Sleep Medicine Reviews (2005) **9**, 25–39

ELSEVIER

SLEEP MEDICINE reviews

www.elsevier.com/locate/smrv

CLINICAL REVIEW

Melatonin as a chronobiotic

Josephine Arendt*[,2,3], Debra Jean Skene[1,2]

School of Biomedical and Molecular Sciences, Centre for Chronobiology, University of Surrey, Guildford, Surrey GU2 7XH, UK

KEYWORDS
Melatonin; Circadian; Rhythm; Sleep; Phase shift

Summary Melatonin, hormone of the pineal gland, is concerned with biological timing. It is secreted at night in all species and in ourselves is thereby associated with sleep, lowered core body temperature, and other night time events. The period of melatonin secretion has been described as 'biological night'. Its main function in mammals is to 'transduce' information about the length of the night, for the organisation of daylength dependent changes, such as reproductive competence. Exogenous melatonin has acute sleepiness-inducing and temperature-lowering effects during 'biological daytime', and when suitably timed (it is most effective around dusk and dawn) it will shift the phase of the human circadian clock (sleep, endogenous melatonin, core body temperature, cortisol) to earlier (advance phase shift) or later (delay phase shift) times. The shifts induced are sufficient to synchronise to 24 h most blind subjects suffering from non-24 h sleep–wake disorder, with consequent benefits for sleep. Successful use of melatonin's chronobiotic properties has been reported in other sleep disorders associated with abnormal timing of the circadian system: jetlag, shiftwork, delayed sleep phase syndrome, some sleep problems of the elderly. No long-term safety data exist, and the optimum dose and formulation for any application remains to be clarified.

Introduction

The word chronobiotic does not yet figure in the Oxford English dictionary. A practical definition would be 'a substance that adjusts the timing of internal biological rhythms' or more specifically 'a substance that adjusts the timing of the central biological clock'. Conditions in which adjustment of the timing of circadian (ca. 24 h) rhythms is of practical benefit include non-24 h sleep–wake disorder, delayed sleep phase syndrome (DSPS), shift work, jet lag, living in very dim light, possibly some sleep disorders in the elderly and probably many other situations yet to be investigated (Fig. 1).

There is good evidence that exogenous melatonin can change the timing of some overt rhythms such as sleep, core body temperature, endogenous melatonin and cortisol, and that in vitro it will shift the timing of activity (electrophysiological and metabolic) within the suprachiasmatic nuclei (SCN), the central circadian rhythm generator or pacemaker. In some circumstances melatonin can synchronise or 'entrain' to the 24 h day circadian rhythms in individuals who are 'free-running',

*Corresponding author. Tel.: +44-1483-689701; fax: +44-1483-689712.
E-mail addresses: j.arendt@surrey.ac.uk, arendtjo@aol.com (J. Arendt), d.skene@surrey.ac.uk (D.J. Skene).
[1] Tel.: +44-1483-689706; fax: +44-1483-300374.
[2] Josephine Arendt and Debra Skene are directors of Stockgrand Ltd, which measures melatonin and related products and conducts clinical trials and basic research on the effects of melatonin. Josephine Arendt is the major shareholder and Debra Skene is a minor shareholder.
[3] Josephine Arendt is a member of the Sleep Advisory Board of Alliance Pharmaceuticals.

1087-0792/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.smrv.2004.05.002

Nomenclature

Acrophase	The time of the peak of a rhythm, usually the peak time of the best-fitting mathematical function approximating the data
Amplitude	The amount of variability due to a given rhythm, usually defined as equal to one-half the peak-to-trough difference
Circadian	Occurring or recurring about (latin-circa) once per day (diem). Biological circadian rhythms are internally generated and, in humans, have a period which is usually slightly longer than 24 h, other terms include circannual: about 1 year, ultradian or pulsatile: with a period shorter than 20 h
Period	The duration of one complete cycle of a rhythmic variation, also known as tau (τ)
Phase	A distinct stage in a process of change, in this case a circadian rhythm
Photoperiod	Strictly the length of the light phase of a particular light–dark cycle, but may be used to describe the whole light–dark cycle
Photoperiodism	The response of an organism to changes in the lengths of the daily periods of light
Synchronizer, time cue or zeitgeber	A periodic stimulus capable of determining the timing, with respect to clock hour or calendar date, of a given endogenous rhythm. A synchronised rhythm having the period of a specific time cue (24 h) does not necessarily have the 'correct' phase, e.g. melatonin peak production at night. An 'entrained' rhythm is synchronised with the correct phase

