Summary

Insomnia and other non-respiratory sleep disorders in children and adolescents are a widespread problem, with a higher prevalence in children with neurodevelopmental or psychiatric co-morbidities. Although non-drug treatments, such as behavioural therapy, can be extremely effective in some forms of paediatric insomnia, clinical experience and studies with children with neuropsychiatric disorders indicate that these patients have lower response rates to behavioural therapy. There are no drugs licensed for the treatment of sleep disorders in children in the UK.

Melatonin (N-acetyl-5-methoxytryptamine) is a neurohormone produced by the pineal gland during the dark hours of the day-night cycle. It is involved in the induction of sleep, and may play a role in the internal synchronization of the circadian system and serve as a marker of the "biologic clock". It is not available as a licensed medicine in the UK but is available from several pharmaceutical companies on a named patient basis – it is believed that there are at least 50 melatonin preparations that are either being imported into, or manufactured in, the UK. In the US it is freely available to purchase as a food supplement.

The use of melatonin is supported by NICE in their Clinical Guideline on the diagnosis and management of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) in adults and children. Within that Guideline it is stated that melatonin may be considered for children and young people with CFS/ME who have sleep difficulties, but only under specialist supervision because of its unlicensed status.

There is at least one systematic review, two meta-analyses and one subsequently published randomised controlled trial which assesses the safety and efficacy of melatonin in children and adolescents. Although somewhat limited by trial size, heterogeneity and specificity, typically these pieces of research support the use of melatonin in that they show it has some beneficial effect in measures of sleep efficiency. Although the evidence base for melatonin is limited, it is actually more substantial that that available to support the use of any alternative hypnotic in this population.

The most commonly reported side-effects with melatonin are headaches, dizziness, nausea, and drowsiness (although several studies report similar incidence of side-effects in placebo groups). There are also concerns that melatonin may adversely affect seizure control, gonadal development and asthma control and at present there are no robust data available to support or refute any of these concerns.

The costs of treating a patient with melatonin can vary substantially, for example the costs of product available from two of the major suppliers in the UK vary between £4.20 and £30 a month to treat a patient with 3mg daily.
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**Introduction**

Insomnia and other non-respiratory sleep disorders in children and adolescents are a widespread problem, with a higher prevalence in children with neurodevelopmental or psychiatric co-morbidities. Insomnia is often reported by a caregiver and is usually described as difficulty in falling asleep and/or staying asleep. Studies have demonstrated the negative consequences of sleeplessness on children and adolescents, as well as on their families. Non-drug treatments, such as behavioural therapy can be extremely effective in some forms of paediatric insomnia and in many circumstances are preferable to pharmacological treatment. However, clinical experience and studies with children with neuropsychiatric disorders indicate that these patients have low response rates to behavioural therapy in the management of their sleep disturbances. (1) Despite this there is a lack of suitable pharmaceutical therapies licensed in the UK for paediatric insomnia.

Melatonin (N-acetyl-5-methoxytryptamine) is a neurohormone produced by the pineal gland during the dark hours of the day-night cycle. The production of melatonin is suppressed by light and serum melatonin levels are very low during most of the day. Melatonin is involved in the induction of sleep, and may play a role in the internal synchronization of the circadian system and serve as a marker of the “biologic clock”. (2)

Based on its physiological roles, melatonin has been investigated for a number of uses including cancer treatment, contraception and jet lag. Its use in sleep disorders has stimulated great interest, particularly in respect to sleep disorders in children with conditions such as visual impairment, cerebral palsy, attention deficit hyperactivity disorder (ADHD) and autism. (3) It is believed that there may be around 5000 children in the UK that are currently receiving melatonin for the treatment of sleep disorders. (4)

In the UK, melatonin is classed as a medicine. There are no UK licensed melatonin preparations available so its availability here is restricted to supply on a prescription on a “named patient” (unlicensed) basis. This is in contrast to how it is regulated abroad; for example, in the US melatonin has over-the-counter status and is freely available as a food supplement. It is believed that there are at least 50 melatonin preparations that are either being imported into, or manufactured in, the UK. Melatonin is available as immediate release capsules and tablets, sustained release capsules and tablets, and as a liquid formulation (4).

