Box 1 Tips for effective sleep hygiene

- Ensure consistent bedtime routines which rhymes with the natural dim-light-melatonin-onset [DLMO] secretion preceding sleep onset by approximately 2h (Mindell et al 2015).
- Avoid late naps or excessive vigorous exercise, use of stimulant substances, arousing or disturbing mental, emotional or physical activities close to bedtime
- Avoid exposure to TV, computers and other electronic screens at last one one before bedtime (Fossum et al 2014).
- Maintain a conducive sleep environment including comfortable bedding, minimal light (or orange goggle), and noise exposure (or ear plugs), use blackout blind with room temperature regulated to around 19 to 220C (Shinoara & Kodama 2011).
- Avoid eating within half hour from bedtime, and do not consume caffeinated or energy drinks after midday. Carbohydrates and foods rich in tryptophan promote sleep (Foley et al 2013).
- Practice self-relaxation (eg. Meditation, mindfulness, paced breathing)

Box 2 outlines common items to be included in a detailed clinical assessment.

1. History taking: Assessment should include information (NICE cg170 2013) about bedtime routines, nature of sleep environment exposure to electronic gadgets, levels of activity and exercise during the day and bedroom sharing. Presence of other physical, emotional or neurodevelopmental comorbidities including ADHD, physical illness or discomfort (for example, reflux, ear or toothache, bedwetting, constipation or eczema), effect of any medications used and emotional state. Any other factors affecting sleep, such as emotional relationships, challenging behaviours, school problems and the impact of the sleep problems on parents or carers, other family members, school performances and other social functioning.
2. All CYP require screening questions about disordered respiratory sleep disorder (sleep apnea, laboured breathing) and Narcolepsy (cataplexy, sleep paralysis, hypnagogic hallucinations).
3. Family history and context should include Impact of the sleep disorder on the

child and on the family structure, Family sleep patterns. Parental expectations. Cultural factors.

4. Detailed clinical assessment should lead to formulation of a sleep disorder diagnosis or consideration of potential differential diagnosis and exclude other physical explanations for insomnia including obesity, tonsil hypertrophy, facial dysmorphism, nasal septal deviation, craniofacial abnormalities, hypotonia, chronic rhinitis or other physical illness or discomfort (for example, reflux, ear or toothache, bedwetting, constipation or eczema).

Box 3 showing List of Licenced Melatonin products

- Circadin 2mg modified release tablets (Flynn Pharma Ltd) (For adults above 55 years as second line treatment up to 13 weeks after zopiclone, zolpidem or a benzodiazepine)
- Slenyto® (melatonin) 1mg and 5mg prolonged release tablets1
- Melatonin 3mg tablets (Colonis Pharma Ltd)2
- Melatonin 1mg/ml oral solution (Colonis Pharma Ltd)

https://www.berkshirewestccg.nhs.uk/media/3235/142171-melatonin-liquid.pdf

Box 4 showing Behavioural interventions to improve sleep in children with chronic insomnia

Bedtime settling problems				**Night-time waking**		**DSPS**
Extinction (crying out)	**Graduated extinction (controlled crying)**	**Bedtime fading**	**Graded withdrawal**	**Robotic parent return**	**Scheduled awakening**	**Chronotherapy**
Parents need to ignore the child's crying in order for the child to self-soothe.	Modified as some parents find this strategy less stressful.	This helps to take the 'flight' out of bedtime.	Parent gradually withdraws from the child's bedroom to enable the child to fall asleep independently.	Parents need to avoid communication and interaction with the child when he/she wakes up at night, crying out loudly or calling out.	This helps if the child wakes up frequently at the same time each night and cannot settle to sleep	This helps to reset the biological clock
• Keep the regular bedtime. • Completely Ignore the child's cries and calls	• Keep the regular bedtime. • Ignore the child's cries and calls for specific	• Keep a sleep diary for 2 weeks to choose the new bedtime • Initially the child needs	• The child relies on the presence of parent to sleep • No change to bedtime needed	• Do not carry or cuddle the child. • There should be no eye contact • Use magic phrase such as 'Time for sleep' but no other	• Wake the child 15 to 30 minutes before the usual wake time	• Keep a sleep diary for 2 weeks to find out the bedtime and wake-up time