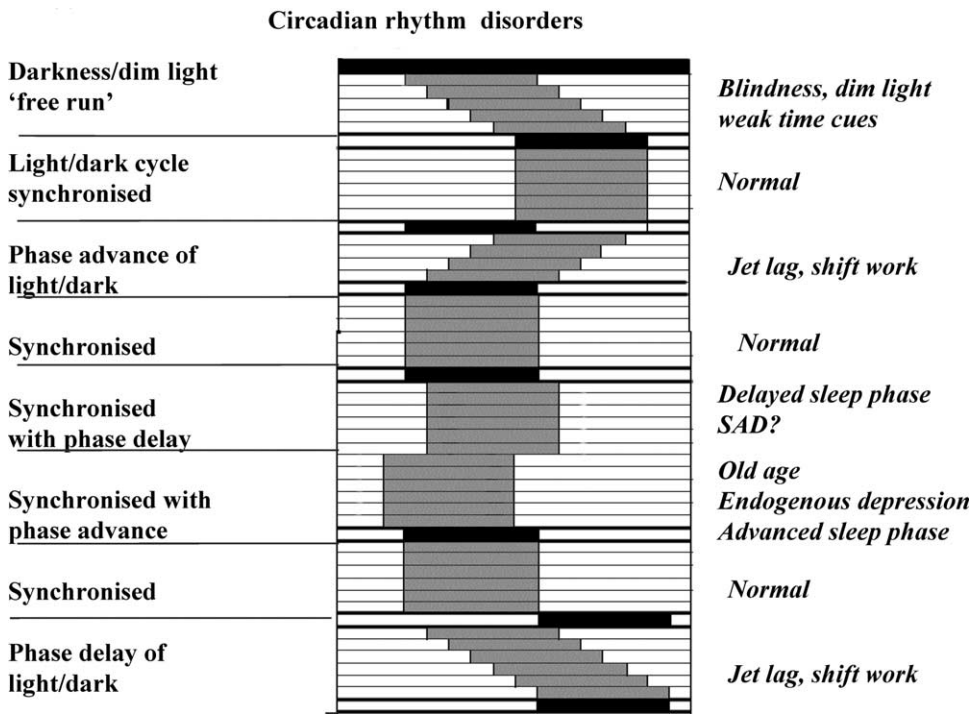

Figure 1. Circadian rhythm disorders in which melatonin has potential therapeutic benefit by normalisation of rhythms and/or enabling sleep during 'biological day'. The grey bars show in diagrammatic form the behaviour of a representative circadian rhythm on sequential days after changes in the light–dark cycle, the black bar represents darkness. Redrawn by permission from an original diagram by Dr Jenny Redman, Thesis. The effects of melatonin on rat circadian rhythms. La Trobe Univeristy, Australia, 1988.

i.e. expressing the natural period of their internal clock. To what extent the effects of melatonin on the SCN dictate overt changes in circadian rhythms remains to be determined. Likewise direct effects of melatonin masking on overt rhythms may well feedback to modify SCN activity. The receptors involved in these effects remain to be properly characterised in humans. This review will evaluate the evidence for phase shifting and entrainment by melatonin, the influence of dose, timing of treatment and formulation, and the therapeutic applications of these properties.

Production and physiological role of melatonin

Melatonin (*N*-acetyl-5-methoxytryptamine) is synthesised primarily in the pineal gland of mammals. It is secreted with a robust circadian rhythm, which in all species, whether nocturnal or diurnal, normally peaks during the dark phase of the day (Fig. 2). The rhythm is generated in the SCN and synchronised (entrained) to the 24 h day largely by the alternation of light and darkness. Light exposure during the dark phase also suppresses melatonin production.[1] Light of suitable intensity, spectral composition and timing is the primary time cue for the synchronisation of the circadian system. Recent data indicate that short wavelength (ca. 465 nm) blue light is the most effective for both suppression and phase shifting of melatonin.[2,3]

In animals and in the right conditions also in humans the profile of melatonin synthesis and secretion is longer during (long) winter nights compared to (short) summer nights. The change in duration of secretion serves as a time cue for the organisation of daylength-dependent (photoperiodic) seasonal functions such as reproduction, behaviour and coat growth in seasonal mammals. This transduction of photoperiodic information is the most important physiological function of melatonin in mammals. Photoperiod-dependent changes in seasonal species also include changes in the waveform of core body temperature and in the timing and distribution of sleep.[1,29]

The role of melatonin in the mammalian circadian system is less obvious. Removal of the pineal induces subtle modifications of rhythmic function, for example rats will adapt more rapidly to an abrupt change in the light–dark cycle (equivalent to crossing several time zones in humans), for references, see Ref. 1. In humans there is very little data

