REVIEW

Medication for sleep-wake disorders

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Medication is indicated for only a limited number of children's sleep disorders. However, correctly chosen and supervised, pharmacological treatment may be justified and helpful. For a given sleep problem it is important to identify the underlying cause (or sleep disorder) which often calls for treatment of a non-medication type. Where medication is appropriate, cautious use and careful review of the child's physical and psychological state is essential in view of the limited information available on effectiveness and possible short and long term effects. It follows that much further research is required to establish the part medication can play in the care of children with sleep disorders, and also to define the possible effects on sleep and wakefulness of other drugs used in clinical practice.

Despite the fact that children's sleep disorders are common and potentially serious in their effects on development and on the family as a whole, the topic is still neglected in paediatric, psychiatric, and other training in children's healthcare. One reflection of this is the little attention paid to medication for sleep-wake disorders in what may otherwise be excellent accounts of paediatric pharmacology.

There are relatively few indications for medication in children's sleep-wake disorders and other forms of treatment are often more appropriate. However, some important uses can be identified, although clinical impressions still feature prominently in the literature because of the very limited amount of systematic research. Observations on adult patients can provide some guidance and, despite the fact that many medications are not licensed for children, their informed use is considered acceptable in paediatric practice.[1]

Rational choice of treatment requires that the underlying cause of the sleep problem (that is, the sleep *disorder*, over 80 of which are now recognised[2]) is identified in the individual child, as distinct from attempting to treat the problem symptomatically. Depending on the sleep disorder, a choice can be made from the range of possible treatments.

This review is principally concerned with medication for sleeplessness as the most common sleep problem, with emphasis on the place of melatonin (MLT) because of the recent interest in this treatment. Pharmacological approaches to excessive sleepiness and the parasomnias will also be considered. Further background information about children's sleep disorders, including additional references for many of the statements made in this review, can be found elsewhere.[3]

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SLEEPLESSNESS

This term mainly covers bedtime settling problems, the child waking at night and demanding parents' attention, or waking too early in the morning. In some cases, enquiry reveals that the child's sleep pattern is within normal limits and that the parents have unrealistic expectations of their child's sleep, or are unable to cope because they are depressed or troubled in some other way.

The many possible causes of sleeplessness, including medical conditions which interrupt sleep or (more usually) parenting practices, each need their own particular form of treatment. However, it seems that sedative-hypnotic medication (mainly antihistamines) is still often prescribed or purchased over the counter. There is very little research support for such prescribing practices as illustrated by recent reviews of treatments for settling and night waking problems in children. In the review by Ramchandani and colleagues,[4] only four randomised controlled trials of treatment for children under 6 years of age could be identified. The overall conclusion was that, although these medications sometimes had a statistically significant effect of improving sleep in the short term, the clinical value of such changes was doubtful and there was no evidence of lasting benefit.

As France and Hudson[5] point out, many parents are unhappy about the use of drugs, there is the possibility that the child may adapt to their use, and sleeplessness may recur (if not intensify) on withdrawal. There are also unresolved issues about safety and daytime psychological effects of sedative drugs. A major additional drawback to their use is that the child does not have the opportunity to learn to go to sleep at bedtime unaided and to return to sleep after waking during the night.

For such reasons as these, conventional drug treatment is rarely justified. In contrast, reviews indicate that behavioural approaches are much more appropriate and effective. An exception to this rule is that short term sedation may be useful in a crisis situation to allow all concerned to obtain a few nights restful sleep before embarking on a more advisable form of treatment. Even so, there is no guarantee that the traditional hypnotic drugs used this way will have the desired effect.

Melatonin

Physiology and pharmacology

Zhdanova[6] and Arendt[7] have reviewed the physiology of MLT and its use in adult sleep disorders. MLT, mainly pineal in origin, is secreted during darkness ("the hormone of darkness") and suppressed by exposure to bright light. Its acts on the

Abbreviations: EDS, excessive daytime sleepiness; MLT, melatonin; SCN, suprachiasmatic nucleus

suprachiasmatic nucleus (SCN) which influences circadian rhythms. In turn, the SCN ("biological clock") regulates MLT secretion by relaying light information to the pineal gland. MLT is absent at birth but afterwards there is a rapid increase until peak levels are reached between 1 and 3 years of age. Levels then decline, especially at puberty. From then they reduce only moderately until old age. Normative data are not well defined at any age.

Individual differences clearly exist, including the pharmacokinetics of exogenous MLT. Its half life is 30–60 minutes. Estimation is possible from plasma, saliva, and urine samples.

