Implications

Clinical practice:

Refusal to sleep alone and/or sleep onset latency should be treated early in development, as they may contribute to the continuation of depressive and anxiety symptoms later in childhood. Identifying treatable precursors to the surge in depression rates during adolescence may curb this increase and associated negative outcomes. Clinicians may need to more carefully screen and assess for sleep disturbances during preschool.

Schools/educational practice:

Enhanced parental education about sleep benefits, healthy sleep routines and overall sleep hygiene may help prevent the continuation of sleep problems from preschool into school age and decrease the impact that these sleep problems may have on emotion functioning.

Recommendations for further science:

The researchers consider that determining how sleep onset latency and refusal to sleep alone bi-directionally influence depressive symptoms in preschool-aged to school-aged children is warranted. Sleep variables may be influenced by parental attitudes and anxiety around bedtime. The researchers recommend future studies that incorporate measures of parental bedtime anxiety as potential mediators of the relations between preschool sleep and school-age depressive severity.

Referring to:

Whalen, D. J., Gilbert, K.E., Barch, D.M., Luby, J.L. & Belden, A.C. (2017) Variation in common preschool sleep problems as an early predictor for depression and anxiety symptom severity across time. *J Child Psychol Psychiatr.* 58: 151-159. doi: 10.1111/jcpp.12639.

Further reading:

¹Gregory, A.M. et al. (2015), Annual Research Review: Sleep problems in childhood psychiatric disorders – a review of the latest science. *J Child Psychol Psychiatr.* 57: 297-313. doi: 10.1111/jcpp.12469.

²Luby, J.L. et al. (2009), The clinical significance of preschool depression: Impairment in functioning and clinical markers of the disorder. *J Affect. Disord.* 112:111-119. doi: 10.1016/j.jad.2008.03.026.

Glossary:

Sleep onset latency: the amount of time it takes to transition from full wakefulness to sleep.

Internalising psychopathology: a spectrum of conditions characterised by negative emotions and includes anxiety, phobias and depressive disorders and their related symptoms and behaviours.



Prescribing in the dark: off-label drug treatments for children with insomnia

By Dr. Jessica K. Edwards

Insomnia is a common problem in children with neurodevelopmental disabilities (NDDs), and has a profound effect on quality-of-life. Earlier this year, **Oliverio Bruni** and colleagues compiled a **Practitioner Review for the Journal of Child Psychology and Psychiatry on the pharmacologic treatment options for insomnia in children with NDDs**. They explain that **well-controlled studies that use objective polysomnography and subjective sleep measures are lacking. Such studies are urgently needed to determine the efficacy, effectiveness and safety of sleep medicines that are currently prescribed to affected children off-label.**

Sleep disturbances affect up to 86% children with neurodevelopmental disabilities (NDDs). Such disturbances include difficulties falling asleep (**sleep onset latency**), night awakenings and short sleep duration. The underlying causes for these disturbances are unclear, but may be due to another co-occurring medical condition, poor sleep hygiene or behavioural insomnia. As such, diagnosis of a sleep disturbance can be difficult, and is often exacerbated by the child's reduced communication skills. In their recent Practitioner Review, **Oliverio Bruni** and colleagues outline the non-pharmacological and pharmacological treatments currently used to treat chronic insomnia in children and adolescents with NDDs. Their key findings are discussed below.

Non-pharmacological treatments

Bruni et al. state that prevention is the best treatment for insomnia. In paediatric cases where the disorder is already chronic, they recommend that regardless of NDD status, good sleep practice and behavioural interventions should be the first approach. Behavioural interventions that employ a gradual approach, such as gradual withdrawal, gradual extinction and fading, are favoured over making an abrupt change. However, the choice of behavioural intervention can be guided by the preference of the parent and there is no evidence that one approach is more effective than another. The researchers noted that further investigations are needed to identify factors that predict treatment success and to tailor behavioural interventions for young children based on child, parental and environmental factors and any underlying pathology.

Parent involvement is critical in changing sleep problems in children. The researchers found that group-based training of parents in behavioural approaches to manage sleep problems may be effective, especially with regards to parent-set goals and the parent's sense of efficacy.¹ They also detailed two novel non-pharmacological approaches based on bed materials and accessories: a weighted blanket² and a novel mattress technology.³ While the former showed no superiority compared to the control condition in improving sleep problems in children with autism spectrum disorder (ASD), the latter promoted improvements in sleep onset latency, duration and efficiency.