• Praise in the morning for better night • Success usually within 7 to 10 days	periods e.g. 3 minutes • Praise in the morning for better night • Success usually within 7 to 10 days	to stay up later, until their natural sleep time • Gradually move the bedtime earlier • Success within a few weeks	• Withdraw from the child's bedroom gradually • Use with 'Robotic parent return' strategy • Success usually within 2 weeks	verbal communication • The child learns bedtime means sleep • Reward the child for better night's sleep and have lots of interaction with the child during daytime	• Use with 'Robotic parent return' strategy • Success within 2 weeks	• The adolescent needs to stay up 3 hours later and get up 3 hours later than the established sleep/wake schedule • Avoid naps

Source: "Sleep problems in children and young people: A simple teaching aid, a flip chart@ written by Dr CR Yemula, Andrea Roberts and edited by Professor Besag)

Appendix 1

An Evidence-based Clinical Guidance for managing children with sleep problems and associated Neurodevelopmental, Emotional, Behavioural and Intellectual disorders (NDEBID) including ADHD, Autism, Visual impairment, Cerebral palsy, Learning disability, Epilepsy and Neurodegenerative disorders

Introduction:

There is paucity of national evidence-based guidelines that emphasises holistic care of this group of children highly vulnerable to significant chronic sleep disorders and also help to resolve the perennial problems of escalating costs of Melatonin prescription in several NHS Trust.

Section 1: Mandatory initial assessment and First-line management for all patients

1.1 **Every child and adolescent with sleep difficulties should have** detailed medical and sleep history, excluding any possible underlying sleep apnoea, other physical explanations for insomnia including obesity, bedwetting, emotional problems or sources of discomfort (for example, reflux, ear or toothache, constipation or eczema), formulation of a sleep disorder diagnosis and consideration of potential differential diagnosis (Section 1.5).

1.2 The initial screening should include:

1. Questions exploring sleep complaints, such as the 5-item instrument known as BEARS (B-Bedtime issues, E-Excessive daytime sleepiness, A-night Awakenings, R-Regularity and duration of sleep, S-Snoring) and the
2. Use of specific sleep questionnaires, such as the Children's Sleep Habits Questionnaire (Cortese et al 2013, Appendix A4).

3. Sleep diaries should be completed over at least 2 weeks (Appendix A4). Actigraphy over the same 2 weeks can provide more precise information on patterns of sleep and wakefulness (if available).

1.3 Approximate hours of sleep needed by children of different ages (Table 2)

1.4 Consider offering treatment if:

- There's evidence of sleep onset latency longer than one hour or total sleep time less than 6 hours
- After excluding sleep apnoea and other physical or emotional explanations for insomnia.
- Significant negative impact on family or daytime functioning

1.5 Diagnose and document main categories of sleep disorder before commencing treatment (Cortese et al 2013)

1. Sleep-onset association type: Falling asleep in a reasonable time is possible only if is associated with a specific form of stimulation (e.g.,watching TV) or setting (e.g., parents'bed). The associations are highly problematic or demanding.
2. Limit-setting type: Parental difficulty in setting limits and managing behaviour. When limits are instituted, sleep onset is not delayed.
3. Delayed sleep Phase syndrome: Delay in the habitual sleep wake times relative to conventional or socially acceptable times. When allowed to choose their preferred schedule, patients exhibit normal sleep quality/duration.
4. Multiple Night wakings: Brief arousals from sleep are common in infancy and childhood. Those who develop inappropriate sleep association to fall asleep (see above) also have difficulty self-soothing after the arousals during the night and thus alert their parents (crying, going into their bed, etc.).