The lack of a licensed medicinal product means that melatonin has not undergone all of the preclinical and clinical study that the licensing process requires. The availability of the product as a food supplement abroad also leaves little financial incentive for a manufacturer to go through the costly process of licensing a product for the UK market. Importing melatonin from countries where it is a food supplement means that it is required to meet quality standards for this category of product; these standards may not necessarily be as rigorous as quality control measures required for licensed medicines.

**Evidence base for melatonin**

**Systematic reviews and meta-analyses**

At least one systematic review and two meta-analyses which address the use of melatonin in sleep disorders in children, or in children and adults have been published.

In 2004, a systematic review of melatonin treatment specifically in children with neurodevelopmental disabilities and sleep impairment was published. (5) For inclusion studies had to be randomised, controlled trials (RCTs) in children up to 18 years old with any type of neurological disorder or neurodevelopmental disability and associated sleep disturbance, where oral melatonin used in any dose (but excluding sustained release formulations) for any length of time was compared with placebo. The studies had to have reported on at least one of several specified primary outcomes. Of 5 studies meeting the inclusion criteria, 2 were subsequently excluded due to concerns regarding randomisation in one and the inability to separate out data for specific age categories in another study where the age range was 2-28 years. The remaining 3 studies reported data on 35 children (age range 1-17 years) in total. All were crossover trials, two of which included a washout period. Two trials considered children with varying neurodevelopmental disabilities and also included children with seizure disorders and visual impairment. The other study considered only children with Rett syndrome, most of whom were receiving antiepileptic medication. The dose of melatonin varied from 0.5mg to 7.5mg. All studies looked at the short term use of melatonin, with the maximum continuous treatment period being 4 weeks in one study, or 5 (non-consecutive) weeks in another. The two studies that reported time to sleep onset showed significant decrease (p<0.05) in this outcome with melatonin compared to placebo. There was no significant effect of melatonin compared with placebo on the other outcome measures of total sleep time, night-time awakenings, and parental opinions.

Information on adverse effects was actively sought by parental questionnaire in one study and commented on in only one of the other two studies. In the study that actively sought information on adverse effects, no clinically significant side-effects were reported. Comments of children being “moody” or “hyperactive” occurred equally in placebo and melatonin groups. There was no reported change in seizure frequency in any of the participants with epilepsy. (5)

Two meta-analyses on the use of melatonin in sleep disorders have been published by the same group of investigators - one looking at primary sleep disorders (6) and the other at secondary sleep disorders. (7) Both meta-analyses pooled data from studies in both children and adults. The meta-analysis that looked at primary sleep disorders (i.e. sleep disorders which are not accompanied by other medical and/or psychiatric conditions likely to be the cause of the sleep disorder) included RCTs which compared melatonin to placebo and reported at least one of several specified outcomes. In the safety assessment, randomised and non-randomised studies were included if they reported on adverse effects of melatonin versus placebo in people with a primary sleep disorder. Fourteen studies were included in the efficacy review (total number of patients n=279) and 10 studies in the assessment of safety (total n=222). Two of the studies included in both the efficacy and safety analyses were in children, and they...
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were the largest studies included in the meta-analysis (n=38 and n=62 patients included for analysis). In the pooled efficacy analysis melatonin decreased sleep onset latency with a weighted mean difference (WMD) of -11.7 minutes (95% confidence interval [CI] = -18.2 to -5.2). A subgroup analysis of subjects with delayed sleep phase syndrome showed a greater decrease in the WMD of -38.8 minutes (95% CI = -50.3 to -27.3, n=2 studies), compared with insomnia, with WMD = -7.2 minutes (95% CI = -12 to -2.4, n=12 studies). The pooled data for sleep efficiency, perceived sleep quality, wakefulness after sleep onset, total sleep time and percentage time spent in REM all favoured melatonin but were not statistically significant.

In the safety assessment the duration of melatonin administration was 3 months or less and adverse events were few. The most common reports were of headaches, dizziness, nausea, and drowsiness. In all cases there was no significant difference between melatonin and placebo.

Although this meta-analysis was of melatonin in primary insomnia, some of the studies included did describe subjects with co-morbidities of potential significance to their sleep disorder. Considerable heterogeneity between the studies was also demonstrated, which may bring into question the validity of pooling data from these studies.