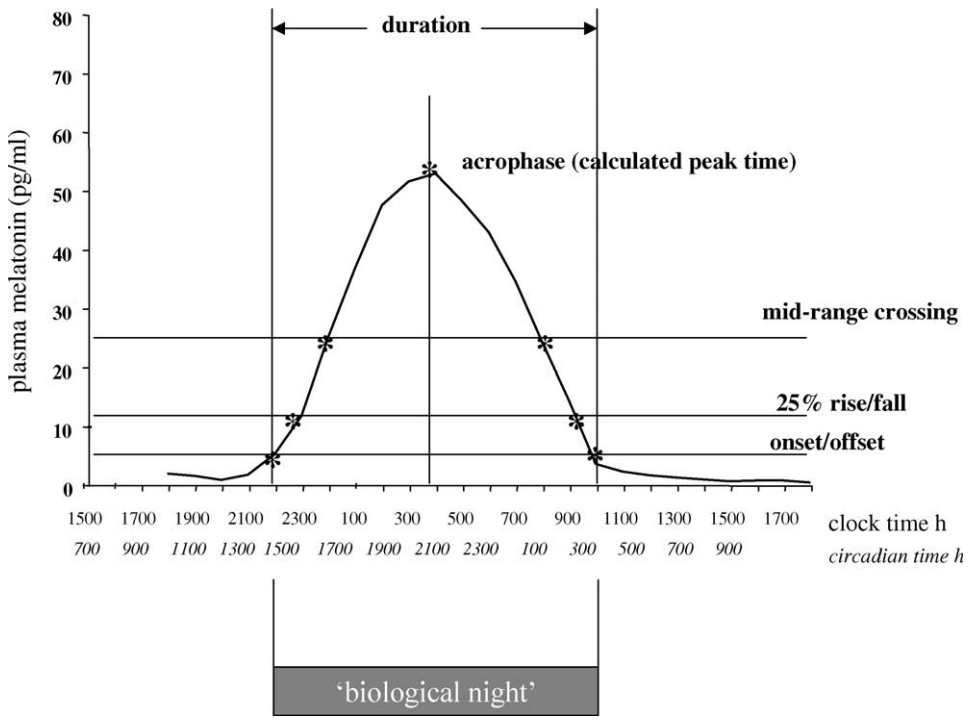

Figure 2. Diagram to illustrate the normal profile of melatonin secretion (plasma) defining 'biological night'. The features of this profile and that of salivary melatonin and urinary 6-sulphatoxymelatonin (acrophase, duration, mid-range crossing, 25% rise and fall, onset and offset of secretion), used to characterise the timing of the circadian clock are indicated. Melatonin treatment timing is often based on 'circadian time' (CT) where by convention CT 14 is melatonin onset. 6-Sulphatoxymelatonin acrophase is approximately 2 h after the plasma melatonin acrophase.

regarding pinealectomy (which abolishes the melatonin rhythm), although there is some recent evidence suggesting a possible increase in sleep problems.[4] However, pharmacological suppression of melatonin with a β-blocker facilitates phase shifts by light.[5] The night time rise of melatonin is strongly correlated with increased sleepiness and lowered core body temperature,[6] and it has been proposed that the profile of melatonin defines the biological night.[7] When melatonin is secreted at an abnormal time (during the daylight hours), it is associated with increased daytime sleepiness/lowered alertness and body temperature,[8] similarly if melatonin is suppressed by light at night it is associated with decreased sleepiness/increased alertness and body temperature.[9,10] There is some evidence for a causal relationship between high melatonin levels and night time events such as increased sleepiness and lowered body temperature.[9,10] These associations have led to the supposition that melatonin is a sleep hormone. In the authors' opinion it is a darkness hormone, and is concerned with the timing and magnitude of events associated with the dark phase—which differ in nocturnal and diurnal species.

Phase shifting and acute effects of exogenous melatonin

Most of the original 'chronobiotic' effects of melatonin were observed in photoperiodic seasonal breeders such as hamsters and sheep. Suitably timed treatment over periods of weeks was equipotent with artificial changes in daylength in the induction or suppression of seasonal events such as reproductive competence. These major physiological changes were accompanied by clear changes in the circadian waveform of prolactin secretion and in the rhythmic characteristics of LH and FSH secretion, suggesting effects of melatonin on central rhythm generator(s).[1] The proposal was made that if photoperiod (daylength) had effects on human physiology, then melatonin should be able to mimic photoperiodic (daylength-dependent) effects in humans.[11]

Aaron Lerner, who first identified melatonin, was also the first to report its ability to induce transient sleepiness during the day.[12] His observations were followed by a number of reports describing acute sleepiness after melatonin in single doses ranging from 0.3 to 85 mg (reviews[1,13]). One exceptional study used doses up to 2 g in a variety of psychiatric patients: some daytime somnnolence was reported, and exacerbation of depression. Only after the time-dependent effects of melatonin in photoperiodic species became evident, was timing taken into account in human studies. Taken during the 'biological day', i.e. when endogenous melatonin is low, melatonin clearly possesses mild transient sleepiness inducing effects and lowers core body temperature.

