**Melatonin adverse effects.**

**Abstracts**

**1**

**The Safety of Melatonin in Humans; Anderson, Lars Peter Holst et al; 2016**

Exogenous melatonin has been investigated as treatment for a number of medical and surgical diseases, demonstrating encouraging results. The aim of this review was to present and evaluate the literature concerning the possible adverse effects and safety of exogenous melatonin in humans. Furthermore, we provide recommendations concerning the possible risks of melatonin use in specific patient groups. In general, animal and human studies documented that short-term use of melatonin is safe, even in extreme doses. Only mild adverse effects, such as dizziness, headache, nausea and sleepiness have been reported. No studies have indicated that exogenous melatonin should induce any serious adverse effects. Similarly, randomized clinical studies indicate that long-term melatonin treatment causes only mild adverse effects comparable to placebo. Long-term safety of melatonin in children and adolescents, however, requires further investigation. Due to a lack of human studies, pregnant and breast-feeding women should not take exogenous melatonin at this moment.

**2**

**Potential safety issues in the use of the hormone melatonin in paediatrics; Kennaway, David J; 2015**

Melatonin is a hormone produced by the pineal gland during the night in response to light/dark information received by the retina and its integration by the suprachiasmatic nucleus. When administered to selected populations of adults, in particular those displaying delayed sleep phase disorder, melatonin may advance the time of sleep onset. It is, however, being increasingly prescribed for children with sleep disorders despite the fact that (i) it is not registered for use in children anywhere in the world; (ii) it has not undergone the formal safety testing expected for a new drug, especially long-term safety in children; (iii) it is known to have profound effects on the reproductive systems of rodents, sheep and primates, as well as effects on the cardiovascular, immune and metabolic systems; and (iv) there is the potential for important interactions with drugs sometimes prescribed for children. In this review, I discuss properties of melatonin outside its ability to alter sleep timing that have been widely ignored but which raise questions about the safety of its use in infants and adolescents.

**3**

**Melatonin improves sleep in children with epilepsy: a randomized, double-blind, crossover study; Jain, Sejal V et al; 2015**

Objective: Insomnia, especially maintenance insomnia, is widely prevalent in epilepsy. Although melatonin is commonly used, limited data address its efficacy. We performed a randomized, double-blind, placebo-controlled, crossover study to identify the effects of melatonin on sleep and seizure control in children with epilepsy.

Methods: Eleven prepubertal, developmentally normal children aged 6–11 years with epilepsy were randomized by a software algorithm to receive placebo or a 9-mg sustained release (SR) melatonin formulation for four weeks, followed by a one-week washout and a four-week crossover condition. The pharmacy performed blinding; patients, parents, and study staff other than a statistician were blinded. The primary outcomes were sleep onset latency and wakefulness after sleep onset (WASO) measured on polysomnography. The secondary outcomes included seizure frequency, epileptiform spike density per hour of sleep on electroencephalogram (EEG), and reaction time (RT) measures on psychomotor vigilance task (PVT). Statistical tests appropriate for crossover designs were used for the analysis.

Results: Data were analyzed from 10 subjects who completed the study. Melatonin decreased sleep latency (mean difference, MD, of 11.4 min and p = 0.02) and WASO (MD of 22 min and p = 0.04) as compared to placebo. No worsening of spike density or seizure frequency was seen. Additionally, slow-wave sleep duration and rapid eye movement (REM) latency were increased with melatonin and REM sleep duration was decreased. These changes were statistically significant. Worsening of headache was noted in one subject with migraine on melatonin.

Conclusion: Sustained-release melatonin resulted in statistically significant decreases in sleep latency and WASO. No clear effects on seizures were observed but the study was too small to allow any conclusions to be drawn in this regard.

**4**

**Paediatric Off-Label Use of Melatonin – A Register Linkage Study between the Norwegian Prescription Database and Patient Register; Hartz, Ingeborg et al; 2015**

The aims were, for the entire Norwegian population aged 4–17 years, to study the prevalence of melatonin use during 2004–2012, recurrent use in incident users and psychiatric and neurological morbidity in recurrent users. Data on dispensed melatonin were retrieved from the Norwegian Prescription Database and linked to diagnostic data from the Norwegian Patient Register. Outcome measures were the following: 1-year prevalence of use, proportion of recurrent use (use over three consecutive 365-day periods among incident users in 2009) and annual number of milligrams and number of prescriptions dispensed in recurrent users. The prevalence of registered ICD-10 diagnoses during the period of 2008–2012 was given for the recurrent users. The prevalence of melatonin use increased annually in both genders during 2004–2012 (boys: 3.4–11.0 per 1000; girls: 1.5–7.7 per 1000). Twenty-nine per cent of boys and 23% of girls were recurrent melatonin users, with highest level of recurrent use among the youngest (aged 4–8 years; boys: 47%, girls: 42%). In the third year, the median annual amount of melatonin dispensed was 1080 (IQR 586–1800) milligrams in boys and 900 (IQR 402–1620) milligrams in girls. Among recurrent users, 91% had a diagnosis of either psychiatric (84%) or neurological (32%) disorder. Off-label recurrent use of melatonin seems to have acquired a role mainly in treating secondary sleep problems in children and adolescents with psychiatric and neurological disorders. Once melatonin has been started, a large proportion of patients continue for at least 3 years, in doses corresponding to daily use in the majority.

**5**

**Add-on prolonged-release melatonin for cognitive function and sleep in mild to moderate Alzheimer’s disease: a 6 month randomized, placebo-controlled multicentre trial; Wade, Alan G et al; 2014**

PURPOSE: A link between poor sleep quality and Alzheimer’s disease (AD) has recently been suggested. Since endogenous melatonin levels are already reduced at preclinical AD stages, it is important to ask whether replenishing the missing hormone would be beneficial in AD and whether any such effects would be related to the presence of sleep disorder in patients.

PATIENTS AND METHODS: The effects of add-on prolonged-release melatonin (PRM) (2 mg) to standard therapy on cognitive functioning and sleep were investigated in 80 patients (men [50.7%], women [49.3%], average age 75.3 years [range, 52–85 years]) diagnosed with mild to moderate AD, with and without insomnia comorbidity, and receiving standard therapy (acetylcholinesterase inhibitors with or without memantine). In this randomized, double-blind, parallel-group study, patients were treated for 2 weeks with placebo and then randomized (1:1) to receive 2 mg of PRM or placebo nightly for 24 weeks, followed by 2 weeks placebo. The AD Assessment Scale–Cognition (ADAS-Cog), Instrumental Activities of Daily Living (IADL), Mini–Mental State Examination (MMSE), sleep, as assessed by the Pittsburgh Sleep Quality Index (PSQI) and a daily sleep diary, and safety parameters were measured.

RESULTS: Patients treated with PRM (24 weeks) had significantly better cognitive performance than those treated with placebo, as measured by the IADL (P=0.004) and MMSE (P=0.044). Mean ADAS-Cog did not differ between the groups. Sleep efficiency, as measured by the PSQI, component 4, was also better with PRM (P=0.017). In the comorbid insomnia (PSQI ≥6) subgroup, PRM treatment resulted in significant and clinically meaningful effects versus the placebo, in mean IADL (P=0.032), MMSE score (+1.5 versus −3 points) (P=0.0177), and sleep efficiency (P=0.04). Median ADAS-Cog values (−3.5 versus +3 points) (P=0.045) were significantly better with PRM. Differences were more significant at longer treatment duration. PRM was well tolerated, with an adverse event profile similar to that of placebo.

CONCLUSION: Add-on PRM has positive effects on cognitive functioning and sleep maintenance in AD patients compared with placebo, particularly in those with insomnia comorbidity. The results suggest a possible causal link between poor sleep and cognitive decline.