The second meta-analysis looked at the use of melatonin in a broad population of people with secondary sleep disorders (including those associated with medical, neurological or substance misuse disorders) and sleep disorders accompanying sleep restriction (e.g. due to shift work or jet lag). Again, there were separate assessments of efficacy and safety with similar inclusion criteria to the previous meta-analysis. The efficacy analysis was divided into two, separating secondary sleep disorders and sleep disorders accompanying sleep restriction. Five of the 12 studies included in the efficacy analysis for secondary sleep disorders were paediatric studies (and 3 of these 5 were included in the systematic review by Phillips et al. 2004). Six RCTs with 97 participants showed no evidence that melatonin had an effect on sleep onset latency in people with secondary sleep disorders, WMD = -13.2 (95% CI = -27.3 to 0.9), although in the subgroup analysis of age 0-18 years a greater decrease in sleep onset latency was observed, WMD of -18.1 (95% CI = -29.4 to -6.8). Improvements of questionable clinical significance were seen in sleep efficiency (1.9%, 95% CI = 0.5 to 3.3) and total sleep time (15.6 minutes, 95% CI = 7.2 to 24.0), and no statistically significant difference was seen in wakefulness after sleep onset or REM sleep.

Again there was substantial heterogeneity among the studies.

No paediatric studies were included in the efficacy analysis for sleep restriction, which found no evidence of an effect with melatonin compared to placebo. No paediatric studies were included in the safety assessment, which showed no evidence of adverse effects with the short term use of melatonin. (7)

Randomised controlled trials

Since the reviews above were undertaken a number of RCTs comparing melatonin to placebo in children have been published. The largest of these is the most recent, published in 2007, and was an RCT comparing the effect of melatonin vs placebo on sleep, behaviour, and cognition in children with rigorously diagnosed ADHD with chronic sleep-onset insomnia. (8) In this study 105 medication-free children between the ages of 6 and 12 years were randomised to receive 3mg or 6mg of melatonin (depending on body weight), or placebo for 4 weeks. Exclusion criteria included epilepsy, IQ<80, pervasive development disorder, earlier use of melatonin, and use of stimulants, neuroleptics, benzodiazepines, clonidine, antidepressants, hypnotics or beta-blockers within 4 weeks before enrolment. Outcome measures were:

- sleep (onset, total time asleep, difficulty falling asleep), measured by actigraphy (using a device worn on the wrist to measure movement which is then correlated with a validated scoring algorithm) and sleep-logs
- dim light melatonin onset (DLMO), a marker of biological clock rhythm
- problem behaviour, cognitive performance, and quality of life, which were assessed using scoring systems.

Adverse events were assessed by an unstructured interview with parents 3 weeks after the start of study treatment, with a follow-up questionnaire after 2 years.

Mean actigraph estimate of sleep onset advanced by 26.9 +/- 47.8 minutes with melatonin, whereas there was a delay of 10.5 +/- 37.4 minutes with placebo (p<0.0001). There was an increase in mean total time asleep of 19.8 +/- 61.9 minutes with melatonin and a decrease of 13.6 +/- 50.6 minutes with placebo (p=0.01). The melatonin group also showed a significant decrease in sleep latency, increase in sleep efficiency and a decrease of nocturnal restlessness. There was an advance in DMLO of 44.4 +/- 67.9 minutes in the melatonin group and a delay of 12.8 +/- 60 minutes in the placebo group (p<0.0001). There was no significant effect on behaviour, cognition, and quality of life, and significant adverse events did not occur. Follow-up at 2 years after participation yielded 24 of 26 completed questionnaires. Nineteen subjects still used melatonin, 1 used it occasionally and 4 stopped after 17.23 +/- 3.3 months (due to remission in 3 cases and dizziness and drowsiness in 1 case). Seven of 24 parents reported one or more of the following adverse events: bedwetting (n=2), abnormal faeces (n=2), drowsiness (n=2), dizziness (n=1), sleep maintenance problems (n=1), skin pigment changes (n=1), and decreased mood (n=1) (8)

This larger study seems to offer the most methodologically robust data to date regarding the efficacy of melatonin for paediatric sleep disorders. It enrolled children with a rigorous diagnosis of ADHD and sleep onset insomnia and used both subjective and objective measures of efficacy. It also offers some insight into the longer term safety of melatonin, about which data are particularly scarce. This is also one of the few studies of its type to avoid using a crossover design. Crossover studies present a problem with a drug such as melatonin where it could be argued that, if the drug does indeed help to “reset” the circadian rhythm, subjects who receive active treatment first may have a persistence of its effects after the washout period (which has typically been 1 week in most paediatric melatonin studies).