In 1983 Redman et al.[14] showed that melatonin could synchronise the free-running activity rhythms of rats kept in constant darkness when the timing of the dose coincided with activity onset and a study by Murakami et al.[15] indicated that implants of melatonin close to the SCN could accelerate reentrainment of the circadian rhythm of cortisol. At this time also, human volunteers took daily melatonin (2 mg, oral, fast release) at 17:00 h for 3–4 weeks to give an extended (long duration) profile in the circulation, comparable in both dose and timing to treatment used to change seasonal functions in sheep. The effects of this daily dose were to advance the timing of sleepiness or sleep and to advance the timing and extend the circadian profile of endogenous melatonin (in subjects where endogenous and exogenous melatonin could be distinguished).[16,17] Even in the early 1980s, melatonin was regarded as the best index of the timing of the circadian system and these data were interpreted as probable chronobiotic effects on a central circadian clock. They led directly to the initial investigations of melatonin in the treatment of circadian rhythm disturbance (see sections on therapeutics).

Timing exogenous melatonin

Phase response curves

A stimulus of any nature, which shifts circadian rhythms is known as a zeitgeber (time cue).[18] Zeitgebers advance or delay circadian rhythms according to the time they are experienced. The direction and magnitude of the change in timing (phase shift) is described by a phase response curve (PRC). The time base of a PRC is 'circadian time' (CT) which is effectively internal biological time usually defined in humans by the timing of the core body temperature rhythm or melatonin secretion (see Fig. 2 for explanation). The phase shifting PRC data for melatonin have mostly been derived from melatonin onset as a phase marker. Several PRCs for melatonin have now been described (Fig. 3).[19–22]

Although the PRCs for melatonin have provided to date the template to determine the time of melatonin administration needed for an appropriate phase shift (advance or delay), they do have some methodological problems. A classic

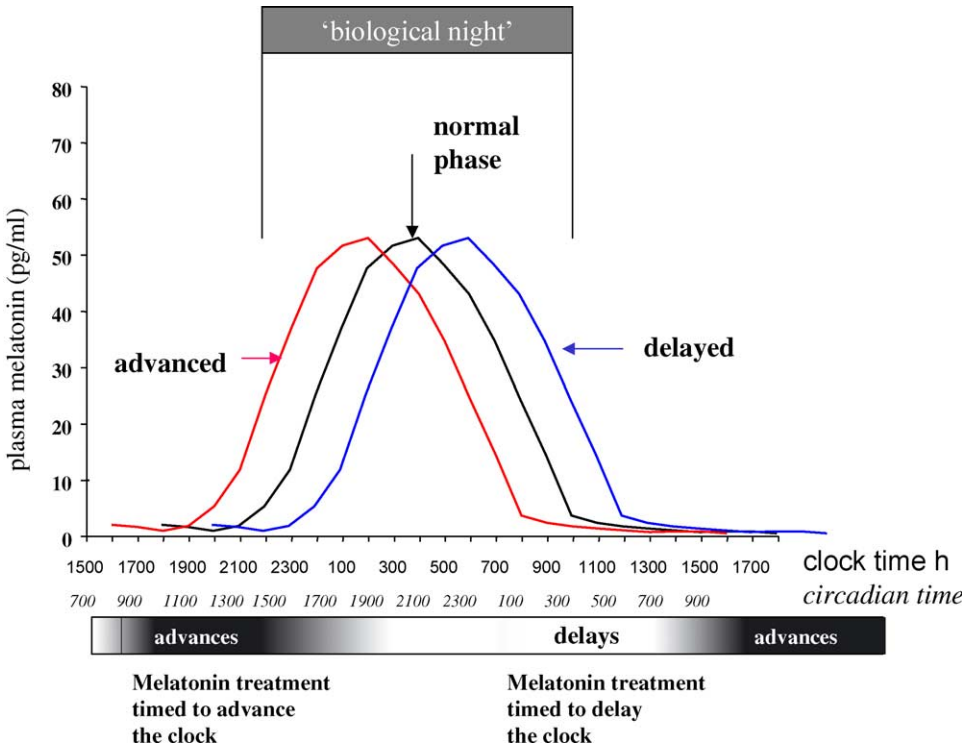

Figure 3. Diagram to illustrate the timing of melatonin treatment, relative to the endogenous melatonin rhythm, to induce phase advances or phase delays, based on published phase response curves.[19-22] The probability of obtaining advances or delays is maximum in the totally dark or the totally light sections of the bar, in grey areas individual differences are apparent.

PRC assesses phase shifts following a single pulse of the zeitgeber under free-running conditions. The use of repeated doses of melatonin, sighted subjects in entrained conditions, possible light confounds and transience following the melatonin dose mean that the current PRCs for melatonin are not ideal. A single pulse PRC for melatonin in subjects with free-running circadian rhythms is therefore still needed to define the degree of phase shift and optimum time of melatonin administration. The study of free-running blind subjects provides an opportunity to carry out this onerous undertaking, although an approach using constant routine protocols is also appropriate.