**6**

**Therapeutic Applications of Melatonin in Pediatrics; Sanchez-Barcelo, Emilio J et al; 2014**

Melatonin actions described in experimental studies include the regulation of circadian rhythms (i.e. sleep/alertness or body termperature) (Arendt and Skene, 2005; Cagnacci et al., 1992), effects on reproductive physiology (Reiter et al., 2009), and antioxidant properties (Allegra et al., 2003) among other properties (Macchi and Bruce, 2004). This variety of actions has encouraged the study of its possible clinical applications in different pathologies. A review of the clincial trials carried out to assess the possible usefulness of melatonin as a therapeutic drug can be found in the article of Sanchez-Barcelo et al. (2010). Pediatrics is also listed among the medical areas investigating possible applications of melatonin. Gitto et al. (2011) and Sanchez-Barcelo et al. (2011) recently published review articles analyzing the clincial uses of melatonin in pediatrics. Since this book focuses on the neuroprotective effects of melatonin, we are now going to review the clinical uses of melatonin in pediatric pathologies involving the central neural system, including epilepsy and sleep disorders, as well as in clinical practices such as anesthesia.

**7**

**Melatonin therapy for REM sleep behaviour disorder: a critical review of evidence; McGrane, Ian R et al; 2014**

REM sleep behavior disorder (RBD) is a parasomnia associated with dream enactment often involving violent or potentially injurious behaviors during REM sleep that is strongly associated with synucleinopathy neurodegeneration. Clonazepam has long been suggested as the first-line treatment option for RBD. However, evidence supporting melatonin therapy is expanding. Melatonin appears to be beneficial for the management of RBD with reductions in clinical behavioral outcomes and decrease in muscle tonicity during REM sleep. Melatonin also has a favorable safety and tolerability profile over clonazepam with limited potential for drug-drug interactions, an important consideration especially in elderly individuals with RBD receiving polypharmacy. Prospective clinical trials are necessary to establish evidence-basis for melatonin and clonazepam as RBD therapies.

**8**

**A systematic review of peri-operative melatonin; Anderson, L P H et al; 2014**

We systematically reviewed randomised controlled trials of peri-operative melatonin. We included 24 studies of 1794 participants that reported eight peri-operative outcomes: anxiety; analgesia; sleep quality; oxidative stress; emergence behaviour; anaesthetic requirements; steal induction; and safety. Compared with placebo, melatonin reduced the standardised mean difference (95% CI) pre-operative anxiety score by 0.88 (0.44–1.33) and postoperative pain score by 1.06 (0.23–1.88). The magnitude of effect was unreliable due to substantial statistical heterogeneity, with I2 87% and 94%, respectively. Qualitative reviews suggested the melatonin improved sleep quality and emergence behaviour, and might be capable of reducing oxidative stress and anaesthetic requirements.

**9**

**Melatonin for sleep problems in children with neurodevelopmental disorders: randomised double masked placebo controlled trial; Gringras, P et al; 2012**

Objective: To assess the effectiveness and safety of melatonin in treating severe sleep problems in children with neurodevelopmental disorders.

Design: 12 week double masked randomised placebo controlled phase III trial.

Setting: 19 hospitals across England and Wales.

Participants: 146 children aged 3 years to 15 years 8 months were randomised. They had a range of neurological and developmental disorders and a severe sleep problem that had not responded to a standardised sleep behaviour advice booklet provided to parents four to six weeks before randomisation. A sleep problem was defined as the child not falling asleep within one hour of lights out or having less than six hours’ continuous sleep.

Interventions: Immediate release melatonin or matching placebo capsules administered 45 minutes before the child’s bedtime for a period of 12 weeks. All children started with a 0.5 mg capsule, which was increased through 2 mg, 6 mg, and 12 mg depending on their response to treatment.

Main outcome measures: Total sleep time at night after 12 weeks adjusted for baseline recorded in sleep diaries completed by the parent. Secondary outcomes included sleep onset latency, assessments of child behaviour, family functioning, and adverse events. Sleep was measured with diaries and actigraphy.

Results: Melatonin increased total sleep time by 22.4 minutes (95% confidence interval 0.5 to 44.3 minutes) measured by sleep diaries (n=110) and 13.3 (−15.5 to 42.2) measured by actigraphy (n=59). Melatonin reduced sleep onset latency measured by sleep diaries (−37.5 minutes, −55.3 to −19.7 minutes) and actigraphy (−45.3 minutes, −68.8 to −21.9 minutes) and was most effective for children with the longest sleep latency (P=0.009). Melatonin was associated with earlier waking times than placebo (29.9 minutes, 13.6 to 46.3 minutes). Child behaviour and family functioning outcomes showed some improvement and favoured use of melatonin. Adverse events were mild and similar between the two groups.

Conclusions: Children gained little additional sleep on melatonin; though they fell asleep significantly faster, waking times became earlier. Child behaviour and family functioning outcomes did not significantly improve. Melatonin was tolerable over this three month period. Comparisons with slow release melatonin preparations or melatonin analogues are required.

**10**

**Melatonin Versus Placebo in Children with Autism Spectrum Conditions and Severe Sleep Problems Not Amenable to Behaviour Management Strategies: A Randomized Controlled Crossover Trial; Wright, Barry; 2011**

Twenty-two children with autism spectrum disorders who had not responded to supported behaviour management strategies for severe dysomnias entered a double blind, randomised, controlled crossover trial involving 3 months of placebo versus 3 months of melatonin to a maximum dose of 10 mg. 17 children completed the study. There were no significant differences between sleep variables at baseline. Melatonin significantly improved sleep latency (by an average of 47 min) and total sleep (by an average of 52 min) compared to placebo, but not number of night wakenings. The side effect profile was low and not significantly different between the two arms.

**11**

**Effect of melatonin on nocturnal blood pressure: meta-analysis of randomized controlled trials; Laudon, Grossman E et al; 2011**

Background: Patients with nocturnal hypertension are at higher risk for cardiovascular complications such as myocardial infarction and cerebrovascular insult. Published studies inconsistently reported decreases in nocturnal blood pressure with melatonin.

Methods: A meta-analysis of the efficacy and safety of exogenous melatonin in ameliorating nocturnal blood pressure was performed using a random effects model of all studies fitting the inclusion criteria, with subgroup analysis of fast-release versus controlled-release preparations.

Results: Seven trials (three of controlled-release and four of fast-release melatonin) with 221 participants were included. Meta-analysis of all seven studies did not reveal significant effects of melatonin versus placebo on nocturnal blood pressure. However, subgroup analysis revealed that controlled-release melatonin significantly reduced nocturnal blood pressure whereas fast- release melatonin had no effect. Systolic blood pressure decreased significantly with controlled- release melatonin (−6.1 mmHg; 95% confidence interval [CI] −10.7 to −1.5; P = 0.009) but not fast-release melatonin (−0.3 mmHg; 95% CI −5.9 to 5.30; P = 0.92). Diastolic blood pressure also decreased significantly with controlled-release melatonin (−3.5 mmHg; 95% CI −6.1 to −0.9; P = 0.009) but not fast-release melatonin (−0.2 mmHg; 95% CI −3.8 to 3.3; P = 0.89). No safety concerns were raised.

Conclusion: Add-on controlled-release melatonin to antihypertensive therapy is effective and safe in ameliorating nocturnal hypertension, whereas fast-release melatonin is ineffective. It is necessary that larger trials of longer duration be conducted in order to determine the long-term beneficial effects of controlled-release melatonin in patients with nocturnal hypertension.

**12**

**Melatonin for disordered sleep in individuals with autism spectrum disorders: Systematic review and discussion; Guénolé, Fabian et al; 2011**

Sleep disturbance is common in autism spectrum disorders (ASD) and melatonin is widely prescribed in such cases despite a lack of guidelines. The aim of this paper is to provide a systematic review of efficacy and safety of exogenous melatonin for treating disordered sleep in individuals with ASD. We performed a Pubmed documentary search enlarged by a manual review of references, which finally supplied 12 citations (4 case reports, 3 retrospective studies, 2 open-label clinical trials, and 3 placebo-controlled trials). As a whole, we found that the literature supports the existence of a beneficial effect of melatonin on sleep in individuals with ASD, with only few and minor side effects. However, considering the small number of studies and their methodological limits, these conclusions cannot yet be regarded as evidence-based. Randomized controlled trials and long-term follow-up data are still lacking to better assess efficacy and safety of exogenous melatonin for disordered sleep in individuals with ASD.