Within about 30–40 minutes of administration exogenous MLT promotes the onset of sleep; for this reason, it has been used in the treatment of initial insomnia in adults. Because of its short half life (30–60 minutes), its value in the treatment of nocturnal waking is less well demonstrated, although preliminary experience with the sustained release form suggests this is a possibility. Depending on when it is administered, MLT is capable of shifting the sleep phase by virtue of its action on the SCN and has been used to good effect in the circadian sleep-wake cycle disorders associated with jet lag, shiftwork, and the delayed sleep phase syndrome, and in mistiming of the sleep phase in blind subjects. In contrast to benzodiazepines, MLT appears to have little effect on sleep architecture although an increase in dream recall is sometimes reported.

Reports of use in children

MLT has also been advocated for use in children, in particular those with neurodevelopmental disorders in whom sleep problems are particularly common.[8] Jan and colleagues[9] have discussed the use of MLT in the 23 published reports that they cite as evidence of its effectiveness in children, including their own large series. Since their review other studies have been published by Miyamoto and colleagues,[10] O'Callaghan and colleagues,[11] Zhdanova and colleagues,[12] Pillar and colleagues,[13] Dodge and Wilson,[14] Cavallo and colleagues,[15] and Ross and colleagues.[16] The total number of children on which these reports are based is about 450. However, the database overlapped with another published study in a number of the cited reports.

Most of the studies have involved children with multiple handicaps, often including blindness and sometimes cerebral palsy, epilepsy, or autism. Some studies have been concerned more specifically with children with tuberous sclerosis, Angelman syndrome, or Rett syndrome. In a minority of studies MLT has been given to children suffering from affective disorders or exhibiting poor school progress. A "good" or "significant" response, or response in approximately 80% or more of the children studied, is reported in 25 of the reports, and "moderate to good" or "minimal to moderate" in two of the (overlapping) series. In one study 44% of the 16 children studied were said to improve, and in one double blind placebo study of six children, none benefited. In some children sleep is said to have worsened.

Important and generally encouraging although these reports appear to be, certain aspects of this body of literature make it difficult to place the claims about the effectiveness of MLT in perspective. The age range of the reported cases is wide—from infancy to late teens, with a few patients in their 20s in some series. Twelve of the publications are single case reports; the remainder describe series of between two and 100. The five largest studies (with over 35 subjects) consisted of uncontrolled clinical trials. Of the remaining reports the methodology involved a control of some type in eight. MLT secretion was studied in six of the individual case reports, two children in another study and in two other overlapping series. The prescribed dose of MLT has varied between 0.3 mg and 20 mg per day. As mentioned, comorbidity was prominent in most of the children, and other medications (for example, antiepileptic drugs) would often have been taken.

Issues arising

Many unresolved issues arise from these reports and further methodologically refined investigations are needed to clarify the place of MLT in the treatment of children's sleep disorders.

A basic issue concerns the type of sleep disorder for which MLT treatment is likely to be effective. The impression gained from the reviewed reports is that the most consistent effect is helping the child to settle to sleep at bedtime. Maintaining sleep by means of the usual fast release form of MLT seems unlikely in view of its short half life, but some reports suggest this can occur. There are preliminary indications that more consolidated sleep is possible by means of a controlled release form.[17] Although the main clinical use of MLT in adults has been in cases of circadian sleep-wake cycle disorders, the value in children with this type of sleep disorder has been less well demonstrated. One problem in many of the cited reports is relatively imprecise descriptions of the sleep disorder being treated; objective sleep measures (for example, actometry) have rarely been used.

There are other difficulties in anticipating who is likely to respond to MLT treatment, and the time before an improvement is seen (some children are described as apparently taking days or weeks to respond[9]). As yet, there is little information about possible age dependent effects, whether or not the treated child had a deficiency of MLT or abnormal timing of its secretion, and the size of dosage that might be needed to explore fully the possible benefit of MLT. The view has been expressed that children generally need a higher dose than adults because of faster metabolism; but also that a higher dose might be more effective in prolonging sleep compared with that required to induce sleep.[9]

A further complication in some of the reported studies is that the use of MLT was accompanied by behavioural forms of treatment for the sleep disturbance, creating uncertainty about the extent to which the reported improvement was a medication effect. Some advocates of MLT treatment appear to understate how effective behavioural treatments for sleeplessness can be, even in severely handicapped children with long-standing sleep problems and very difficult behaviour.[18] This last mentioned study also adds to the evidence that sometimes parental reports of improvement in their child's sleep (on which the vast majority of the MLT studies rely exclusively as their outcome measure) are not accompanied by objective change in sleep patterns. In clinical practice, subjective parental reports have to be the main indicator of response to treatment. However, research should ideally include objective sleep measures to distinguish between genuine, pharmacological action and alterations in parents' perception of their child's sleep without any objective change.