Although this study found a positive effect of melatonin on several of the sleep related criteria, this did not produce the expected gains with problem behaviour, cognitive performance, and quality of life. Longer studies may be needed to assess whether these parameters can be in-

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proved by the use of melatonin after a longer treatment period. It should be borne in mind that the population studied here was highly specific which limit the generalis-ability of the data; notably ADHD was the only condition included, children were medication free (including stimu-lants), and no children had epilepsy. Other recent RCTs investigating melatonin in sleep disorders include:

- A study (n=31, 16 assigned to melatonin and 15 to placebo) of add-on melatonin in children with epi-lepsy taking sodium valproate monotherapy. Improvements in total sleep score and parasomnias score were reported. All children remained seizure free and no adverse effects were noted. (9)

- A crossover study (n=32, 7 of whom dropped out and were not included in the analysis) of melatonin in children, adolescents and young adults (age range 3.6 to 26 years) with mental retardation, with or without epilepsy. Eighteen of the participants were taking at least one antiepileptic medicine and seizure frequency ranged from seizure free to 1 seizure per day. A significant treatment effect on sleep latency was reported and the drug was well tolerated although contrasting effects were noted with respect to seizure frequency (recurrence or worsening of seizures seen in some patients, whilst improvements were seen in others). (10)

- A two-phase treatment study (n=33) of sleep hy-giene followed by melatonin or placebo (in those not responding to sleep hygiene measures) in chil-dren and adolescents with ADHD (stimulant treated). Five patients had consent withdrawn and 5 responded to sleep hygiene, so 23 patients were eligible for the crossover melatonin vs. placebo phase, of whom 19 were evaluable. A positive benefit of sleep hygiene plus melatonin was reported in the majority of cases. Adverse events reported were mild or moderate, with the exception of 1 migraine, rated as severe. (11)

- A small (n=11, 7 completed the study and were included in the analysis) crossover study of mel-a-tonin in children with autistic spectrum disorders. Improvements in sleep parameters were reported. (12)

- A small (n=8) crossover trial of melatonin in chil-dren with tuberous sclerosis complex. No evi-dence of a dose effect between 5mg and 10mg of melatonin was found, although the authors state that they might have missed a small beneficial effect of 10mg melatonin. (13)

Long-term data for melatonin

A recently published open-label study has provided some longer-term data for melatonin in children with sleep disorders. (14) Forty-four children with neurodevelopmental disabilities and treatment-resistant circadian rhythm sleep disorders (CRSD) who had participated in a previous RCT of controlled release melatonin were recruited to continue with melatonin treatment (initially 5mg controlled release preparation, which was changed to a fast release 5mg preparation part way through the study due to a change in formulation by the manufacturer). The median age at time of survey 8.6 years, range 4.8-19.3 years. Caregivers were interviewed every 3 months for up to 3.8 years, and were asked about changes in medical management and adverse events to see whether they were related to mela-tonin. At the completion of the study all the caregivers were asked to participate in a structured telephone inter-view to collect ratings of satisfaction, adverse effects, benefits, persistence with treatment and additional medications. Three subjects died prior to completion (unrelated to melatonin treatment), but their caregivers provided endpoint responses. Three subjects were lost to follow-up. Adverse reaction to melatonin therapy and development of tolerance were not evident. There was no suggestion from the parents at any time that therapy acti-vated an epileptic event in the 19 subjects who had sei-zure disorder, and no new cases of seizures were noted. The median age of the onset of puberty was 11.5 (range 2-15 years). Precocious puberty developed in five children who had severe neurodevelopmental disorders, all prior to the melatonin therapy, at ages 2, 3, 4, 6 and 7 years. In others with signs of puberty, the onset age was appropriate. Better sleep was associated with reported improvement in health, behaviour and learning. At the end of the study, parental comments regarding the effec-tiveness of long-term melatonin therapy were highly posi-tive.