Much work has now confirmed the time-dependent phase advancing effects of melatonin with regard to the rhythms of sleep, endogenous melatonin itself, core body temperature and cortisol. Phase delaying effects of melatonin given during the 'biological morning', i.e. during the declining phase of melatonin secretion, originally reported by Lewy et al., and later by others, are slightly more contentious. One report[23] failed to find a delaying effect of oral melatonin in a carefully controlled study, however delays were observed after intravenous infusion of melatonin in amounts giving circulating concentrations comparable to physiological night time values.[21] In fact the oral administration approach commonly used to induce phase shifts may not be appropriate for the demonstration of delays. One reasonable assumption is that the declining phase of endogenous melatonin signals the end of the biological night, and that a delay of this decline is responsible for phase delays. Large individual differences in the pharmacokinetics of oral melatonin[1] given in the early morning to induce delays mean that the decline of exogenous melatonin will differ substantially from one subject to another. Thus some individuals may experience a decline at a suitable delaying phase, others may not. Indeed with slow clearance of the exogenous dose melatonin may be present at both delaying and advancing times, possibly negating any overall effect (for further discussion see section on entrainment). The infusion approach is likely to be the most appropriate, and even here variable clearance with differing rates of metabolism will provide a heterogeneous signal.

Dose and formulation

The question of appropriate dose and formulation of melatonin for the adjustment of circadian

rhythms has not been resolved. Most information derives from fast release preparations. Acute phase advances derived from single dose administration at 17:00 h, in normally synchronised individuals, are clearly dose dependent with respect to sleepiness, endogenous melatonin and cBT (core body temperature), in the range of 0.05–5 mg in controlled conditions (dim light, 50 lux, recumbency following the dose).[24] The conditions during which melatonin is administered appear to be very important and may dictate the effectiveness of any given dose, particularly with respect to acute changes in cBT and sleepiness. During daily administration (2 mg, fast release, 17:00 h) without control of light or posture, earlier sleepiness or sleep was only evident after 3–4 days treatment.[16] With dim light and recumbency small doses (0.1–10 mg fast release) induced sleepiness or sleep.[25] Further careful investigation of postural effects indicated that the acute induction of sleepiness and lowering of cBT by 5 mg melatonin at 17:00 h were dependent on recumbency.[10] Most recently, the daily administration of 1.5 mg (surge-sustained release, with peak values comparable to 0.5 mg fast release) at 16:00 h for 8 days, followed by 16 h of very dim light (<5 lux in the angle of gaze) and recumbency, led to very substantial phase advances (3–4 h) of endogenous melatonin and cortisol together with an earlier timing and redistribution of sleep.[26] Notably, the amount of total sleep time was not changed, underlining the timing function of melatonin with regard to sleep (and other rhythms) rather than a hypnotic effect.[27]

These observations can be interpreted as relating to the short-term effects of changed photoperiod on human circadian rhythms, whereby application of a 'winter' night led to phase advances.[28] Moreover, the redistribution of sleep during a long artificial 'melatonin night' may well relate to the phenomenon seen in photoperiodic species, where sleep homeostasis is conserved but a redistribution of sleep occurs with changing photoperiod.[29] Longer term effects (2 months) of an artificial long night in humans included an increased duration of the endogenous melatonin profile, changes in the waveform of cBT and redistribution of sleep,[30] however, such a lengthy controlled experiment using melatonin administration is probably not feasible.

The combination of artificially advancing the evening rise in melatonin over several days, with recumbency and very dim light, appears to be a very effective method of advancing circadian rhythms. Few consistent deleterious effects have been observed in healthy subjects during administration over periods from 8 days to several weeks with regard to daytime alertness and pituitary/gonadal hormones, with the exception of acute elevation of prolactin after the dose.[1,31]

Entrainment/re-entrainment, synchronisation/resynchronisation

The term 'entrained' is usually used to describe a circadian system which is synchronised to the 24 h day with appropriate timing of overt rhythms (e.g. peak melatonin and trough of cBT around 03:00–05:00 h). Synchronisation usually means that the period (τ) of the circadian system is 24 h but that the timing of overt rhythms is not necessarily at the correct phase (for example, persistent peak of melatonin and trough of cBT during the day). Re-entrainment describes the process of re-establishing the correct timing with respect to the 24 h day.

Intrinsic circadian period is displayed in a time free environment.[18] The overt phenomenon is known as free-running. It is very difficult indeed however to keep humans for long periods in a completely time free environment and various alternative protocols have been employed to try to define human τ. At present, average human τ in sighted individuals is thought to be around 24.2 h.[22,32,33] Circadian period is an inherited characteristic and has been shown to closely relate to diurnal preference and the early or late timing of the circadian system (melatonin, cBT) in a normal entrained situation.[34,35] Subjects with longer periods will have more of an evening preference than those with a shorter intrinsic period. Recently, a strong association of a length polymorphism in a human clock gene (*per3*) with diurnal preference has been identified, with an even stronger relationship to the extreme diurnal preference of DSPS.[36] In order to remain entrained to 24 h, the circadian system needs to be reset frequently. For example, a subject with an intrinsic τ of 24.5 h will need to be advanced by 0.5 h per day, with a τ of 24.1 h, the advance required is 0.1 h per day and with a τ of 23.8 h a delay of 0.2 h per day is required. Ocular light exposure is the primary resetting time cue. This is evident particularly from studies in the blind.