**13**

**Efficacy and Safety of Melatonin as an Anxiolytic and Analgesic in the Perioperative Period A Qualitative Systematic Review of Randomized Trials; Yousaf, M B B S et al; 2010**

Melatonin possesses sedative, hypnotic, analgesic, antiinflam- matory, antioxidative, and chronobiotic properties that distin- guish it as an attractive alternative premedicant. A qualitative systematic review of the literature concerning the perioperative use of melatonin as an anxiolytic or analgesic in adult patients was carried out using the recommended guidelines provided by the Cochrane Handbook for Systematic Reviews of Interven- tions. Nine of the 10 studies showed statistically significant re- duction of preoperative anxiety with melatonin premedication compared with placebo. An opioid-sparing effect or reduced pain scores were evident in five studies whereas three studies were contradictory. Thus, melatonin premedication is effective in ameliorating preoperative anxiety in adults, but its analgesic effects remain controversial in the perioperative period. Addi- tional well designed randomized controlled trials are necessary to compare melatonin premedication with other pharmacolog- ical interventions, investigate its effect on more varied surgical populations, and to delineate its optimal dosing regimen.

**14**

**Complementary, holistic, and integrative medicine: melatonin; Shamseer, Larissa;l 2009**

Melatonin is synthesized primarily in the pineal gland, although it also can be produced in the retina and gastrointestinal tract. Melatonin helps regulate circadian rhythms, specifically sleep-wake cycles. These cycles are under the control of the suprachiasmatic nucleus, through which patterns of light and darkness are transferred from the retina to the pineal gland. Melatonin is formed from the essential amino acid tryptophan via serotonin, based on specific patterns. Simply stated, in the presence of light, melatonin production is inhibited; in the darkness, it is synthesized.

Melatonin also can be taken as an exogenous supplement, which is synthesized to be chemically identical to its endogenous counterpart, and is classified as a natural health product by Health Canada or dietary supplement by the United States Food and Drug Administration. Due to its involvement in the sleep cycle, exogenous melatonin has been investigated extensively for sleep disorders.

**15**

**A randomized, placebo-controlled trial of controlled trial of controlled release melatonin treatment of delayed sleep phase syndrome and impaired sleep maintenance in children with neurodevelopmental disabilities; Wasdell, Michael B; 2008**

The purpose of this study was to determine the efficacy of controlled-release (CR) melatonin in the treatment of delayed sleep phase syndrome and impaired sleep maintenance of children with neurodevelopmental disabilities including autistic spectrum disorders. A randomized double-blind, placebo-controlled crossover trial of CR melatonin (5 mg) followed by a 3-month open-label study was conducted during which the dose was gradually increased until the therapy showed optimal beneficial effects. Sleep characteristics were measured by caregiver who completed somnologs and wrist actigraphs. Clinician rating of severity of the sleep disorder and improvement from baseline, along with caregiver ratings of global functioning and family stress were also obtained. Fifty-one children (age range 2–18 years) who did not respond to sleep hygiene intervention were enrolled. Fifty patients completed the crossover trial and 47 completed the open-label phase. Recordings of total night-time sleep and sleep latency showed significant improvement of approximately 30 min. Similarly, significant improvement was observed in clinician and parent ratings. There was additional improvement in the open-label somnolog measures of sleep efficiency and the longest sleep episode in the open-label phase. Overall, the therapy improved the sleep of 47 children and was effective in reducing family stress. Children with neurodevelopmental disabilities, who had treatment resistant chronic delayed sleep phase syndrome and impaired sleep maintenance, showed improvement in melatonin therapy.

**16**

**Effect of melatonin administration on subjective sleep quality in chronic obstructive pulmonary disease; Nunes, D M et al; 2008**

Disturbed sleep is common in chronic obstructive pulmonary disease (COPD). Conventional hypnotics worsen nocturnal hypoxemia and, in severe cases, can lead to respiratory failure. Exogenous melatonin has somnogenic properties in normal subjects and can improve sleep in several clinical conditions. This randomized, double-blind, placebo-controlled study was carried out to determine the effects of melatonin on sleep in COPD. Thirty consecutive patients with moderate to very severe COPD were initially recruited for the study. None of the participants had a history of disease exacerbation 4 weeks prior to the study, obstructive sleep apnea, mental disorders, current use of oral steroids, methylxanthines or hypnotic-sedative medication, nocturnal oxygen therapy, and shift work. Patients received 3 mg melatonin (N = 12) or placebo (N = 13), orally in a single dose, 1 h before bedtime for 21 consecutive days. Sleep quality was assessed by the Pittsburgh Sleep Quality Index (PSQI) and daytime sleepiness was measured by the Epworth Sleepiness Scale. Pulmonary function and functional exercise level were assessed by spirometry and the 6-min walk test, respectively. Twenty-five patients completed the study protocol and were included in the final analysis. Melatonin treatment significantly improved global PSQI scores (P = 0.012), particularly sleep latency (P = 0.008) and sleep duration (P = 0.046). No differences in daytime sleepiness, lung function and functional exercise level were observed. We conclude that melatonin can improve sleep in COPD. Further long-term studies involving larger number of patients are needed before melatonin can be safely recommended for the management of sleep disturbances in these patients.

**17**

**Melatonin treatment in individuals with intellectual disability and chronic insomnia: a randomized placebo-controlled study; Braam, W et al; 2008**

Background  While several small-number or open-label studies suggest that melatonin improves sleep in individuals with intellectual disabilities (ID) with chronic sleep disturbance, a larger randomized control trial is necessary to validate these promising results.

Methods  The effectiveness of melatonin for the treatment of chronic sleep disturbance was assessed in a randomized double-blind placebo-controlled trial with 51 individuals with ID. All of these individuals presented with chronic ideopatic sleep disturbance for more than 1 year. The study consisted of a 1-week baseline, followed by 4 weeks of treatment. Parents or other caregivers recorded lights off time, sleep onset time, night waking, wake up time and epileptic seizures. Endogenous melatonin cycle was measured in saliva before and after treatment.

Results  Compared with placebo, melatonin significantly advanced mean sleep onset time by 34 min, decreased mean sleep latency by 29 min, increased mean total sleep time by 48 min, reduced the mean number of times the person awoke during the night by 0.4, decreased the mean duration of these night waking periods by 17 min and advanced endogenous melatonin onset at night by an average of 2.01 h. Lights off time, sleep offset time and the number of nights per week with night waking did not change. Only few minor or temporary adverse reactions and no changes in seizure frequency were reported.

Conclusions  Melatonin treatment improves some aspects of chronic sleep disturbance in individuals with ID.

**18**

**Melatonin therapy to improve nocturnal sleep in critically ill patients: encouraging results from a small randomized controlled trial; Bourne, Richard S et al; 2008**

Introduction: Sleep disturbances are common in critically ill patients and when sleep does occur it traverses the day-night periods. The reduction in plasma melatonin levels and loss of circadian rhythm observed in critically ill patients receiving mechanical ventilation may contribute to this irregular sleep- wake pattern. We sought to evaluate the effect of exogenous melatonin on nocturnal sleep quantity in these patients and, furthermore, to describe the kinetics of melatonin after oral administration in this patient population, thereby guiding future dosing schedules.

Methods: We conducted a randomised double-blind placebo- controlled trial in 24 patients who had undergone a tracheostomy to aid weaning from mechanical ventilation. Oral melatonin 10 mg or placebo was administered at 9 p.m. for four nights. Nocturnal sleep was monitored using the bispectral index (BIS) and was expressed in terms of sleep efficiency index (SEI) and area under the curve (AUC). Secondary endpoints were SEI measured by actigraphy and nurse and patient assessments. Plasma melatonin concentrations were measured in nine patients in the melatonin group on the first night.

Results: Nocturnal sleep time was 2.5 hours in the placebo group (mean SEI = 0.26, 95% confidence interval [CI] 0.17 to 0.36). Melatonin use was associated with a 1-hour increase in

nocturnal sleep (SEI difference = 0.12, 95% CI -0.02 to 0.27; P = 0.09) and a decrease in BIS AUC indicating 'better' sleep (AUC difference = -54.23, 95% CI -104.47 to -3.98; P = 0.04). Results from the additional sleep measurement methods were inconclusive. Melatonin appeared to be rapidly absorbed from the oral solution, producing higher plasma concentrations relative to similar doses reported in healthy individuals. Plasma concentrations declined biexponentially, but morning (8 a.m.) plasma levels remained supraphysiological.