Pharmacological treatments

Bruni and colleagues outlined the plethora of pharmacological treatments commonly used in chronic insomnia in children with NDDs. They explain that before initiating any drug treatment in children with NDDs, clinicians should pay attention to: (1) potential interactions with other drugs, (2) the child's age and clinical history, (3) the child's sleep history and sleep goals, (4) dosage and discontinuation plan, and (5) the nature of the primary complaint to guide drug choice.

Melatonin: This **chronobiotic** and hypnotic agent regulates the sleep-wake cycle. In general, systematic reviews and meta-analyses of placebo-controlled, randomised controlled trials in children with NDDs have demonstrated that melatonin significantly improves sleep onset latency and/or sleep duration compared to controls.⁴ Various studies that have also investigated the effects of melatonin for specific NDDs, and have confirmed that melatonin (1–10mg 30–60 min before bedtime) administered alone or in combination with **cognitive behavioural therapy** is effective for treating insomnia in children with ASD, Angelman syndrome, Rett syndrome and attention deficit hyperactivity disorder (ADHD). Although the researchers found no evidence for significant adverse effects associated with melatonin, a key concern is its loss of efficacy after an initial good response. The researchers thus recommend starting treatment with a low dose <6mg.

Antihistamines: Histamine promotes wakefulness and its suppression or inactivation can have a sedative effect. Antihistamines are the most prescribed or obtained over-the-counter agents for paediatric insomnia. The most commonly used antihistamine is diphenhydramine — a competitive H₁-histamine receptor blocker — with a recommended dose of 0.5 mg/kg up to 25 mg for children. Despite their widespread use, **randomised controlled trials** for antihistamines in children are lacking and the available data are conflicting. Bruni et al. detail that a common adverse effect of antihistamines is impaired consciousness, and tolerance can develop quickly. Furthermore, some children instead experience dramatic overarousal.⁶ Consequently, Bruni et al. do not recommend antihistamines as a first-line option to treat sleep disturbances in children with NDDs, due to the current lack of controlled trials and poor tolerability profile.

Clonidine: This adrenergic agonist is currently approved by the FDA in the USA to treat hypertension and ADHD. Bruni et al. describe that since clonidine has sedative effects, it is commonly prescribed to children off-label as a sleep aid despite no available well-controlled studies. A literature review of non-controlled studies, however, found that clonidine was effective for treating sleep disturbances in children with co-morbid ASD and other NDDs when used at a dose of 0.05–0.225 mg per day.⁷

Benzodiazepines: These hypnotic drugs have long been used to treat adults with insomnia, but few studies have evaluated their use in children. While some positive effects have been reported from small trials in children with Williams syndrome



and children with autism, concerns regarding their tolerability profile limit their use in children. The researchers report that one benzodiazepine, clonazepam, may be a good treatment option for children with arousal disorders, periodic leg movement disorder or restless legs syndrome but trials that assess objective sleep measures and safety are first needed.

Z drugs: These non-benzodiazepine sedative-hypnotics have not been evaluated to a great extent in children. The studies conducted thus far have not shown benefits over placebo groups and adverse events, including dizziness and headache, have been reported.

Antidepressants:

Tricyclic antidepressants: Two tricyclic antidepressants — amitriptyline and trimipramine — have sedative effects in adults. Bruni et al. identified no data to support their use in children with NDDs, yet amitriptyline is commonly prescribed at a very low dose in children with NDDs.

Mirtazapine: This agent can induce a high level of sedation at very low doses. One open-label study in children with autism and children with other pervasive developmental disorders showed some efficacy for mirtazapine in treating insomnia. Responders (34.6% patients) exhibited improvements in various symptoms, including aggression, anxiety and insomnia.⁸

Trazodone: Bruni and colleagues describe trazodone as the most sedating antidepressant available, and as such, it has been extensively studied in terms of its effects on sleep in adults. A survey of child and adolescent psychiatrists in the USA found that trazodone was the most commonly prescribed insomnia medication for children with mood and anxiety disorders;⁹ however, very few studies have actually assessed its efficacy as a sleep medication and tolerability in children and adolescents.

