the medicine cabinet: sleep glorious sleep..

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Sleep disorders are extremely common in children with developmental difficulties with reports ranging from 40 to 80% when compared to typically developing children (Cortesi *et al*, 2010). Often these patients prove extremely refractory to behavioural measures and other psychosocial interventions and thus resort to medication to help alleviate both personal and family stress.

Intrinisic biological and genetic abnormalities that alter neuronal pathways in the brain may contribute to Autism Spectrum Disorder (ASD) sleep problems (Cortesi *et al*, 2010). Various exogenous or environmental factors can affect sleep from the amount and intensity of light during the day to medications as well as exercise. So a multifactorial evaluation needs to be done prior to prescribing medication. Medications act on different pathways to generate the drowsiness to lead to sleep and these can also affect the different stages of sleep.

Table 1. Changes in sleep content and length with age (ref Lavie et al, Sleep Disorders, 2002)

	Sleep time (h)	Stages 1-2 (%)	Stages 3-4 (%)	REM (%)
Infants	13-16	10-30	30-40	40-50
Children	8-12	40-60	20-30	20-30
15-25y	6-9	45-60	15-25	15-25

As sleep and wakefulness are associated with different brain neurotransmitters, food as well as medications can affect the balance of these signals and thus how alert or drowsy one feels. Caffeinated drinks such as Coca Cola® and Mother® and drugs such as cold and flu decongestants especially those containing pseudoephedrine can stimulate the brain and cause insomnia. Many antidepressants suppress REM (rapid eye movement) sleep which also affects temperature regulation during REM sleep so extreme hot or cold temperatures will affect sleep quality. During the REM sleep is the time of increased production of proteins which also stimulates the brain regions used in learning.

Sleep initiation and maintenance problems resulting in reduced sleep duration are the most common concerns expressed on parental interview. Some studies report children with ASD taking more than an hour to fall asleep. Periods of nocturnal awakenings lasting 2-3 hours have also reported by parents of ASD children. Besides medications affecting quality of sleep, there are some that are also used to help with sleep initiation and maintaining restorative sleep.

Even before medication would be trialled, establishment of normal sleep hygiene through behavioural interventions is important as adherence to positive and consistent bedtime routine is associated with reduction in sleep problems (Cortesi *et al*, 2010). Sleep problems can also pose a challenge to independence and separation from parents, although it is not the avoidance of waking in the night but the capacity to sleep on one's own and return to sleep if aroused. Identifying the maladaptive sleep habits and educating parents and carers in basic sleep hygiene principles is cornerstone for success. These include a selection of an appropriate bedtime and wake time, establishment of bedtime routine and no-reinforcing interactions with the child during night arousals (Johnson *et al*, 2008).

Children with significant sleep problems often lead to daytime dysfunction and as a result sleep difficulties should always be investigated as part of an assessment for the daytime impairments. The recognition that interventions can improve sleep and may result in better daytime functioning has fuelled a growing research interest (Johnson *et al,* 2008).

Medications to Aid Sleep

Melatonin (N-acetyl-5-methoxytryptamine)

Some hypothesise, one of the reasons for sleep dysregulation is an alteration in hormone/neurotransmitter (melatonin/serotonin) production. Melatonin is an endogenous or natural hormone produced by the pineal gland from the essential amino acid tryptophan, in response to failing light levels as picked up by the eyes. Over a series of pathways melatonin is then converted to serotonin or dopamine in the brain.

In North America, synthetic melatonin is classified as a food supplement whereas in Australia it is a prescription product. It is important to distinguish the synthetic melatonin from the homeopathic product which is available in Australia in homeopathic strengths in health food stores or community pharmacies. Homeopathic

strengths refers to the strength of the melatonin and then the dilution factor such as 3mg 10x means that 3mg of melatonin has then been diluted 10 x 10 fold ie 10^{-10}, which is almost nothing.

All studies have used full strength melatonin in an immediate release form. There is a product available on prescription which is a controlled release form under the trade name of Circadin®. Studies using this form have mainly been carried out in adults over 55. Studies of immediate release melatonin use in children with ASD provide good evidence for its effectiveness and safety.

Melatonin has poor bioavailability when given orally and young children appear to metabolise melatonin more rapidly when compared to older children. The peak blood level is obtained within 1hour of administration and half the melatonin has been eliminated by 40 minutes. Melatonin can be highly beneficial, short term, rapid onset and safe treatment for intractable sleep disturbance. Although there was a report that melatonin affected epileptic control this has now been refuted.

To increase the body's own melatonin LED (light emitting diodes) equivalent to 2000 to 2500 lux have been used in the mornings usually between 6am to 9am for 30-60 minutes especially for delayed sleep phase syndrome (Chesson A *et al,* 1999)

Clonidine

Clonidine is a noradrenergic alpha 2-agonist that is widely used in paediatric and psychiatric practice. Originally used as an agent to control blood pressure, it is commonly used to target the sleep delay in children with ADHD as well as reducing the symptomology of restlessness, reactivity,

impulsivity and anxiety in some patients with ASD as well as PTSD.