Conclusion: In our patients, nocturnal sleep quantity was severely compromised and melatonin use was associated with increased nocturnal sleep efficiency. Although these promising findings need to be confirmed by a larger randomised clinical trial, they do suggest a possible future role for melatonin in the routine care of critically ill patients. Our pharmacokinetic analysis suggests that the 10-mg dose used in this study is too high in these patients and may lead to carryover of effects into the next morning. Reduced doses of 1 to 2 mg could be used in future studies.

**19**

**Melatonin for Insomnia in Children With Autism Spectrum Disorders; Anderson, Ivy M et al; 2008**

We describe our experience in using melatonin to treat insomnia, a common sleep concern, in children with autism spectrum disorders. One hundred seven children (2—18 years of age) with a confirmed diagnosis of autism spectrum disorders who received melatonin were identified by reviewing the electronic medical records of a single pediatrician. All parents were counseled on sleep hygiene techniques. Clinical response to melatonin, based on parental report, was categorized as (1) sleep no longer a concern, (2) improved sleep but continued parental concerns, (3) sleep continues to be a major concern, and (4) worsened sleep. The melatonin dose varied from 0.75 to 6 mg. After initiation of melatonin, parents of 27 children (25%) no longer reported sleep concerns at follow-up visits. Parents of 64 children (60%) reported improved sleep, although continued to have concerns regarding sleep. Parents of 14 children (13%) continued to report sleep problems as a major concern, with only 1 child having worse sleep after starting melatonin (1%), and 1 child having undetermined response (1%). Only 3 children had mild side-effects after starting melatonin, which included morning sleepiness and increased enuresis. There was no reported increase in seizures after starting melatonin in children with pre-existing epilepsy and no new-onset seizures. The majority of children were taking psychotropic medications. Melatonin appears to be a safe and well-tolerated treatment for insomnia in children with autism spectrum disorders. Controlled trials to determine efficacy appear warranted.

**20**

**Melatonin and sleep disorders associated with intellectual disability: a clinical review; Sajith, S G et al; 2007**

Background:  Melatonin is used to treat sleep disorders in both children and adults with intellectual disability (ID), although it has no product license for such use. The evidence for its efficacy, potential adverse effects and drug interactions are reviewed in the context of prescribing to people with ID.

Methods:  A literature search was performed using multiple electronic databases. More literature was obtained from the reference lists of papers gathered through the searches.

Results  Most of the studies were uncontrolled and the few controlled trials available were of small size. Melatonin appears effective in reducing sleep onset latency and is probably effective in improving total sleep time in children and adolescents with ID. It appears to be ineffective in improving night-time awakenings. Melatonin is relatively safe for short-term use. Its safety for long-term use is not established. Potential drug interactions, possible effects on puberty and concerns regarding the use of melatonin in epilepsy, asthma and depressive disorders are discussed.

Conclusions  Melatonin appears to be an effective sleep-initiator for children and adolescents with ID and probably has a similar effect for adults. There may be heterogeneity of response depending on the nature of the sleep problem and cause of the ID or associated disabilities. Further studies are necessary before firm conclusions can be drawn and guidelines for the use of melatonin for people with ID formulated.

**21**

**Randomized controlled trial of melatonin for children with autistic spectrum disorders and sleep problems; Garstang, J et al; 2006**

Background:  Melatonin is often used for autistic children with sleep disorders, despite a lack of published evidence in this population.

Methods:  A randomized, placebo-controlled double-blind crossover trial of melatonin was undertaken in 11 children with autistic spectrum disorder (ASD).

Results:  Seven children completed the trial. Sleep latency was 2.6 h [95% confidence intervals (CI) 2.28–2.93] baseline, 1.91 h (95% CI 1.78–2.03) with placebo and 1.06 h (95% CI 0.98–1.13) with melatonin. Wakings per night were 0.35 (95% CI 0.18–0.53) baseline, 0.26 (95% CI 0.20–0.34) with placebo and 0.08 (95% CI 0.04–0.12) with melatonin. Total sleep duration was 8.05 h (95% CI 7.65–8.44) baseline, 8.75 h (95% CI 8.56–8.98) with placebo and 9.84 h (95% CI 9.68–9.99) with melatonin.

Conclusions  Although the study was small owing to recruitment difficulties, it still provides evidence of effectiveness of melatonin in children with sleep difficulties and ASD, which we predict a larger study would confirm.

**22**

**Efficacy and safety of exogenous melatonin for secondary sleep disorders and sleep disorders accompanying sleep restriction: meta-analysis; Buscemi, Nina et al; 2006**

Objective: To conduct a systematic review of the efficacy and safety of exogenous melatonin in managing secondary sleep disorders and sleep disorders accompanying sleep restriction, such as jet lag and shiftwork disorder.

Data sources: 13 electronic databases and reference lists of relevant reviews and included studies; Associated Professional Sleep Society abstracts (1999 to 2003).

Study selection: The efficacy review included randomised controlled trials; the safety review included randomised and non-randomised controlled trials.

Quality assessment: Randomised controlled trials were assessed by using the Jadad Scale and criteria by Schulz et al, and non-randomised controlled trials by the Downs and Black checklist.

Data extraction and synthesis: One reviewer extracted data and another reviewer verified the data extracted. The inverse variance method was used to weight studies and the random effects model was used to analyse data.

Main results: Six randomised controlled trials with 97 participants showed no evidence that melatonin had an effect on sleep onset latency in people with secondary sleep disorders (weighted mean difference −13.2 (95% confidence interval −27.3 to 0.9) min). Nine randomised controlled trials with 427 participants showed no evidence that melatonin had an effect on sleep onset latency in people who had sleep disorders accompanying sleep restriction (−1.0 (−2.3 to 0.3) min). 17 randomised controlled trials with 651 participants showed no evidence of adverse effects of melatonin with short term use (three months or less).

Conclusions: There is no evidence that melatonin is effective in treating secondary sleep disorders or sleep disorders accompanying sleep restriction, such as jet lag and shiftwork disorder. There is evidence that melatonin is safe with short term use.

**23**

**Melatonin: prescribing practices and adverse events; Waldron, D L et al; 2005**

Melatonin is currently an unlicensed, ‘‘named patient only’’ medicine in the UK, although it is available as a dietary supplement in the United States and over the internet. It is used for a variety of sleep disorders in children who often have neuro- developmental impairments. There remains a dearth of robust randomised controlled trials to demonstrate its efficacy, while lack of pharmacokinetic, pharmacodynamics, and toxicology data limits knowledge of therapeutic dose ranges, formulations, and adverse effects.

We carried out an anonymous question- naire survey to examine prescribing practices of members of the British Association for Community Child Health (BACCH) and the British Academy of Childhood Disability (BACD) (

From a newsletter circulation reaching an estimated 926 paediatricians, responses to the questionnaire were received from 148 (about 15%) (table 1). Of these 98% were currently prescribing, or had prescribed melatonin in the last year; data on a total of 1918 children were obtained. The dose prescribed (0.5–24 mg) varied widely (table 2).

Autism (68%) and attention deficit hyperactivity disorder (44%) were the most frequent clinical diagnoses in the children prescribed melatonin. On a crude four point scale of perceived effectiveness (never, rarely, usually, always), over 95% of respondents found melatonin ‘‘usually’’ or ‘‘always’’ effective. Adverse events were reported by 18% (n = 27) of respondents including: new onset seizure activity (n = 2), increased seizure frequency (n = 3), hyperactivity (n = 5), agitation/behavioural changes (n = 6), worsening sleep pattern (n = 6), nightmares (n = 2), and constipation (n = 2).

**24**

**The Efficacy and Safety of Exogenous Melatonin for Primary Sleep Disorders; Buscemi, Nina et al; 2005**

Background: Exogenous melatonin has been increasingly used in the management of sleep disorders.

Purpose: To conduct a systematic review of the efficacy and safety of exogenous melatonin in the management of primary sleep disorders.