5. Partial arousal parasomnias: These are Sleep terror, sleep walking and confusional arousals occurring in deep sleep state. They occur within 1-3 hours after sleep onset and are characterized by retrograde amnesia, autonomic or skeletal muscle disturbance. The child has the appearance to be awake but (s)he is not.
6. Rhythmic movement disorders: Repetitive movements of large muscles occurring mainly during sleep-wake transitions such as head-banging and body rocking.
7. Sleep disordered breathing: A group of disorders characterized by abnormalities of respiratory pattern or the quantity of ventilation during sleep. The most common of these is obstructive sleep apnea.
8. Restless legs syndrome: Irresistible urge to move the legs, often accompanied by uncomfortable sensations which are relieved by movement and worse in the evening or night and at rest.
9. Periodic limb movement disorder: Periodic episodes of repetitive and stereotyped limb movements during sleep, often associated with a partial arousal or an awakening.

1.6 Which child should be considered for referral to specialist sleep centre for Polysomnography?

- Obstructive sleep apnea affects about 2 percent of children and any suspicion of it should trigger an urgent referral to the ENT surgeons.
- Circadian Rhythm Sleep Disorders (as evidenced from the sleep diary and standard sleep questionnaire) not responding to first, second or third line treatments.
- Daytime hypoarousal, excessive sleepiness state resembling narcolepsy

1.7 Stage 1: Evidence based behaviour interventions should be offered for at least 4 to 6 weeks*

- Detailed assessment should lead to the formulation of a **sleep plan** with the parents or carers (this will often be a specific sleep behavioural intervention) to help address the identified sleep problems and to establish a regular night-time sleep pattern. This plan needs to be reviewed regularly until a regular sleep pattern is established.
- This will include evidence-based behavioral interventions of unmodified extinction, graduated extinction, bedtime fading/positive routines and scheduled awakenings parent training, sleep behaviour advice booklet, sleep hygiene tips, pink or white noise, reward charts and alternative therapies (massage therapy, aromatherapy).
- Cognitive-behavioral therapy is more commonly used for older children and adolescents.

Evidence: Behavioral interventions for pediatric insomnia in young children have shown small to large effect sizes for specified sleep outcomes: Sleep Latency, number and duration of night-wakings and total sleep time (Meltzer & Mindell 2014; Arboledas et al 2017)

* See Definitions and resources for sleep hygiene and behavioural sleep therapy in **Boxes 1 & 4**

Section 2: Tiered trial of various pharmacotherapies and combined treatments

2.1 Stage 2: Trial of Melatonin (Dosage and treatment duration)

- Trial of Melatonin will be second-line for selected children with abnormal Melatonin production or evidence of circadian rhythm sleep disorder. Dysregulated melatonin metabolism nay be found in about 50% of children with ASD (and this improves with age) and other genetic syndromes like Rett's disease, Smith-Magenis, Angelman, and Williams Syndromes, severe learning disability and those with physical disabilities such as blindness and other sensory disorders, chronic fatigue syndrome or myalgic

encephalomyelitis. The prevalence among children with ADHD is not yet confirmed, but most children with ADHD have behavioural insomnia and best managed with behavioural interventions.

- Most children with EBND benefit from low or moderate dose of Melatonin, with only a small minority benefiting from any dose above 6mg (Ayyash et al 2015).
- It's important to be aware that the overall effectiveness of Melatonin compared to placebo is modest, increasing total sleep time (TST) by 23 minutes and reducing sleep onset latency by an average of 45 minutes (Gringras et al 2012). The upper limit of the confidence interval for increased TST is less than 1 hour, and therefore may not be considered to clinically significant. However, for some families, these relatively short timescales may provide significant relief.
- Trial of Melatonin should be combined with other behavioral and psychological strategies.

Evidence: There is no evidence that extended-release melatonin confers advantage over immediate release. There Is limited evidence about effect of Melatonin on night awakenings. There are ongoing longitudinal efficacy studies of Melatonin but there are several areas of uncertainties including long-term effects on puberty development and immune system (Rossignol & Frye 2014). The use of melatonin is supported by NICE in the clinical guideline on the diagnosis and management of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) in children (2007).