Atypical antipsychotics: These drugs are typically prescribed to reduce disruptive behaviours in children with psychiatric or developmental disorders. Risperidone and olanzapine, however, have been prescribed for childhood sleep disturbances despite a lack of studies evaluating their safety and effectiveness. Bruni and colleagues report that the poor tolerability of these drugs is problematic, especially as they may even exacerbate sleep problems in children with **sleep-disordered breathing**. The researchers do not recommend these drugs to treat insomnia in children, due to the lack of data and poor tolerability profile.

Gabapentin: Although approved to treat seizures, neuropathic pain and restless legs syndrome, gabapentin has reportedly beneficial effects on sleep. A case series showed gabapentin to be safe and well-tolerated when used to treat sleep onset and sleep maintenance insomnia in a cohort of 23 children, of whom 87% had NDDs.¹⁰ This beneficial response was evident at low doses (5-15 mg/kg at bedtime), much lower than the dose prescribed to treat epileptic seizures.

Chloral hydrate: Bruni et al. recommend that chloral hydrate be avoided in children with NDDs at risk of sleep apnoea due to adverse effects such as respiratory depression. Although originally considered a safe agent in infants and young children, chloral hydrate can elicit a wide range of adverse effects, from gastric distress, to fatigue and paranoia.

Orexin antagonists: Orexins have an excitatory effect on wake-promoting neurons and are critical modulators of the sleep-wake cycle. In healthy patients and patients with insomnia, orexin receptor antagonists may reduce the number of awakenings and sleep latency, and increase total sleep time.¹¹ The reported adverse effects thus far include headaches, dizziness and abnormal dreams. Bruni et al. consider, therefore, that these compounds might be a promising treatment strategy for children with NDDs, especially because they act on a different neurotransmitter system with fewer interactions with the drugs commonly prescribed for NDDs. They explain, however, that randomised controlled trials are first needed to assess the short-term and long-term effects.

Tryptophan/5-hydroxytryptophan (serotonin): Although tryptophan and serotonin-based strategies have been used to treat sleep disorders since the 1980's, no data are available on their effects on insomnia symptoms in children with NDDs.

Iron: Iron deficiency anaemia has been associated with high motor activity during sleep, short night sleep duration and a high frequency of night waking in infants. Consistently, iron supplementation has been associated with longer sleep duration¹² and one review found an increased incidence of periodic limb movements during sleep, sleep fragmentation and poor sleep efficiency in paediatric patients with ASD and low serum ferritin levels compared to controls.¹³ Bruni and colleagues thus recommend measuring ferritin levels in children, as iron deficiency is relatively common in this population. Furthermore, they consider that parents should be asked for a personal and family history of iron disorders.

Vitamin D: Preliminary data suggest that altered vitamin D metabolism may be involved in the presentation and severity of sleep disorders. Indeed, the available data thus far suggest that vitamin D supplementation may improve sleep quality. Bruni et al. propose that future studies that investigate vitamin levels in association with iron parameters in children with NDDs and insomnia associated with motor hyperactivity during sleep could be of value.

In summary, insomnia in children with NDDs affects quality-of-life for the affected child and their family. Although non-pharmacological interventions should be the first course of action, Bruni et al. warn that many cases will likely require pharmacological intervention. Well-designed controlled studies on the efficacy/effectiveness, tolerability, dose and safety profile of hypnotic medications in children are, however, urgently needed to facilitate on-label prescribing. Although Bruni et al. suggest possible management algorithms for children with NDDs and chronic insomnia, they explain that the lack of head-to-head trials renders it impossible to provide an evidence-based hierarchy of available medications in terms of efficacy and effectiveness. From the available data thus far, however, they do discourage the use of antipsychotics and benzodiazepines in children with NDDs, due to their poor tolerability profile. Hope lies in the development of a drug in the near future that has proved efficacy and a good safety profile in children and adolescents with NDDs and insomnia.