Studies on totally blind subjects have proved to be very valuable with respect to the investigation of human circadian rhythms and the phase shifting ability of exogenous melatonin. Many blind people with no conscious perception of light cannot remain entrained to the 24 h day and exhibit non-24 h sleep–wake disorder. This phenomenon is universal in our subjects with no eyes (albeit with a small number of study subjects to date, $n = 13$).[37,38] The sleep disorder is comparable to intermittent jet lag,

whereby when the circadian system is out of phase, with melatonin production during the day, subjects experience daytime sleepiness/naps, and problems sleeping at night. The frequency with which subjects suffer from these cyclic sleep problems depends on an individual's τ. For example, with an intrinsic period of 24.5 h subjects will delay by 0.5 h per day and will be in the same phase every 49 days. Their out-of-phase sleep problems will thus occur with a 49 day periodicity, referred to as a circadian beat cycle.

Sighted people living in very dim light with other weak time cues (for example, little social contact, no structured daily activities) may show either complete desynchronisation and free-run, or very late timing of the circadian system (delayed phase). Examples include life in the Polar winter (no natural sunlight) with little structured activity,[39,40] living in artificial very dim light for extended periods with no imposed activity.[22] It is possible that some elderly people encounter weak time cues due to poor mobility, few social contacts and reduced exposure to light both by natural reduction of lens transmittance with age and remaining indoors. In these situations circadian entrainment is required.

The maximum phase shifts induced by melatonin (combined or not with other zeitgebers) are theoretically sufficient to entrain most people to 24 h.[19,20,22,24,41] In principle, a person with a long free-running τ (e.g. 25 h) will require a greater adjustment than someone with a τ close to 24 h. It has proved difficult until recently to show entrainment of free-running rhythms in humans. Redman et al.[14] described entrainment of the free-running rest activity cycle in rats by daily melatonin injections, started at various CTs, in 1983. Entrainment only occurred when the injections corresponded to activity onset (which is equivalent to CT 9–11 in humans). In principle therefore, treatment of a person with free-running rhythms at the same time every day, starting at any CT, should entrain the circadian system when the free-run brings the internal clock into the appropriate phase (Figs. 4 and 5). This approach was used in 10 sighted subjects transferred from a normal environment to very dim light (<8, or <5 lux in the angle of