2.2 Contraindications to use of Melatonin

- The manufacturers of Circadin® state that it should not be taken in patients with rare hereditary problems of galactose intolerance, the LAPP lactase deficiency or glucose-galactose malabsorption.

- Melatonin is not recommended for use in patients with autoimmune diseases or taking immunosuppressants and can cause Increased blood pressure with Nifedipine.
- Hypersensitivity to the active substance or to any of the excipients (BNF-Child).

Stage 3: Management for CYP on treatment for ADHD

2.3 ADHD Treatment modifications

1. Consider modifying the dose regimens of stimulants (MPH or Lysdexamfetamine preparations) or switching no non-stimulants like daily Guanfacine or Atomoxetine.
2. Consider evening Clonidine with regular monitoring
3. Trial of Melatonin for CYP with evidence of circadian rhythm disorder other hypnotics for other non-respiratory-related problems

Evidence: Limited evidence supports the use of alpha-agonists such as clonidine to improve sleep onset latency, especially in attention deficit/hyperactivity disorder subjects. There is generally poor evidence for prescribing drugs for behavioural insomnia in children with ADHD **without concomitant ASD (NICE 2003)**. Zolpidem, Eszopiclone and Guanfacine failed to show any improvement when compared with placebo for managing insomnia in children (Anand et al 2017).

2.4 Stage 4: Pharmacological treatment for CYP not at risk of abnormal Melatonin metabolism or who have not responded to Melatonin

- Antihistamine agents such as Alimemazine, Promethazine, Hydroxyzine or Diphenhydramine, are the most widely prescribed sedatives in the pediatric practice but evidence supporting their use is still limited.
- Clonidine (a central alpha2-adrenergic receptor agonist) has unclear mechanism for its hypnotic action for sedation but commonly prescribed with limited evidence base.
- Consider selective serotonin reuptake inhibitors (SSRIs) such as Sertraline for disabling bedtime anxiety
- Benzodiazepines and Tricyclic antidepressants are not recommended in children.
- Other medications such as Clonazepam for severe parasomnia/night terrors and Trazodone (in Angelman syndrome) can be used with specialist advice from a tertiary sleep centre.

2.5 Stage 5: Management for other non-respiratory and non-circadian rhythm disorders

Restless legs syndrome RLS/ Periodic Limb movement disorders (Requires an updated literature review)

1. Consider oral iron supplementation (50–65 mg of elemental iron once or twice a day) in children with RLS and a serum ferritin <50 mg/L, with a recheck of serum ferritin in 2 to 3 months.
2. Establishing healthy sleep habits, physical exercise, and avoiding exacerbating factors, such as insufficient sleep for age, irregular sleep schedule, low body iron stores, pain, caffeine, nicotine, alcohol, and certain drugs (e.g., selective serotonin reuptake inhibitors [SSRIs], antihistamines, and neuroleptics)
3. Melatonin may, in rare cases, worsen restless legs syndrome

Evidence: The underlying pathophysiology of RLS is not fully understood, although it is likely that there is dysfunction of the dopaminergic system. There are yet no validated tools for assessing RLS in children but the Pediatric Emory RLS questionnaire,

the IRLS (International Restless Legs Scale) and pediatric Restless Legs Syndrome Severity Scale (P-RLS-SS) have been utilized in childhood studies (Stubbs & Walters 2020). There is conflicting evidence on using iron therapy for RLS and PLMD in children (Rosen et al 2019). Dopamine agonists and anticonvulsants have not been trialled in children.

Section 3: Special circumstances

3.1 Potential problems with Suspension Preparations

- Oral suspension solutions prepared for children are sugar free. There are some concerns about the propylene glycol (PG) or ethanol components of the 1mg/1ml Melatonin solution (Colonis Pharma Ltd). In generally this solution is safe for children above the age of 5 to 6 years, unless they are requiring very high doses of if there are concerns about low weight in older children (Cambridge/Peterborough Shared care; EMA, 2014).