Recommendations

Given these uncertainties, what recommendations are currently justified about the use of MLT for children's sleep disorders? As Jan and colleagues[9] themselves say, "MLT is not a blanket treatment for every sleep disturbance and its indiscriminate use is not recommended". They point out (as emphasised earlier) that children's sleep disorders have many causes, some of which are physical, others psychological. The basic principle of identifying each child's sleep disorder (sometimes multiple, especially in handicapped children) should be observed and type of treatment chosen accordingly.

A trial of MLT can be considered appropriate if a physical cause requiring treatment in its own right has been excluded, if the sleep disorder is of a type likely to respond (not parasomnias, for which it is sometimes used), and where behavioural treatment has either been adequately tried but failed, or is not feasible because of the child's limited ability to comply with the programme or the parents' own difficulties in doing so. In such circumstances, MLT seems preferable to conventional sedative-hypnotic drugs because of their very limited value and adverse effects.

According to adult studies, timing of MLT administration is important. It is considered to be most effective when taken about the time when endogenous MLT secretion can be expected to begin.[19] If given at inappropriate times, it may have harmful effects of the quality of sleep,[20] and, if taken well before bedtime, various adverse effects on mood, behaviour, and performance may result.[21] The same unwanted effects might be expected from a high dose of MLT (especially the sustained release form) which can increase daytime MLT levels.[6]

For predominantly sleep onset problems, the fast release form of MLT can be administered 20–30 minutes before bedtime, disguised with food or drink if necessary, but perhaps best without too full a stomach to aid absorption. As absorption can apparently be reduced by antiepileptic medication (for example, valproate), it is felt that such treatment is best given about an hour before the MLT. To maintain sleep during the night, and in an attempt to delay early morning waking, a sustained release form can be tried, but the tablets need to be taken whole. The smallest available initial dose of either preparation (usually 3 mg in the UK) seems advisable, increasing (as the usual reported response is quite rapid) at intervals of several days as necessary. The upper safe limit is not known. Because of the apparently delayed response in some children, treatment can be continued for a few weeks before the usefulness of MLT is decided.

When MLT appears to have been effective, clinical impressions further suggest that it may be possible to withdraw it after several months without relapse. Otherwise, administration over an indefinite period might need to be considered while acknowledging that the safety of very long term use is unknown. Some children may benefit from intermittent use during illness or in other circumstances which are known to predispose the child to worsened sleep problems.

In the absence of well established guidelines on the uses of MLT, and the reported individual differences in response, these suggestions about dosage and duration of MLT treatment need to be applied flexibly.

From the pragmatic point of view, the use of MLT is best combined with such attempts as are feasible to encourage a consistent sleeping routine and other sleep hygiene principles. Ideally, the successful use of MLT would increase the prospects of non-pharmacological treatment being effective including, for example, encouraging the child's ability to go to sleep (and return to sleep during the night) without the need for the company and attention of the parents. This potentially valuable interaction between MLT use and behavioural measures does not seem to have been explored systematically.

Supervision of its use: possible adverse effects

Careful and comprehensive supervision, including follow up, is appropriate after the introduction of treatment with MLT. The impression gained is that acute adverse effects are unusual, but some concerns have been expressed about sedation, headache, or other complaints in some adults.[22] Jan and colleagues[9] consider that sedation is the only significant side effect in children.

The following additional anxieties that have been expressed reflect MLT's very widely distributed binding sites in different tissues. The justification for such concerns remains uncertain as yet.

Examples have been quoted of an increase of seizures (or their first appearance) in a high proportion of cases where MLT has been used for sleep problems in children with neurodevelopmental disorders.[23] In contrast, others have claimed that epilepsy is not a contraindication to the use of MLT[9]; indeed antiepileptic properties for MLT have been reported by some authors.[24] The relation between MLT treatment and epilepsy certainly needs to be clarified in view of these inconsistent reports and also the use of MLT for recording sleep EEGs in children undergoing investigation for epilepsy.[25] Until the relation between MLT and epilepsy has been investigated further, it seems advisable to consider that MLT *might* acccount for an otherwise unexplained increase in seizure frequency.