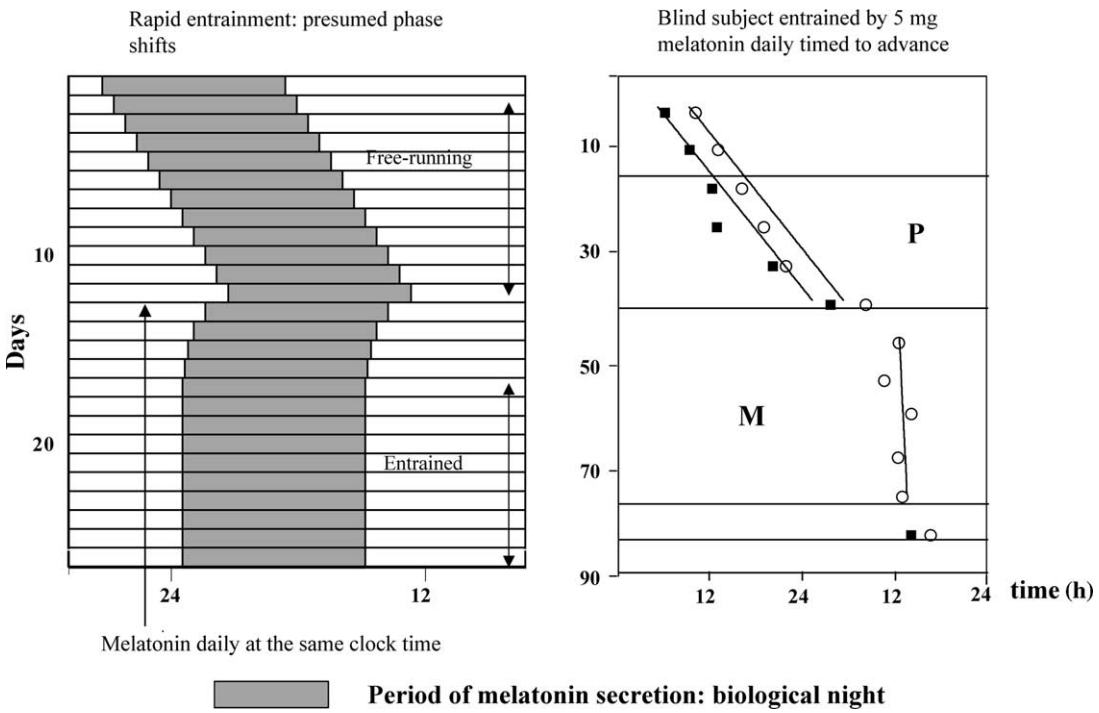

Figure 4. Use of melatonin to entrain free-running subjects to 24 h. Left panel, theoretical diagram: the grey bars show the period of melatonin secretion (biological night) free-running with placebo or no treatment, with presumed phase shifts due to melatonin treatment (21:30 h). Melatonin (daily from day 12 of free-run) is timed to phase advance with respect to the circadian clock. The right panel shows actual data from a totally blind subject treated with melatonin (M, 5 mg fast release) or placebo (P, lactose-gelatine) daily at bedtime, initially in a phase advance window. Circadian rhythm markers urinary cortisol (open circles) and 6-sulphatoxymelatonin (closed squares) acrophases are derived at weekly intervals. Endogenous melatonin cannot be used as a rhythm marker during melatonin treatment. Free-running rhythms are evident during placebo treatment followed by entrainment after one week with melatonin. Right panel from Ref. 46 by permission of the Society for Endocrinology.

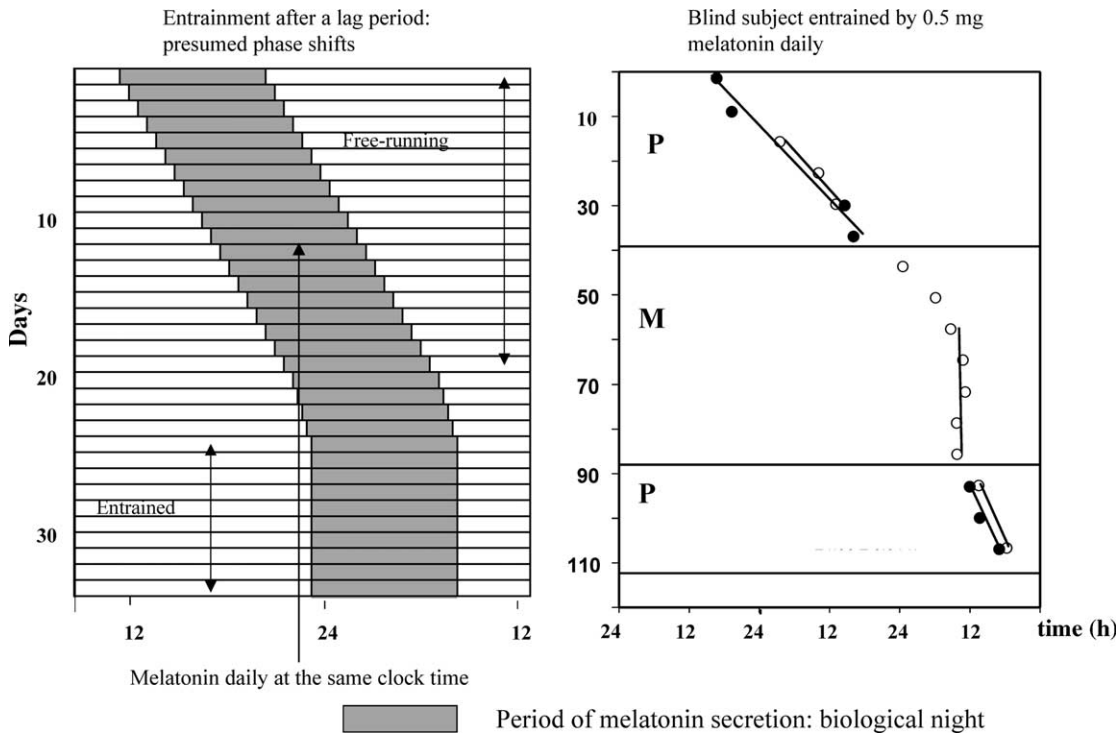

Figure 5. Use of melatonin to entrain free-running subjects to 24 h. Left panel, theoretical diagram: the grey bars show the period of melatonin secretion (biological night) free-running with placebo or no treatment, with presumed phase shifts due to melatonin treatment (21:30 h). Melatonin (daily from day 12 of free-run) is initially timed such that the daily circadian delay due to free-run moves the treatment time into a phase advance position. Small phase advances (shortening the period) and eventual entrainment occur. The right panel shows actual data from a totally blind subject treated with melatonin (M, 0.5 mg fast release) or placebo (P, lactose-gelatine) daily at bedtime, initially in a phase delay window, entrainment after a lag (3–4 weeks) occurs when the treatment falls within a phase advance window. Urinary cortisol (open circles) and 6-sulphatoxymelatonin (closed circles) acrophases are derived at weekly intervals. Free-running rhythms are evident during placebo treatment followed by entrainment with melatonin. Most subjects treated with 0.5 mg fast release melatonin have been entrained.[38,48,49] Right panel from Ref. 38 by permission of Sage Publications Inc.

gaze).[22] Melatonin (5 mg) at 20:00 h daily for 2 weeks was able to maintain entrainment (cBT) when treatment started immediately after transfer to dim light from a normal environment, albeit with irregular sleep in two subjects. However, if subjects were allowed to free-run in the dim light with placebo treatment for 2 weeks and melatonin was then given daily at 20:00 h, each individual started melatonin at different CTs. Under these conditions, some subjects entrained to 24 h, others showed a shorter free-running τ (cBT). Both delays and advances were seen, in general consistent with the first published PRC. There was little effect of melatonin on cBT of the subject with the longest average τ (24:52 h), only stabilisation of sleep onset to 24 h: almost certainly an acute sleep inducing effect of melatonin.