Daily dose of melatonin 1mg/1ml oral solution relating to maximum PG content should not exceed:

- For a 3 yr. old weighing up to 14kg: 4mg of melatonin
- For a 5 yr. old weighing up to 18kg: 60mg of melatonin
- For a 10 yr. old weighing up to 32kg: 106mg of melatonin

Evidence: The American Academy of Pediatrics (AAP) suggests blood ethanol concentration (BEC) < 25 mg/100 mL (0.025%) following a single dose of an alcohol containing medication. However, the amount of alcohol containing medication that is considered toxic to a pediatric patient is still unclear.

3.2 Children who cannot swallow tablets

- Children who are 5 years or older can be successfully trained to swallow tablets using simple procedures that can be mastered within a single 5 – minute session.
- Circadin can be crushed to provide an immediate release profile.
- Biomelatonin (Pharmanord) 3 mg tablets (immediate release is licensed in Europe) can be dissolved in a small amount of water if broken.
- Slenyto® (prolonged-release tablets) is a miniature paediatric tablet that is easier to swallow (licensed only for children with Autism and Smith Magenis syndrome).

Evidence: Young Children from the age of 3 years can be successfully trained to swallow tablets using simple procedures that can be mastered within a single 5 – minute session (Tse Y et al 2020). Circadin® 2mg modified release tablet is the cheapest Melatonin formulation licensed the UK and should be prioritised.

3.3 Transitional Process

Melatonin is not licensed among adult population below the age of 55 years. Most of the CYP under CCH will have no specialist adult services that may be able to recommend non-licensed use of Melatonin after their discharge from Child health services. Most of them will be under the GP for at least annual review. It is essential for these YP to be supported to increasingly take personal responsibility for consistent implementation of effective sleep hygiene strategies that will enable them to be gradually weaned off Melatonin. Treatment may be continued into adulthood for those commenced on treatment in childhood, if it is clinically appropriate and there is adequate arrangement for ongoing supply in primary care.

3.4 GP cost remuneration under shared care agreement

All medicines included in a shared care agreement that meet the criteria for a "high cost expensive medicine" and are prescribed in accordance with the shared care agreement are automatically accounted for in the "high cost/ expensive medicines list" for budget-setting purposes. No additional action is therefore required by GPs to request funding (Glasgow shared care: https://ggcmedicines.org.uk/media/uploads/shared_care_protocols/melatonin_sca_revised_ver_oct_17_final.pdf).

3.5 Information for patients and parents/carers about Melatonin: Useful information about Melatonin available for the medicines for children website (Table 3)

Section 4: Mandatory follow-up and regular assessment

4.1 Mandatory Follow-up

- Patients who have been prescribed melatonin or any other sleep medications continuously for more than 6 months should have a discussion with their clinician regarding a trial discontinuation or dose reduction, to assess for on-going need.
- Regular withdrawal (washout) of Melatonin for up to 2 or 3 weeks, especially during long school breaks
- Regular monitoring of Height, Weight and Blood Pressure annually with pubertal development as required.
- Regular review of the Personal Sleep Plan
- Referral to tertiary sleep centre for complex /resistant cases

Evidence: Decreased CYP 1A2 activity, genetically determined or from concomitant medication, can slow metabolism, with loss of

variation in melatonin level and loss of effect. In patients with loss of response to melatonin, a period of melatonin clearance for up to 3 weeks and considerable dose reduction has been advised (Braam et al 2010; Bruni et al 2015). Some clinical experience from the National Child and Adolescent Learning Disability Psychiatry Network suggests that the efficacy may be lost if melatonin is prescribed for longer than two years continuously (2008). It suggests that if the melatonin is withdrawn prior to this, sensitivity may be re-established, and melatonin successfully re-introduced at a lower dose. Hypertension along with Anxiety, asthenia, chest pain, dizziness; dry mouth; gastrointestinal discomfort; nausea; night sweats; skin reactions; urine abnormalities and weight increase are listed as "Uncommon" side effects of Melatonin (NICE-BNFc).

Appendix 2: Recommended Sleep Management Flow chart