Data Sources: A number of electronic databases were searched. We reviewed the bibliographies of included studies and relevant reviews and conducted hand-searching. Study Selection: Randomized controlled trials (RCTs) were eligible for the efficacy review, and controlled trials were eligible for the safety review. Data Extraction: One reviewer extracted data, while the other verified data extracted. The Random Effects Model was used to analyze data.

Data Synthesis: Melatonin decreased sleep onset latency (weighted mean difference [WMD]: −11.7 minutes; 95% confidence interval [CI]: −18.2, −5.2)); it was decreased to a greater extent in people with delayed sleep phase syndrome (WMD: −38.8 minutes; 95% CI: −50.3, −27.3; n=2) compared with people with insomnia (WMD: −7.2 minutes; 95% CI: −12.0, −2.4; n=12). The former result appears to be clinically important. There was no evidence of adverse effects of melatonin.

Conclusions: There is evidence to suggest that melatonin is not effective in treating most primary sleep disorders with short-term use (4 weeks or less); however, additional large-scale RCTs are needed before firm conclusions can be drawn. There is some evidence to suggest that melatonin is effective in treating delayed sleep phase syndrome with short-term use. There is evidence to suggest that melatonin is safe with short-term use (3 months or less).

**25**

**Systematic review of melatonin treatment in children with neurodevelopmental disabilities and sleep impairment; Phillips, Louise et al; 2004**

Sleep disturbances in children with neurodevelopmental disabilities are common and frequently difficult to treat with conventional pharmacological and behavioural methods. Melatonin is a pineal hormone known to be important in the regulation of the circadian rhythm, including the sleep–wake cycle. This systematic review of available evidence from randomized clinical trials assesses whether melatonin plays a beneficial role in these children and, in particular, its effect on total sleep time, time to sleep onset (sleep latency), and number of awakenings. We also looked at a parental view of the effect. Randomized clinical trials were identified where oral melatonin was compared with a placebo in children with any type of neurodevelopmental disability and associated sleep disturbance. Only three studies, reporting a total of 35 children, fulfilled the criteria for inclusion. The two studies that reported time to sleep onset showed a significant decrease (p<0.05) in this specific outcome where melatonin was compared with a placebo. There was no significant effect of melatonin compared with a placebo on the other outcome measures of total sleep time, night-time awakenings, and parental opinions. Despite the extremely limited randomized clinical trial data, melatonin appears to remain a commonly prescribed drug for disturbed sleep in children with neurodevelopmental abnormalities.

**26**

**Melatonin Improves Sleep in Asthma; Francineide, L Campos et al; 2004**

Disturbed sleep is common in asthma. Melatonin has sleep-inducing activity and reportedly affects smooth muscle tone and inflammation. The aim of this study was to evaluate the effect of melatonin on sleep in patients with mild and moderate asthma. This was a randomized, double-blind, placebo-controlled study. Twenty-two consecutive women with asthma were randomized to receive melatonin 3 mg (n = 12) or placebo (n = 10) for 4 weeks. Sleep quality and daytime somnolence were assessed by the Pittsburgh Sleep Quality Index and the Epworth Sleepiness Scale, respectively. Pulmonary function was assessed by spirometry. Use of relief medication, asthma symptoms, and morning and evening peak expiratory flow rate were recorded daily. Melatonin treatment significantly improved subjective sleep quality, as compared with placebo (p = 0.04). No significant difference in asthma symptoms, use of relief medication and daily peak expiratory flow rate was found between groups. We conclude that melatonin can improve sleep in patients with asthma. Further studies looking into long-term effects of melatonin on airway inflammation and bronchial hyperresponsiveness are needed before melatonin can be recommended in patients with asthma.

**27**

**Melatonin in the treatment of insomnia in children and adolescents; Armour, David et al; 2004**

AIMS AND METHOD:

To review the efficacy and safety of melatonin in the treatment of insomnia in children and adolescents, through a Medline search covering the years 1966 to November 2003.

RESULTS:

Five placebo-controlled studies and several case series were identified. Melatonin reduces sleep latency, but does not consistently improve other aspects of sleep disturbance. Safety, particularly in the medium- and longterm, is poorly evaluated; short-term concerns include exacerbation of epilepsy and asthma.

CLINICAL IMPLICATIONS:

Melatonin might be effective in the short-term treatment of sleep onset insomnia. The optimal dose is unknown. It cannot currently be recommended for the treatment of other forms of sleep disturbance or for routine long-term use. Melatonin is not a licensed medicine in the UK.

**28**

**Neurobehavioural performance effects of daytime melatonin and temazepam administration; Rogers, Naomi L et al; 2003**

Exogenous melatonin is a potential treatment for circadian disruption and insomnia. Hence, it is important to determine and quantify neurobehavioural performance effects associated with its use. The present study compared neurobehavioural performance following administration of melatonin and the benzodiazepine temazepam, using a within-subjects design. Following a training day, 16 healthy, young subjects (six males, 10 females; mean age ± SEM, 21.4 ± 6 years) participated in a 3-day protocol. After sleeping overnight in the laboratory, subjects completed a battery of tests at hourly intervals between 08:00 and 11:00 hours and at two hourly intervals between 13:00 and 17:00 hours. The neurobehavioural performance tasks included: unpredictable tracking, spatial memory, vigilance and logical reasoning. Subjective sleepiness was measured at hourly intervals using a visual analogue scale. At 12:00 h subjects were administered a capsule containing 5 mg melatonin, 10 mg temazepam or placebo, in a randomized, double-blind crossover fashion. A significant drug × time interaction was evident on the unpredictable tracking, spatial memory and vigilance tasks (P < 0.05). Greater changes in performance were evident following temazepam administration than melatonin administration, relative to placebo. Administration of melatonin or temazepam significantly elevated subjective sleepiness levels, relative to placebo (P ≤ 0.05). The present findings demonstrate that melatonin administration induces a smaller deficit in performance on a range of neurobehavioural tasks than temazepam. Given melatonin's soporific and chronobiotic properties, these results suggest that melatonin may be preferable to benzodiazepines in the management of circadian and sleep disorders.

**29**

**Melatonin for treatment of REM sleep behaviour disorder in neurologic disorders: results in 14 patients; Boeve, Bradley F et al; 2003**

Objective: To describe the treatment response with melatonin for rapid eye movement (REM) sleep behavior disorder (RBD) associated with other neurologic disorders.

Background: Clonazepam has been considered the treatment of choice for RBD. However, an alternative treatment is desirable for those with RBD refractory to clonazepam, for those who experience intolerable side-effects with clonazepam, and for those in whom clonazepam precipitates or aggravates obstructive sleep apnea (OSA). To date, there is minimal published data and limited follow-up regarding the use of melatonin for patients with RBD associated with other neurologic syndromes and disorders.

Design/methods: The response to melatonin treatment for RBD was reviewed on consecutive patients the investigators treated with this agent at Mayo Clinic Rochester from January 2000 to June 2001. The coexisting neurologic disorders, reasons for using melatonin, effective doses, side-effects, and duration of follow-up were also reviewed on all patients.

Results: Fourteen patients were commenced on melatonin over the specified time period (13 male, median RBD onset age 56 years, range 20–77 years). The coexisting neurologic findings/disorders were dementia with Lewy bodies (n=7), mild cognitive impairment with mild parkinsonism (n=2), multiple system atrophy (n=2), narcolepsy (n=2), and Parkinson's disease (n=1). The reasons for using melatonin in these cases were incomplete response of RBD to clonazepam in six patients, existing cognitive impairment in five, intolerable side-effects with clonazepam in two, and presence of severe obstructive sleep apnea and narcolepsy in one. With seven patients continuing to use clonazepam at 0.5–1.0 mg/night, RBD was controlled in six patients, significantly improved in four, and initially improved but subsequently returned in two; no improvement occurred in one patient and increased RBD frequency/severity occurred in one patient. The effective melatonin doses were 3 mg in two cases, 6 mg in seven cases, 9 mg in one case, and 12 mg in two cases. Five patients reported side-effects, which included morning headaches (2), morning sleepiness (2), and delusions/hallucinations (1); these symptoms resolved with decreased dosage. The mean duration of follow-up was 14 months (range 9–25 months), with eight patients experiencing continued benefit with melatonin beyond 12 months of therapy.