The role of pineal MLT in human reproductive physiology is uncertain, but concerns have been voiced about the possible effects of pharmacological levels on reproduction, especially potential delayed timing of puberty and inhibition of reproduction function.[26] As MLT receptors are greater in number and more widely distributed during early development than later, it has been conjectured that any developmental adverse consequences of treatment with melatonin could be more serious at a prenatal or early postnatal stage. For this reason, particular caution seems appropriate in the use of exogenous MLT during pregnancy and lactation.[27] At present, conservative use of MLT in children also seems wise in view of the role of MLT in growth hormone secretion[28] and immune system function.[29]

Interactions between MLT treatment and other medications also need to be explored. It is relevant to children with neurodevelopmental disorders and epilepsy, that sodium valproate and other GABAergic antiepileptic drugs are reported to suppress nocturnal levels of MLT,[30] and benzodiazepines may block its production.[31] A further source of concern is that commercial preparations of MLT might contain contaminants with potentially harmful consequences if ingested long term.[32]

The current enthusiasm by some for the use of MLT for almost any kind of sleep disturbance should be tempered by the thought that the fact that it is normally secreted each night does not ensure that exogenous MLT, taken at other times and/or in supraphysiological doses, will not have adverse effects.[33] Clearly, there is a need for detailed and systematic evaluation of the short and long term adverse effects of MLT treatment which, theoretically, could be wide ranging in nature.[34] MLT is not licenced in the UK and is available only on a named patient basis. On the positive side, it is important to acknowledge that, where MLT treatment does significantly improve sleep, this is likely to benefit the child's learning and behaviour as well as the wellbeing of the family as a whole.

EXCESSIVE DAYTIME SLEEPINESS

Excessive daytime sleepiness (EDS), affecting children's daytime functioning and general wellbeing, was highlighted long ago as a problem seriously neglected by physicians.[35] The same judgement still seems to apply despite increasing evidence of its serious effects on school progress and behaviour in children and adolescents.[36] It is difficult to say how many children are affected, because sleepiness is easily misconstrued as laziness or some other essentially psychological shortcoming as illustrated by childhood narcolepsy which is often not correctly diagnosed for years, if at all.[37]

As in sleeplessness, there are many possible causes of EDS. These include the reasons already considered for loss of sleep, but the restorative value of sleep depends not only on its duration but also on its quality, which is impaired in many disorders of a physical type (for example, obstructive sleep apnoea) or psychiatric nature. In other cases, EDS is the result of a condition characterised by an increased tendency to sleep, such as narcolepsy.

It is evident from this differential diagnosis that there can be no one treatment for EDS, whether pharmacological or otherwise. Accurate assessment and precise diagnosis are again the guide to choice of treatment. Insufficient sleep may need to be corrected by the various means discussed in the last section. Poor quality sleep, or an increased need for sleep, caused by an underlying medical or psychiatric condition can be expected to improve if the condition is treated successfully. In this connection, antidepressant drugs are indicated in the presence of a depressive disorder rather than as a treatment for the sleep disturbance itself. Medication has little part to play in upper airway obstruction during sleep; indeed benzodiazepines are contraindicated because of their depressant

effect on respiration. On the other hand, periodic limb movements in sleep (which, if frequent, "fragment" sleep, reducing its restorative properties as in some cases of attention deficit hyperactivity disorder) may be responsive to dopaminergic drugs,[38] although such treatments have been little evaluated in children. Preliminary findings suggested that oestrogen treatment might have a part to play in EDS (rarely) associated with menstruation.[39]

Stimulant medication is often indicated, particularly in narcolepsy, about which recent reviews have been published,[40 41] although again the research on such treatment in children is very limited. The traditional drugs principally used for the sleepiness in narcolepsy have been sympathomimetics acting on central dopamine systems, especially the amphetamines and methylphenidate. More recently, modafinil (possibly acting mainly as a GABA release inhibitor) has become a preferred alternative to some extent. The properties considered to be in its favour include little or no effect on nocturnal sleep, once daily dosage, few adverse effects in general including low abuse potential, and absence of rebound hypersomnolence when withdrawn. In addition to medication, other measures such as planned naps and regular sleep routines can be important. Where cataplexy, hypnagogic hallucinations, and sleep paralysis (other classic components of the narcolepsy syndrome) require treatment, tricyclic antidepressants are mainly used (for example, clomipramine); alternatives are selective serotonin reuptake inhibitors such as fluoxetine.

Idiopathic CNS hypersomnia is an apparently rare cause of EDS with prolonged overnight sleep and great difficulty getting up in the morning, but without any of the REM sleep abnormalities which characterise narcolepsy. It may respond to stimulant drugs, but the condition has the reputation of being difficult to treat. A preliminary report suggests that modafinil may be useful, even in children.[42] Stimulants are not usually indicated for the periods of EDS in the Kleine-Levin syndrome in which (classically) periods of prolonged sleep associated with hypersexuality, hyperphagia, and various bizarre behaviours alternate with periods of normality.[43] In this condition medication, such as tricyclic antidepressants or lithium, is mainly directed at attempts to prevent recurrent episodes of this type.