Finally, in a recently published NICE clinical guideline on the diagnosis and management of chronic fatigue syn-drome/myalgic encephalomyelitis (CFS/ME) in adults and children, it was stated that melatonin may be considered for children and young people with CFS/ME who have sleep difficulties, but only under specialist supervision because of its unlicensed status. (15) However this recom-mendation appears to be based on expert consensus opinion rather than being derived from clinical trial evidence.

Safety and adverse-effects

The most commonly reported side-effects with melatonin are headaches, dizziness, nausea, and drowsiness, although several studies report similar incidence of side-effects in the placebo group.

There have been conflicting reports on the effect of ex-ogenous melatonin on seizure activity. Literature reports include cases of increased seizure activity after starting melatonin, which returned to baseline after discontinuation of melatonin, and recurred with rechallenge at a lower dose. (16) Much of the clinical trial data with melatonin does not report an increase in seizure frequency, but data must be treated cautiously due to the short term nature, size, and heterogeneous nature of the populations studied. Some studies excluded children with pre-existing seizure disorders, although there are others that have included or looked specifically at subjects with epilepsy which have not reported an increase in seizures with mel-a-tonin. Until more is known prescribers need to approach melatonin use in children with epilepsy highly cautiously and be alert for alterations in seizure activity.

Concern has been expressed that exogenously adminis-tered melatonin could, at least theoretically, adversely affect gonadal development if used in children. Young people up to the age of 20 years produce melatonin endogenously in high levels and levels are inversely re-lated to gonadal development. (17) In the clinical trials included in this review, none reported an association be-tween melatonin and delayed onset of puberty, but most study of melatonin has been short term, and longer term follow-up will be needed to fully address this concern. (18)
Endogenous serum melatonin concentration is elevated in nocturnal asthmatic patients. (19) Although the clinical trial data presented here do not indicate an increase in asthma symptoms, melatonin should be used with caution in this group.

Most commercial melatonin is synthesized in the laboratory. However, in rare cases it has been derived from animal pineal gland. Melatonin from animal sources should be avoided due to the possibility of contamination. (17)

Because of the lack of a licensed medicinal product and the preclinical and clinical study this would entail, information about melatonin pharmacokinetics and potential drug interactions is limited. From case reports in the literature, clinical experience and theoretical principles it has been suggested that interactions may occur with anticoagulant/antiplatelet drugs, antidiabetic agents, benzodiazepines/CNS depressants, contraceptives, flumazenil, fluvoxamine, immunosuppressants, nifedipine and verapamil. (17)

Other pharmacological treatments for sleep disorders

Clinical trial evidence for other pharmacological treatments for insomnia in children is also scarce. A systematic review published in 2000 addressed treatments for settling problems and night waking in young children. Nine studies that met the inclusion criteria were identified, only 4 of which were of pharmacological therapy. Two of the drug trials used trimetrazine (alimemazine) vs. placebo, 1 used extinction (ignoring child’s crying) plus trimetrazine vs. extinction alone, and the fourth used niaprazine (an antihistamine unavailable in the UK) versus chlordesmethyldiazepam. The authors concluded that the drugs seem to be effective in the short term but evidence of long-term effect is patchy and contradictory. (19)

Antihistamines

Sedating antihistamines have been used as pre-operative medication in children, and so it is not surprising that they have been considered as potentially useful in managing insomnia in the paediatric population. In addition to the studies included in the systematic review above, the TIRED study investigated the use of diphenhydramine in infants aged from 6 to 15 months with frequent parent-reported night-time awakenings. (20) This double-blind RCT randomised 44 infants to either diphenhydramine (1mg/kg) or placebo to be given 30 minutes before bedtime for 7 days, which was commenced after a 7 day observation period during which no study medication was given. The primary outcome was either improved or not improved number of night awakenings requiring parental intervention during the intervention week. Outcomes were assessed on days 15 (i.e. after 7 days of study medication), 29 and 43. No parents reported adverse effects that caused them to stop the study drug early, however the drug safety monitoring board stopped the trial early because of a lack of effectiveness of diphenhydramine over placebo. Only 1 of 22 children receiving diphenhydramine showed improvement compared to 3 out of 22 receiving placebo. The investigators concluded that during 1 week of therapy and at follow-up 2 and 4 weeks later, diphenhydramine was no more effective than placebo in reducing night-time awakening. It should be borne in mind that this study excluded children with chronic illness and those that had seen a sleep or development specialist in the past.