Conclusions: In this series, persistent benefit with melatonin beyond 1 year of therapy occurred in most but not all patients. Melatonin can be considered as a possible sole or add-on therapy in select patients with RBD. Prospective, long-term, controlled trials with melatonin are warranted in a larger number of patients with RBD associated with a variety of neurologic symptoms and disorders.

**30**

**Melatonin administration alters semen quality in healthy men; Luboshitzky, Rafael et al; 2002**

The role of melatonin in the regulation of reproduction in humans is unknown. We conducted a 6-month, double-blind, crossover study of a daily treatment dose of 3 mg melatonin or pla- cebo given orally at 1700 hours in 8 healthy men. Semen quality (concentration, motility, and morphology), serum and seminal plasma 17-􏰉estradiol (E2), testosterone, melatonin, and serum gonadotropin levels were determined every 3 months throughout the study. In 6 men, there was no change in semen quality or in serum and seminal plasma hormone levels during the study period. In 2 men, during the melatonin treatment period, sperm concentration de- creased to 3 􏰇 106/mL and 12 􏰇 106/mL, and motility declined to 32% and 30%. These coincided with a decline in seminal plasma and serum E2 levels and with an increase in testosterone:E2 ratios. Six months after the cessation of melatonin, sperm concentration and motility were normal in 1 man but remained abnormal in the other one with a still elevated testosterone:E2 ratio. Serum gonad- otropin levels were unchanged during the study in all 8 men. Our preliminary observations suggest that long-term melatonin administration is associated with decreased semen quality in a number of healthy men, probably through the inhibition of aromatase at the testicular level.

**31**

**Melatonin for the prevention and treatment of jet lag; Herxheimer, Andrew; 2002**

Background: Jet lag commonly affects air travellers who cross several time zones. It results from the body's internal rhythms being out of step with the day-night cycle at the destination. Melatonin is a pineal hormone that plays a central part in regulating bodily rhythms and has been used as a drug to re-align them with the outside world.

Objectives: To assess the effectiveness of oral melatonin taken in different dosage regimens for alleviating jet lag after air travel across several time zones.

Search methods: We searched the Cochrane Controlled Trials Register, MEDLINE, EMBASE, PsychLit and Science Citation Index electronically, and the journals 'Aviation, Space and Environmental Medicine' and 'Sleep' by hand. We searched citation lists of relevant studies for other relevant trials. We asked principal authors of relevant studies to tell us about unpublished trials. Reports of adverse events linked to melatonin use outside randomised trials were searched for systematically in 'Side Effects of Drugs' (SED) and SED Annuals, 'Reactions Weekly', MEDLINE, and the adverse drug reactions databases of the WHO Uppsala Monitoring Centre (UMC) and the US Food & Drug Administration. An updating search was carried out on 12/2/2008 but no new studies were identified.

Selection criteria: Randomised trials in airline passengers, airline staff or military personnel given oral melatonin, compared with placebo or other medication. Outcome measures should consist of subjective rating of jet lag or related components, such as subjective well being, daytime tiredness, onset and quality of sleep, psychological functioning, duration of return to normal, or indicators of circadian rhythms.

Data collection and analysis: Ten trials met the inclusion criteria. All compared melatonin with placebo; one in addition compared it with a hypnotic, zolpidem. Nine of the trials were of adequate quality to contribute to the assessment, one had a design fault and could not be used in the assessment. Reports of adverse events outside trials were found through MEDLINE, 'Reactions Weekly', and in the WHO UMC database.

Main results: Eight of the ten trials found that melatonin, taken close to the target bedtime at the destination (10pm to midnight), decreased jet-lag from flights crossing five or more time zones. Daily doses of melatonin between 0.5 and 5mg are similarly effective, except that people fall asleep faster and sleep better after 5mg than 0.5mg. Doses above 5mg appear to be no more effective. The relative ineffectiveness of 2mg slow-release melatonin suggests that a short-lived higher peak concentration of melatonin works better. The estimated number needed to treat (NNT) is 2, based on the only two trials that gave the necessary data. The benefit is likely to be greater the more time zones are crossed, and less for westward flights. The timing of the melatonin dose is important: if it is taken at the wrong time, early in the day, it is liable to cause sleepiness and delay adaptation to local time. The incidence of other side effects is low. Case reports suggest that people with epilepsy, and patients taking warfarin may come to harm from melatonin.

Authors' conclusions: Melatonin is remarkably effective in preventing or reducing jet lag, and occasional short-term use appears to be safe. It should be recommended to adult travellers flying across five or more time zones, particularly in an easterly direction, and especially if they have experienced jet lag on previous journeys. Travellers crossing 2-4 time zones can also use it if need be. The pharmacology and toxicology of melatonin needs systematic study, and routine pharmaceutical quality control of melatonin products must be established. The effects of melatonin in people with epilepsy, and a possible interaction with warfarin, need investigation.

**32**

**Melatonin for chronic sleep onset insomnia in children: a randomized placebo-controlled trial; Smits, M G et al; 2001**

To establish the efficacy of melatonin treatment in childhood sleep onset insomnia, 40 elementary school children, 6 to 12 years of age, who suffered more than 1 year from chronic sleep onset insomnia, were studied in a double-blind, placebo-controlled study. The children were randomly assigned to receive either 5-mg melatonin or placebo. The study consisted of a 1-week baseline, consecutively followed by a 4-week treatment period. After that period, treatment was continued if the parents wished so. The study's impact was assessed by measurements of lights-off time, sleep onset, and wake-up time, recorded in a diary (n = 33). Sleep onset was also recorded with an actigraph (n = 25). Endogenous dim light melatonin onset was measured in saliva (n = 27). Sustained attention was evaluated with the Bourdon-Vos reaction time test (n = 36). In the melatonin group, mean (95% CI) lights-off time advanced 34 (6-63) minutes, diary sleep onset 63 (32-94) minutes, actigraphic sleep onset 75 (36-114) minutes, and melatonin onset 57 (24 to 89) minutes; total sleep time increased 41 (19-62) minutes. In the placebo group, these parameters did not shift significantly. The change during the 4-week treatment period differed between the treatment groups significantly as to lights-off time, diary and actigraphic sleep onset, sleep duration, and melatonin onset. There were no significant differences between the treatment groups in the change of sleep latency, wake-up time, and sustained attention reaction times. Mild headache occurred in 2 children during the first 2 days of the melatonin treatment. Eighteen months after the start of the trial, in 13 of the 38 children who could be followed up, melatonin treatment was stopped because their sleep problem was solved and in 1 child because sleep was not improved. Twelve children used melatonin 5 mg, the other 1.0 to 2.5 mg. One child developed mild generalized epilepsy 4 months after the start of the trial. The results show that melatonin, 5 mg at 6 PM, was relatively safe to take in the short term and significantly more effective than placebo in advancing sleep onset and dim light melatonin onset and increasing sleep duration in elementary school children with chronic sleep onset insomnia. Sustained attention was not affected.

**33**

**Melatonin Effect on Seizures in Children with Severe Neurologic Deficit Disorders; Peled, Nir et al; 2001**

Purpose: Recently, melatonin has been associated with antiepileptic activity, most probably because of its antioxidant activity as a free radical scavenger. This study aimed to expand the clinical experience with melatonin as an antiepileptic drug (AED) in humans.

Methods: Six children (aged 2–15 years), with severe intractable seizures, were treated with 3 mg of oral melatonin 30 min before bedtime, in addition to their previous AED treatment for 3 months. A diary of clinical seizure activity (time of day, duration, and type) was kept by parents for a month before and during treatment. Five patients underwent a baseline polysomnography, and three also were monitored during melatonin treatment.

Results: With the exception of the parents of one child, all reported a significant clinical improvement in seizure activity during treatment, particularly during the night. Sleep studies showed a decrease in epileptic activity in two of the three patients who were monitored during treatment, and a change of sleep efficiency from 84.2% to 89.7% (NS). Improvement in daytime behavior and in communication abilities was reported by parents, although it was not objectively measured.