Rarely, non-convulsive status epilepticus takes the form of EDS,[44] and prolonged periods of hypersomnolence apparently triggered by localised seizures have also been reported.[45] In such cases the introduction or adjustment of antiepileptic medication might help.

The seemingly rare condition of idiopathic recurring stupor (mainly described in adults, but also in children[46]) can be mistaken for intermittent EDS. It is characterised by high plasma and CSF levels of an endogenous benzodiazepine-like substance (endozepine 4). The stuporous episodes can be promptly terminated by treatment with the benzodiazepine antagonist flumazenil.

PARASOMNIAS

Parasomnias are episodic changes of behaviour or experience related to sleep. More than 30 types are described in the International Classification of Sleep Disorders. Some are primary sleep phenomena; others are sleep related manifestations of medical or psychiatric disorders. The primary parasomnias are grouped according to the stage of sleep with which they are usually associated. A common problem seems to be that the different parasomnias, especially those of a dramatic nature, are often confused with each other.

In the main, non-medication approaches to treatment are more appropriate but, where these have failed to achieve satisfactory control of frequently occurring or particularly troublesome parasomnias, medication can be tried. As few drugs for treating the parasomnias have been evaluated adequately, it may be necessary to assess the effect of different medications.

Medications reported to be effective in selected cases of primary parasomnia grouped according to stage of sleep

Sleep onset
- Hypnagogic/hypnopompic hallucinations (TCAs, SSRIs)
- Sleep paralysis (TCAs, SSRIs)
- Headbanging (short term, low dose benzodiazepines, TCAs)

Deep NREM sleep ("arousal disorders", including sleepwalking, sleep terrors)
- Short term, low dose benzodiazepines
- TCAs
- SSRIs

REM related
- Nightmares (anxiolytics if severe and symptomatic)
- REM sleep behaviour disorder (clonazepam)

Unrelated to sleep stage
- Enuresis (desmopressin, TCAs)

TCAs, tricyclic antidepressants; SSRIs, selective serotonin reuptake inhibitors

Treatments that have been reported to sometimes be effective in primary parasomnias are shown in the box. So-called hypnagogic (sleep onset) and hypnopompic (waking) hallucinations are seemingly common as isolated phenomena in the general population and are usually benign, although they can be frightening. The same is true of sleep paralysis, which consists of brief episodes of inability to move or speak. Treatment in the form of antidepressant-type drugs is best reserved for particularly troublesome cases which are likely to be rare.

Headbanging and other "rhythm movement disorders" do not usually require medication. In severe cases, however, benzodiazepines may be tried when other measures, including those of a behavioural nature have failed.[47]

Similarly, a trial of medication (a short course of a benzodiazepine, such as low dose clonazepam, or tricyclic antidepressant) is only justified in serious cases of sleepwalking or sleep terrors, where other measures (for example, scheduled waking) are ineffectual or impractical. Safety measures to prevent accidental injury should accompany treatment, whatever its nature.

REM sleep behaviour disorder (in which dreams can be enacted because of an abnormal preservation of skeletal muscle tone in REM sleep) has been described in children and adolescents.[48] Some cases of this condition can be viewed as primary parasomnias; others are secondary to neurological disease or drug treatment. The main pharmacological interest of the condition lies in the very frequent effectiveness of clonazepam even in the presence of physical disorder, although other medications including tricyclic drugs and melatonin have also been reported to be effective.

Nocturnal enuresis is usually best treated by a conditioning procedure, but desmopressin or low dose antidepressants (for example, imipramine) are said to be effective second line treatments but with a high relapse rate when withdrawn.[49]

Improvement in secondary parasomnias can be expected if the underlying condition is treated effectively. Examples include epilepsy, asthma, panic attacks, the parasomnias that form part of post-traumatic stress disorder (PTSD), and also tics including those in Tourette syndrome.

IATROGENIC CAUSES OF SLEEP DISTURBANCE

Although not the subject of this review, the fact that a wide range of medications used in general medicine, neurology, psychiatry, and paediatrics have been reported to affect sleep is clinically relevant when assessing the treatment needs of a

child with disturbed sleep.[50] This is a generally under-researched area and knowledge is very incomplete. The effects on sleep of medication and the underlying condition can be difficult to disentangle. However, the possibility should be entertained that medication might be playing some part in the onset of sleep disturbance, and sometimes this is evident from the time relationships. Withdrawal or substitution of treatment or adjustment of its dosage, may be helpful.

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