Referring to:

Bruni, O., Angriman, M., Calisti, F., Comandini, A., Esposito, G., Cortese, S. & Ferri, R. (2018), Practitioner Review: Treatment of chronic insomnia in children and adolescents with neurodevelopmental disabilities. *J Child Psychol Psychiatr.* 59: 489-508. doi: 10.1111/jcpp.12812

Further Reading

¹Stuttard, L. et al. (2015), A preliminary investigation into the effectiveness of a group-delivered sleep management intervention for parents of children with intellectual disabilities. *J Intellect Disabil.* 19:342-355. doi: 10.1177/1744629515576610

²Gringras, P. et al. (2014), Weighted blankets and sleep in autistic children—a randomized controlled trial. *Pediatrics* 134:298-306. doi: 10.1542/peds.2013-4285

³Frazier, T.W. et al. (2017), A randomized, crossover trial of a novel sound-to-sleep mattress technology in children with autism and sleep difficulties. *J Clin Sleep Med.* 13:95-104. doi: 10.5664/jcsm.6398

⁴Braam, W. et al. (2009), Exogenous melatonin for sleep problems in individuals with intellectual disability: A meta-analysis. *Dev Med Child Neurol.* 51:340-349. doi: 10.1111/j.1469-8749.2008.03244.x

⁸Posey, D.J. (2001), A naturalistic open-label study of mirtazapine in autistic and other pervasive developmental disorders. *J Child Adolesc Psychopharmacol.* 11:267–277.

⁹Owens, J.A. et al. (2010), Use of pharmacotherapy for insomnia in child psychiatry practice: A national survey. *Sleep Med.* 11:692–700. doi: 10.1016/j.sleep.2009.11.015

¹⁰Robinson, A.A. et al. (2013), Gabapentin shows promise in treating refractory insomnia in children. *J Child Neurol.* 28:1618–1621. doi: 10.1177/0883073812463069.

¹¹Kumar, A. et al. (2016), Emerging role of orexin antagonists in insomnia therapeutics: An update on SORAs and DORAs. *Pharmacol Rep.* 68: 231–242. doi: 10.1016/j.pharep.2015.09.002

¹²Kordas, K. et al. (2009), The effects of iron and/or zinc supplementation on maternal reports of sleep in infants from Nepal and Zanzibar. *J Dev Behav Pediatr.* 30:131–139. doi: 10.1097/DBP.0b013e31819e6a48

¹³Youssef, J. et al. (2013), Relationship of serum ferritin levels to sleep fragmentation and periodic limb movements of sleep on polysomnography in autism spectrum disorders. *Pediatr Neurol.* 49:274–278. doi: 10.1016/j.pediatrneurol.2013.06.012

Glossary:

Sleep onset latency: the amount of time it takes to fall asleep.

Chronobiotic: a chemical agent that can cause a phase adjustment of the body clock, i.e. shift the biological circadian rhythm.

Cognitive behavioural therapy (CBT): a form of talking therapy that encourages patients to manage their psycho-social problems by changing the way they think and behave; CBT focuses on current problems and finds practical ways to improve state-of-mind on a day-by-day basis.

Randomised controlled trial: an experimental setup whereby participants are randomly allocated to an intervention/treatment group or a control/placebo group. Randomisation of participants occurs after assessments for eligibility, and is used to minimise selection bias.

Sleep disordered breathing: repeated episodes of hypopnoea (under breathing) and apnoea (not breathing) during sleep.

Learning Outcomes:

1. Insomnia is a common problem in children with NDDs and can have poor developmental outcomes and exacerbate behavioural disturbances.
2. Good sleep practice and behavioural interventions are the recommended first-line treatment for paediatric insomnia.
3. Pharmacological treatments for paediatric insomnia are currently prescribed off-label or off-license.
4. Melatonin seems to be the safest pharmacologic intervention for children with NDDs; benzodiazepines are not recommended for use in children.

Areas for future research:

The researchers highlight that despite wide-spread pharmacological treatment, well-designed, controlled studies on the efficacy/effectiveness, tolerability, dosage and safety profile of hypnotic medications in children are lacking. Further research is, therefore, needed in this field of sleep medicine. Well-conducted trials based on the physiopathology for the NDD that also evaluate the presence of other co-morbid sleep disorders are also required.

Improvements of adolescent psychopathology after insomnia treatment: Results from a randomized controlled trial over one year

By Dr. E.J. de Bruin

This article is a summary of the Original Article in JCPP: Improvements of adolescent psychopathology after insomnia treatment: results from a randomized controlled trial over 1 year – by de Bruin et al. (<https://doi.org/10.1111/jcpp.12834>)

Many adolescents experience sleep problems, which can be caused by hormonal changes during puberty, and social changes with increasing complexity of daily life while growing up. The interplay of these biological and social factors can lead to inadequate sleeping behaviours and can disturb the biological clock. When troubles with initiating and maintaining sleep or inadequate sleep quality become chronic they can result in insomnia disorder.