Conclusions: This clinical observation adds to the growing data showing the antiepileptic effect of melatonin. However, owing to the paucity of well-controlled studies, using melatonin as an AED should be limited to this specific group of patients with intractable seizures.

**34**

**Randomized, double-blind clinical trial, controlled with placebo, of the toxicology of chronic melatonin treatment; Seabra, Maria de Lourdes V et al; 2000**

The objective of the present study was to assess the toxicology of melatonin (10 mg), administered for 28 days to 40 volunteers randomly assigned to groups receiving either melatonin (N=30) or placebo (N=10) in a double-blind fashion. The following measurements were performed: polysomnography (PSG), laboratory examinations, including complete blood count, urinalysis, sodium, potassium and calcium levels, total protein levels, albumin, blood glucose, triglycerides, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL), urea, creatinine, uric acid, glutamic-oxalacetic transaminase (GOT), glutamic-pyruvate transaminase (GPT), bilirubin, alkaline phosphatase, gama-glutamic transaminase (GGT), T3, T4, TSH, LH/FSH, cortisol, and melatonin serum concentrations. In addition, the Epworth Somnolence Scale (ESS) and a sleep diary (SD) were also applied to the volunteers 1 wk before each PSG. In addition, the volunteers were asked about possible side effects (SE) that appeared during the treatment. The study was carried out according to the following timetable: Visit 0, filling out the term of consent and inclusion criteria; Visit 1, PSG, laboratory examinations, ESS, SD, melatonin serum concentrations; Visit 2, SD, melatonin serum concentrations, SE; Visit 3, melatonin serum concentrations, PSG, ESS, SE; Visit 4, laboratory examinations, SE, melatonin serum concentrations, SD; and Visit 5, PSG, ESS, SE. Analysis of the PSG showed a statistically significant reduction of stage 1 of sleep in the melatonin group. No other differences between the placebo and melatonin groups were obtained. In the present study we did not observe, according to the parameters analyzed, any toxicological effect that might compromise the use of melatonin at a dose of 10 mg for the period of time utilized in this study.

**35**

**Clinical trials of controlled-release melatonin in children with sleep-wake cycle disorders; Jan, J E et al; 2000**

This is the first study to examine effective doses of controlled-release (CR) melatonin in children with chronic sleep wake cycle disorders. All 42 subjects had severe neurodevelopmental difficulties. Initially, a randomized double-blinded cross-over design was used in 16 children, comparing the effectiveness of fast-release (FR) and CR melatonin. In the remainder of the patients, the CR melatonin was studied on a clinical basis. The effectiveness of treatment was assessed by sleep charts and clinical follow-up. Emphasis was placed on the judgement of the parents, who had guidance from the physicians. The average final CR melatonin dose in the 42 patients was 5.7 mg (2-12 mg). The studies showed that the FR melatonin was most effective when there was only delayed sleep onset, but CR formulations were more useful for sleep maintenance. Children appeared to require higher doses than adults.

**36**

**Pro-convulsant effects of oral melatonin in neurologically disabled children; Sheldon, Stephen H; 1998**

Children with multiple neurological deficits often experience sleeping disorders. Melatonin has been used to correct a variety of sleep-wake disturbances, with few side-effects. We speculated that melatonin would improve, with minimum side-effects, sleep in children with neurological disabilities.

**37**

**Evaluating the Role of Melatonin in the Long-Term Treatment of Delayed Sleep Phase Syndrome (DSPS); Dagan, Yaron et al; 1998**

Delayed sleep phase syndrome (DSPS) involves a mismatch between the usual daily schedule required by the individual's environment and his or her circadian sleep-wake pattern. Patients suffering from DSPS are treated with chronotherapy, light therapy, or melatonin administration. While chronotherapy and light therapy are demanding and difficult treatments that usually lead to compliance problems, melatonin administration is a relatively simple and easy treatment option. Previous studies carried out on relatively small samples of DSPS patients have shown that melatonin has a sleep-promoting and entraining action when taken in the evening. The present study, which accompanied routine treatment in our sleep clinic, examined the efficiency of melatonin treatment in a relatively large population of DSPS subjects by means of subjective reports. The 61 subjects, 37 males and 24 females, were diagnosed with DSPS by means of clinical assessment and actigraphy at our sleep clinic. Their mean pretreatment falling asleep and waking times were 03: 09 (SD = 86.22 minutes) and 11: 31 (SD = 98.58 minutes), respectively. They were treated with a 6-week course of 5 mg of oral melatonin taken daily at 22: 00. A survey questionnaire was sent to the home of each subject 12-18 months after the end of the treatment; the survey investigated the efficiency of the melatonin treatment and its possible side effects. Of the patients, 96.7% reported that the melatonin treatment was helpful, with almost no side effects. Of these, 91.5% reported a relapse to their pretreatment sleeping patterns within 1 year of the end of treatment. Only 28.8% reported that the relapse occurred within 1 week. The pretreatment falling asleep and waking times of patients in whom the changes were retained for a relatively long period of time were significantly earlier than those of patients whose relapse was immediate (t = 2.18, p <. 05; t = 2.39, p <. 05, respectively), with no difference in sleep duration. The implications of these findings, as well as further research possibilities, are discussed.

**38**

**Reproductive Safety of Melatonin: A “Wonder Drug” to Wonder About; Weaver, David R; 1997**

By some accounts, melatonin is the wonder drug of the 1990s. This previously obscure hormone came to the public's full attention as the result of a series of popular books claiming therapeutic benefits of melatonin ingestion. Some of these claims deserve serious consideration and investigation, whereas others appear unfounded. Without waiting for the outcome of the ongoing scientific debate, however, melatonin set astounding sales records. The hormone is now ingested on a daily basis by many thousands of people. There is little information on the potential adverse effects of melatonin ingestion in humans. Melatonin, its analogs, and its metabolites are not mutagenic, and melatonin possesses remarkably low acute toxicity in animals and humans. It is more difficult to exclude toxic effects of long-term melatonin treatment. The fact that melatonin is normally secreted each night does not ensure that exogenous melatonin, taken at other times and/or in supraphysiological doses, will not have adverse effects. Despite the well-recognized role of melatonin in the regulation of reproduction in photoperiodic species, it seems unlikely that chronic ingestion of moderate melatonin doses will have a profound impact on reproductive function in humans. Evidence that melatonin modulates steroid hormone action in some steroid-responsive tissues suggests that these tissues should be carefully examined when attempting to assess whether melatonin has chronic toxicity in humans. In the absence of sufficient information regarding the long-term safety of exogenous melatonin, the conservative course of action is to restrict melatonin use to those therapeutic applications in which a significant benefit is expected. The decision to ingest melatonin should be preceded by careful consideration of the expected benefits as well as the potential costs of treatment, with recognition of the fact that there has been exaggeration of the benefits and little attention paid to the potential costs in most discussions of this issue to date.