General considerations when prescribing sedating antihistamines include their prolonged duration of action which can cause drowsiness the following day. Tolerance can develop meaning their sedative effect may diminish after a few days of continued treatment. They are associated with headache, psychomotor impairment and antimuscarinic effects. Although unconfirmed, a possible association between phenothiazine sedatives and sudden infant death syndrome has also been suggested. Trimiprazine is no longer licensed in the UK for short-term sedation in children and it is recommended that it is not generally recommended in infants less than 2 years of age. (21)

Benzodiazepines

The systematic review above identified one study where chlordesmethyldiazepam was used (in comparison to an antihistamine). The Committee on Safety of Medicines have advised that benzodiazepines are indicated for the short-term relief (two to four weeks only) of anxiety that is severe, disabling or subjecting the individual to unacceptable distress, occurring alone or in association with insomnia or short-term psychosomatic, organic or psychotic illness. Further, the CSM state that benzodiazepines should be used to treat insomnia only when it is severe, disabling, or subjecting the individual to extreme distress. (3) The CSM’s advice is not specific to any patient group and, from the perspective of insomnia in paediatrics, needs to be considered alongside the additional problems of scarce data and unlicensed use.

Others

Chloral hydrate and triclofos were formerly popular hypnotics for children but are now mainly used for sedation during diagnostic procedures. (3)

Cost implications

Although melatonin is not licensed, it is available in the UK from a number of Specials manufacturers; alternatively it can also be imported from companies such as IDIS Ltd. Penn Pharmaceuticals and Pharmanord were identified as two companies that are able to supply melatonin that is manufactured in the UK. Penn Pharmaceuticals supply melatonin in a number of strengths of immediate release capsule ranging from 1mg to 5mg and also as a 3mg modified release tablet. It costs between £25.50 and £33 per month to treat a patient using melatonin from this supplier. Conversely Pharmanord only produce a 3mg immediate release tablet. To treat a patient using melatonin from this company costs £4.24 per month (if using a dose of 3mg daily).

Clinical Governance issues

It is important to emphasise that as melatonin is an unlicensed medicine, it may not be manufactured to the standards outlined in Good Manufacturing Practice (GMP). Therefore a comprehensive risk assessment should be undertaken by any prescriber that is considering use of melatonin. Typically such an assessment may include:

- an appraisal of the strength of the evidence base (as summarised here)
- an assessment of the potential risk to the patient that is being considered for treatment (as
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- the evidence to support potential alternative treatments (as summarised here)
- an assessment of the risk if the medicine is not used as intended
- an assessment of the manufacturer and supplier
- a QA assessment of the product itself – to include label and packaging, information to support manufacturing standards (e.g., Certificate of Analysis as there are some anecdotal reports of significant variation in melatonin content between formulations) and quality of active ingredients and excipients.
- an assessment of the adequacy of any patient information supplied.

In the case of melatonin it is probably advisable to source melatonin from a recognised UK Specials Manufacturer and obtaining a certificate of analysis for each batch used.

Ongoing research

A large multicentre randomised trial, known as the MENDS trial (The use of Melatonin in children with Neuro-developmental Disorders and impaired Sleep; a randomised, double-blind, placebo-controlled, parallel study) has just started in 12 centres in the UK. In this trial 172 children with a diagnosis of neuro-developmental disorder in conjunction with a minimum six month history of impaired sleep will be randomised to receive titrated dose immediate-release melatonin (0.5mg up to a maximum of 12mg if necessary) or matching placebo. The primary outcomes of the trial are total night-time sleep and sleep onset latency (based on sleep diaries). Adverse effects and assessment of effects on aspects such as cognitive function, behavioural problems and impact on seizure control will be assessed as secondary outcomes. It is envisaged that this trial will continue until March 2009. (4)

Shared care

In some PCTs GPs are encouraged to prescribe melatonin under the auspices of a shared care protocol – listed below are two examples of such protocols identified from a search of the Internet.

http://www.derbyshirecountypct.nhs.uk/content/files/shared%20care%20guidelines/Melatonin%20SC%202007%204_.pdf

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The document reflects the views of LNDG and may not reflect those of the reviewers.