Insomnia has a bi-directional relationship with psychopathology, which implies that it can be caused by or exacerbate other mental disorders, such as depression, anxiety, and ADHD. For adolescents there appears to be little evidence that depressive symptoms predict the development of sleep disturbances, whereas prior insomnia in adolescents is associated with a four times higher risk of subsequent depression. Moreover, adolescents with a sleep problem have a two times higher risk for any other psychiatric disorder. Because of the accumulating evidence of the bi-directional relation of insomnia with other mental disorders, in the Diagnostic and Statistical Manual Fifth edition (DSM-5) insomnia is regarded as a mental disorder per se (i.e. not necessarily comorbid with, and/or caused by, another mental disorder) and a target for intervention in itself.

Cognitive behavioural therapy for insomnia (CBTI) consists of a set of techniques that in combination have been shown to be the most effective treatment for insomnia, and is recommended as first-line treatment for adults for over ten years. CBTI consists of psycho-education sleep hygiene, stimulus control, cognitive therapy, restriction of time in bed (also known as 'sleep restriction'), and relaxation exercises. Sleep hygiene consists of aspects of behaviour and the sleep environment that influence sleep, such as diet, exercise, substance use, light (including light from devices), noise, and bedroom temperature. Sleep hygiene advice is usually combined with psycho-education on sleep-need, sleep-regulation, and functions of sleep. Stimulus control is aimed at dissociating the conditioned response of insomnia from cues that are normally associated with sleep, such as the bed and bedroom, and re-associating these cues with rapid sleep onset. In practical terms, a person is instructed to use the bed and bedroom only for sleep, to go to bed only when sleepy, and to get up for a short period of time when unable to fall asleep or return to sleep for longer than 15-20 minutes.



Relaxation exercises are aimed at decreasing (physiological and cognitive) arousal that interferes with sleep. Cognitive therapy is aimed at altering dysfunctional beliefs and cognitions that interfere with sleep, such as "I have to sleep now otherwise I won't be able to do well at my exam tomorrow" or "I need at least 9 hours of sleep". And finally, restriction of time in bed consists of curtailing the time spent in bed to the amount the person actually sleeps. By restricting time in bed a mild state of sleep deprivation is induced that facilitates a rapid sleep onset.

Recently, CBTI has also been shown to be effective for insomnia in adolescents in individual internet-therapy and in group-therapy formats. Besides improvements in sleep, CBTI also leads to improvements in other mental health problems, such as depression. However, it is still largely unknown whether these improvements in other mental health problems are caused by the CBTI directly, or are related to mitigation of insomnia.

In a study published in the Journal of Child Psychology and Psychiatry we investigated CBTI for adolescents aged 12-19 using internet-therapy (39 participants) and group therapy (38 participants), and compared the results to a waiting list control group (39 participants). Adolescents received six weekly sessions of CBTI, and a booster-session two months after the sixth session. We measured psychopathology with the Youth Self-Report (YSR), and sleep with a questionnaire on insomnia symptoms, and daily sleep-logs and actigraphy (an accelerometer that measures movement and is worn like a wrist-watch on the non-dominant hand) for a week at each measurement.



Actigraphy are considered to be a reliable and objective measurement of sleep parameters, such as sleep onset latency (SOL), total sleep time (TST) and sleep efficiency (SE). From multilevel regression analyses we found that after CBTI both treatment-groups improved with large effect sizes for SE and SOL, and a small effect size for TST. Insomnia symptoms decreased with a large effect size after CBTI. Regarding psychopathology, we found medium effect size improvements for Affective, Somatic and ADHD problems, for both treatment groups. Anxiety problems decreased in the group treatment and Oppositional defiant problems decreased in the internet-treatment after CBTI. All improvements were sustained over one year or showed further improvements.

To investigate whether improvements in psychopathology could be attributed to improvements in insomnia, we conducted mediation analyses for both groups with measurements of insomnia and psychopathology at baseline, directly after treatment, and at 2-months follow-up. These analyses indicated that the decrease of affective and anxiety symptoms at 2-months follow-up after CBTI were fully mediated by the decrease of insomnia symptoms directly after treatment. The decrease of ADHD symptoms was partially mediated.

These findings indicate, first, that sleep problems play an important role in causing and maintaining psychopathology in adolescents, and, second, CBT for insomnia may be an effective additional instrument in treating certain types of psychopathology. Common neural and behavioural mechanisms underlying insomnia and psychopathology may explain the effectiveness of CBTI in treating psychopathology.