Benzodiazepines such as Diazepam, Temazepam

Although these induce sleep, tolerance and dependence may develop very quickly. These should only be used for short term use.

Chloral Hydrate

Usually only used for short term sedation such as for a procedure as the effect can be wear off after only 2 weeks and it is also known to cause drug dependence in adults. The use of chloral has been superseded by the benzodiazepines.

Antipsychotics and Anitihistamines

These are used for controlling challenging behaviours such as risperidone, olanzapine and quetiapine, as mentioned previously some can have sedating properties. These in time can lessen as the body adjusts to the medication and a slight medication decrease or change in dosage form or timing of doses can be helpful if the daytime sedation is problematic. They can also help by reducing anxiety and agitation.

Some have sedative actions such as Promethazine (Phenergan®), Trimeprazine (Vallergan®) and Dexchlorpheniramine (Polaramine®) due to the effect of the histaminergic receptors which also increase appetite and lead to weight gain. Weight gain can affect sleep by causing obstructive sleep apnoea which in turn leads to a disrupted night's sleep. So long term use of antipsychotics to improve sleep is not ideal. Although these medications can be purchased from the community pharmacy there are now more restrictions on the purchase due to small difference between a toxic dose and a therapeutic dose. Also when investigated by Food and Drug Administration (USA) there was a very poor level of effectiveness as cold and cough medications and risks in the under 2 years far outweighed the potential for benefit.

Complementary and Alternative Medications

1. Valerian is likely to be safe to use as large adult short term studies have been shown to be safe. Use is usually for anxiety based sleeplessness and there are reports about effectiveness in sleep latency (initiating sleep) and quality of sleep, these studies have not been done in children with ASD although widely used by clinicians. Valerian is also standardised to valerenic acid constituent but most trials do not specify the strength of the valerenic acid component used. So efficacy can change when changing brands.
2. St Johns Wort is primarily used to mild to moderate depression so for the insomnia associated with depression. It has been shown to be effective in adult patients for mild depression. But it does interact with many other medications not just other serotonergic antidepressants that also have a small risk of a serotonin syndrome. As with valerian the active component of the products can vary between brands and one stick to the one brand and take according to the instructions.
3. Hot chocolate/ hot milk increase tryptophan. L-tryptophan as the precursor to serotonin (one of the body's neurotransmitters) has also been shown to be effective as an aid to initiation of sleep but has been associated with a significant adverse reaction – eosinophilia myalgia and even deaths in 1990s. There is some evidence to suggest that this might have been due to contamination of the raw ingredient. Now the main source of l-tryptophan is food such as dairy, soy, nuts and red meat products. Calcium in milk helps the brain convert the tryptophan in the milk to melatonin thus the warm milk drink just before bed aids in sleep initiation. Together with honey this combination of complex carbohydrate, calcium and protein is an traditional remedy for bedtime insomnia.

Sleep that is Affected by Medications

Besides those medications that are prescribed to help with maintaining sleep or initiating sleep there are many medications that can affect sleep. Some are widely known such as the psychostimulants – methylphenidate and dexamphetamine and the sedating antihistamines but there are others that affect sleep due the adverse effects of the medication on the body. Although the list is not comprehensive if there are medications that are affecting the daily living of a person then these effects should be mentioned to the prescriber.

Selective serotonin reuptake inhibitors (ie. sertraline, fluoxetine and citalopram) have all been reported as causing insomnia. As these are taken once a day the best time to take them would be in the morning so sleep architecture is not affected. They may also cause sedation in which case they should be taken at night.

Antiepileptics or Mood Stabilisers

Although being used to controls seizures or stabilise mood, both sodium valproate and carbamazepine have some sedating properties especially early in treatment. Lamotrigine although primarily used for epilepsy is also used as a mood stabiliser can also cause insomnia, if troublesome then discussion about changing or reducing the dose of the antiepileptic might be needed. Topiramate another common antiepileptic is also known to cause fatigue in adults if bothering then this should be raised with the prescriber.

Corticosteroids

These are often used for severe allergic conditions such as asthma or short term for croup or topically for eczema although the conditions may also have effect on sleep when given to children they can have a stimulatory effect leading to insomnia.

Beta Agonists

These inhaled medications are used for asthma and can have the effect of being excitatory and thus causing insomnia.

So to achieve a good night's sleep there are many factors that may affect the actual sleep initiation and staying asleep not just pharmaceutical. Having a good routine and following basic sleep hygiene recommendations helps even when given medication to help with the sleep. Once it is decided to use a medication it is important to use the time while taking the medication to help achieve good sleep hygiene habits so that when off the medication, sleep can be achieved.

A combination of multiple sedatives could lead to excessive sedation and there is the potential to cause impairment in judgement.

References and Further Reading

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