**39**

**Toxicology of Melatonin; Guardiola-Lemaitre, Béatrice; 1997**

Despite the fact that melatonin has been released for public use in the United States by the Food and Drug Administration and is available over the counter nationwide, there currently is a total lack of information on the toxicology of melatonin. In Europe, melatonin has a completely different status in that it is considered a "neurohormone" and cannot be sold over the counter. Even though administration of melatonin in humans, as well as in animals (even at supraphysiological doses), has not shown evidence of toxicological effects (i.e., no deaths), a drug toxicological file still would need to be prepared and approved by the regulatory authorities. Several features that are specific to this neurohormone need to be taken into consideration. Whatever the species concerned, melatonin is secreted during the night; it is the "hormone of darkness." It presents a circadian rhythm and a circannual rhythm (in photoperiodic species). The duration of these secretions could have an impact on the reproductive system, for example, showing the importance of the pharmacodynamics of melatonin. An inappropriate time schedule of melatonin administration could induce supraphysiological concentrations of the neurohormone and a desensitization of melatonin receptors. A long duration of exposure to melatonin also could mimic an "artificial darkness" condition when a circadian rhythm with a basal zero level during the day needs to be conserved for a physiological function. Furthermore, administration of large doses of melatonin could induce high concentrations of melatonin and of different metabolites that could have deleterious effects per se. Numerous books, magazines, and articles have praised melatonin as a "miraculous cure-all" for ailments ranging from sleeplessness, to aging, without any clinical evidence of efficacy (with the exception of its chronobiotic and resynchronizing effect). Very little attention has been paid to the possible side effects of melatonin. Nightmares, hypotension, sleep disorders, abdominal pain, etcetera, have been reported. In fact, analysis of the known pharmacological profile of melatonin and/or of its metabolites, based on scientific preclinical studies, constitutes a basis for prediction of adverse drug reactions or side effects. These include (1) the central nervous system, (2) the cardiovascular system and platelet aggregation, (3) glucose metabolism, (4) immunology, and (5) cancer. The knowledge of the fundamental mechanism of action of melatonin, including molecular biology, also needs to be taken into account for evaluation of possible side effects. Two types of melatonin receptors have been cloned (related to cyclic AMP), and the possibility of intracellular action of melatonin cannot be excluded. Melatonin receptors are present in the periphery and also at the level of the central nervous system, particularly on the suprachiasmatic nucleus that "drives" a circadian rhythm to many other areas on which it projects. Among those, the hypothalamus (which has melatonin receptors) plays a fundamental role in the hormonal homeostasis and modulation control of the organism. Special preclinical and pharmacological studies that take into account all these parameters need to be designed for safety evaluation and risk assessment of this specific neurohormone.

**40**

**Melatonin: Role in Development; Davis, Fred C; 1997**

Melatonin is the mammalian fetus's window to periodicity of the outside world. Through melatonin, the fetus "knows" what time of year it is and, in all likelihood, also knows the time of day. The best known function of melatonin during development is to communicate information about photoperiod and thereby adaptively regulate reproductive development. A second likely function of melatonin during development, which may be related to but more widespread than the first, is to entrain the developing circadian pacemaker. Prenatal maternal entrainment occurs in all of the eutherian mammals in which it has been examined, and in Syrian hamsters exogenous melatonin during development causes entrainment. The broader distribution and greater abundance of melatonin receptors during development, relative to mature animals, suggests that developmental effects of melatonin are greater and more diverse. The human fetal suprachiasmatic nucleus expresses melatonin binding sites and is therefore likely to be affected by both endogenous and exogenous melatonin with consequences for the prenatal and postnatal expression and entrainment of circadian rhythms. Caution is warranted, not only concerning the use of exogenous melatonin during pregnancy and lactation but also concerning behavior that might disrupt the mother's endogenous melatonin rhythm.

**41**

**Safety of Melatonin in Long-Term Use; Arendt, Josephine; 1997**

There are no published long-term safety data on the use of melatonin for whatever purpose, assuming long term to mean more than 6 months of daily medication. In the light of its physiological role in animals, the potential deleterious effects include inhibition of reproductive function, delayed timing of puberty, and influence (when taken during pregnancy and lactation) on the circadian status of the fetus and neonate and on future development. Its interactions with other medications are virtually unexplored. For most positive effects published, there also exist negative reports. There are insufficient data on its use in organic or psychiatric disease for any evaluations to be made. There are insufficient data on dose, formulation, and consequent relationships of individual pharmacokinetics and pharmacodynamics for recommendations at present. However, in normal healthy adults over 18 years old, not pregnant or lactating, with no personal or family histories of psychiatric disorder, and unmedicated except for oral contraceptives and minor analgesics (if necessary), the only significant short-term side effect in the author's experience has been sleepiness following oral ingestion of synthetic melatonin (5 mg or less, oral fast release), licensed for human experimental use and for prescription on a named-patient basis.

**42**

**Melatonin: a survey of suspected adverse drug reactions; Nagtegaal, J E et al; 1996**

Melatonin, the major hormone produced by the pineal gland, is increasingly prescribed as a drug for certain specific sleep disorders, including the Delayed Sleep Phase Syndrome (DSPS). DSPS is a form of insomnia in which patients prefer to sleep at hours that are much too late to be compatible with a conventional lifestyle. As a result, they usually wake up before sufficient sleep has been achieved. Other applications of melatonin are: prevention of jet lag and treatment of negative effects of shift work.

Many studies on melatonin treatment have been published, but only a few adverse reactions have been described. Several authors have even mentioned the absence of adverse reactions during or after melatonin treatment. Arendt reviewed suspected adverse drug reactions (SADRs) in animals treated with melatonin and some case reports about SADRs in humans [1]. Melatonin appears to be relatively non-toxic, but it is a hormone with several physiological functions and therefore the absence of side-effects seems unlikely.

**43**

**Melatonin potentially useful but safety, efficacy remain uncertain; Lamberg, L et al; 1996**

Melatonin users are the unwitting subjects in a large-scale uncontrolled experiment, according to specialists in sleep and biological rhythms attending a workshop on melatonin and sleep at the National Institutes of Health (NIH) in Bethesda, Md, in August. The scientists urged the NIH to support a multicenter controlled clinical trial to determine melatonin's efficacy and long-term safety.The widespread use of melatonin, the scientists said, highlights the pervasiveness of sleep disorders and the need for physicians to give more weight to sleep complaints. Although no medical catastrophes are known to be associated with melatonin, until solid evidence is in, they said, physicians should prescribe pharmacological and behavioral treatments of known value for sleep disorders, caution patients against the chronic use of melatonin, and monitor those who do take it.

**44**

**Melatonin and insomnia; Ellis, C M et al; 1996**

The hypnotic action of melatonin 5 mg p.o. was explored in 15 subjects with psychophysiological insomnia in a double-blind controlled self-report questionnaire study. Melatonin or placebo was taken at 20.00 hours for a 1-week period in random order. Effects on sleep and wakefulness were monitored by visual analogue scale and structured interview. Bedtime, sleep onset time, estimated total sleep and wake time, as well as self-rated sleep quality, were not altered by melatonin, and estimates of next-day function did not change. The period of melatonin treatment was retrospectively correctly identified by 8 of 15 subjects. Despite unchanged ratings of night sleep quality on the last night of each treatment, 7 of 15 subjects reported that sleep had subjectively improved to a minor extent in the week of active treatment. Side-effects attributed to melatonin included headache and an odd taste in the mouth. These data indicate that melatonin is probably of no clinical value in the management of psychophysiological insomnia.

**45**

**Melatonin and sleep in humans; Dawson, Drew et al; 1993**

Early studies on the physiological effects of melatonin typically reported hypnotic ‘side-effects’. Later studies, specifically addressing this action, failed to reliably replicate hypnotic effects using standard polysomnography. This difference may be related to differences in the basic physiological action of melatonin compared with more conventional hypnotics. It is suggested that melatonin exerts a hypnotic effect through thermoregulatory mechanisms. By lowering core body temperature, melatonin reduces arousal and increases sleep-propensity. Thus, in humans, one role of melatonin is to transduce the light-dark cycle and define a window-of-opportunity in which sleep-propensity is enhanced. As such, melatonin is likely to be an effective hypnotic agent for sleep disruption associated with elevated temperature due to low circulating melatonin levels. The combined circadian and hypnotic effects of melatonin suggest a synergistic action in the treatment of sleep disorders related to the inappropriate timing of sleep and wakefulness. Adjuvant melatonin may also improve sleep disruption caused by drugs known to alter normal melatonin production (e.g., β-blockers and benzodiazepines). If melatonin is to be developed as a successful clinical treatment, differences between the pharmacological profile following exogenous administration and the normal endogenous rhythm should be minimized. Continued development as a useful clinical tool requires control of both the amplitude and duration of the exogenous melatonin pulse. There is a need to develop novel drug delivery systems that can reliably produce a square-wave pulse of melatonin at physiological levels for 8–10 hr duration.

**46**

**Negative effects of melatonin on depression; Carman, John S et al; 1976**

In order to test the efficacy of the pineal neurohumor melatonin on depression, the hormone was administered in varying doses to six moderately to severely depressed patients and two patients with Huntington’s chorea in a double-blind crossover study. Melatonin exacerbated symptoms of dysphoria in these patients, as well as causing a loss of sleep and weight and a drop in oral temperature. Melatonin increased cerebrospinal fluid 5-hydroxyindoleacetic acid and calcium in three of four patients studied. The authors discuss the implications of this finding.