Concerning the bi-directional relationship between insomnia and psychopathology, an important question is whether it is best to (a) treat the insomnia first and then to assess the effect of that treatment on the psychopathology (and only treat the latter if still necessary), (b) to treat the psychopathology first and then to assess the effect of that treatment on the insomnia (and only treat the latter if still necessary), or (c) to combine both treatments from the outset. In our present study we have shown that CBT for insomnia can improve adolescent psychopathology, so treating insomnia first appears to be a viable and feasible alternative to other treatment options.

The results of our study are also important for clinical practice. Research shows that though prevalence of psychopathology is high among adolescents, many adolescents do not get the mental healthcare they need. Our study shows that a relatively short treatment programme for insomnia can have a strong positive influence on mental health problems in the young. Moreover, we have found broadly similar results for Internet and group therapy.

To conclude, our study shows the importance of sleep for healthy adolescent functioning and the ability to improve both sleep and psychopathology through a relatively short and accessible treatment program.

Bio: Dr. Eduard J. de Bruin is a post-doctoral researcher and somnologist at the Research Institute of Child Development and Education of the University of Amsterdam, Netherlands. His research on sleep in children and adolescents focuses on behavioural treatment of adolescent insomnia, and the application of innovative treatment techniques, such as mindfulness and the use of internet and mobile technology.

Implications

- Clinical practice: In case of adolescent comorbid disorders including sleep problems/insomnia, treating the sleep problems first can be considered. Treating sleep problems regardless of other mental health problems is always indicated, and can lead to mitigation of other mental health problems.
- Service development/delivery: Internet-delivered behavioural sleep treatment is equally effective in treating insomnia in adolescents as face-to-face group therapy.
- Gaps and recommendations for further science: Further research into models of adolescent insomnia, and common underlying mechanisms of insomnia and other psychopathology is warranted

Sleep partially mediates the link between adverse childhood experiences and delinquency

By Dr Jessica K Edwards

Adverse childhood experiences (ACEs) can be traumatic or highly stressful events, and are associated with numerous mental and physical health problems. A recent study has now investigated the mechanisms underlying the apparent link between ACEs and high rates of delinquency in children in foster care, with a specific focus on sleep. The researchers conducted interviews with >500 maltreated children (aged 9-11 years) currently in foster care and their carers. They asked the participants to report on exposure to ACEs, sleep problems, engagement in delinquent acts, symptoms of post-traumatic stress disorder and current psychotropic medication use. More than 30% of the youths reported engaging in at least one delinquent act, and >20% caregivers reported that their foster children had sleep problems. After controlling for various factors, including age, placement type and length of time in placement, the researchers found that sleep partially mediated the association between ACEs and delinquency. Specifically, sleep problems accounted for ~7-9% of the large effect of ACEs on delinquent acts across levels of ACEs exposure. The researchers explain that determining the risk factors for delinquency in children in foster care is vital to reduce later juvenile justice-system involvement. Sleep problems should be assessed in this population and foster caregivers should help establish good sleep hygiene in children as one strategy to help reduce delinquency.

Referring to:

Hambrick, E.P., Rubens, S.L., Brawner, T.W. & Taussig, H.N. (2018), Do sleep problems mediate the link between adverse childhood experiences and delinquency in preadolescent children in foster care? 59: 140-149. doi: 10.1111/jcpp.12802.

Study Implications

Professor Erin Hambrick outlines some of the key implications from her study data:

Clinical practice:

"Both sleep problems and delinquent behaviours are prevalent amongst preadolescents in foster care, perhaps due to the high rates of adverse childhood experiences in this population. Screening for both sleep problems and delinquent behaviours in children living in foster care prior to when they reach adolescence, when more severe and frequent delinquent acts are often observed in this population, may result in more successful remediation of both problems."

Service development/delivery:

"When screening for and planning to intervene on sleep problems for youth in foster care, providers should be aware of "foster care specific" risk factors for sleep problems. These include high rates of post-traumatic stress and autonomic hyperarousal, changes in sleep routine, sleep hygiene, and the sleep environment due to transitioning to new living situations, and the child's perceived safety in their new sleep setting."

Recommendations for further science:

"It is important for future studies to determine whether improving sleep problems results in decreased delinquency amongst youth in foster care."