Initial attempts to entrain free-running blind subjects preceded those in sighted subjects and used a similar approach. Treatment (5 mg daily) was given at 'bedtime' when the subjects were in a self-assessed 'good' sleep phase. Theoretically, the timing of the daily dose combined with a delaying free run should have placed the treatment within a phase advance 'window' from which entrainment should occur. However, this design led to stabilisation of sleep timing, substantial reduction of daytime naps, but little evidence of circadian entrainment in some studies.[42–44] In others phase shifts were observed, and either entrainment or shortening of τ in one subject.[45] Subsequently, we were able to show entrainment in a small number of blind subjects (3/7) when treatment (5 mg fast release) was timed to start in the 'phase advance' region of the PRC.[46] Similar observations were later reported in six of seven totally blind subjects by Sack et al.[47] In the latter case timing of treatment was not assessed in relation to circadian phase, but in relation to bedtime. As with the first attempts to entrain blind subjects, we started treatment,

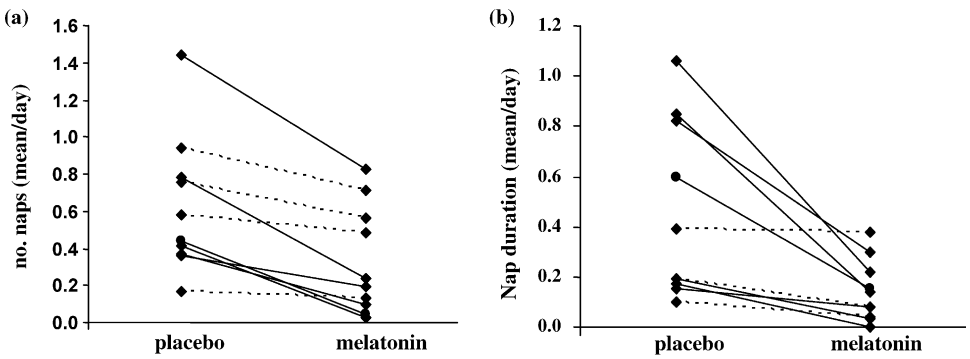

Figure 6. Reduction in the number and duration of naps in 10 free-running totally blind subjects treated daily with 0.5 mg melatonin (fast release) for a complete circadian 'beat' cycle (see text for definition). From Ref. 38 by permission of Sage Publications Inc.

just before bedtime, as subjects moved into a subjectively 'good' sleep phase (Fig. 4). This approach to treatment is designed to try and maintain subjects in an appropriate phase, assuming that when in a good sleep phase their circadian system is correctly timed. If this assumption is valid then treatment just before bedtime should phase advance a delaying circadian clock and also maximise the soporific effects of melatonin. With a subject who phase advances daily, it would be necessary to time the treatment differently, however such subjects are rare.

Following this initial success in entraining blind patients it has proved possible to entrain, and maintain entrainment, with much lower doses (0.5 mg fast release and in some cases even less) in most subjects with substantial benefits for sleep[38,48] (Figs. 5 and 6). At present however, it is not clear which factors dictate the ability of melatonin to entrain. Discussion is ongoing concerning the dose, formulation, timing, length of treatment required and indeed the characteristics of the blind patients themselves and their environment. It is likely that 0.5 mg fast release is sufficient to entrain most subjects and maintained entrainment may require less. Slow release formulations may be more effective, but no comparative data exist to address this question. We have found that entrainment is more likely when treatment is started in the phase advance region of the PRC,[46] however Lewy et al.[49] and our subsequent experiments[38] have shown that entrainment may also occur with treatment started in a delay phase of the PRC. Effectively with daily treatment at the same clock time, the circadian system delays until the treatment timing corresponds to the phase advance part of the PRC as in the experiments of Redman et al.[14] (Fig. 5). Specifically, and probably importantly, this has only been observed with the lower 0.5 mg dose.

Lewy et al.[49] have proposed that higher doses may compromise entrainment in some individuals if melatonin is present during both the advanced and delay parts of the PRC. This of course is more likely with the higher 5 mg dose, however his group have also reported increasing the dose to 10 mg for entrainment to occur.[47] Failure to entrain with any dose may be associated with the intrinsic τ of the subjects themselves. A longer τ needs a greater daily phase shift to maintain entrainment and in some cases this may exceed melatonin's phase shifting ability (this of course also applies to sighted subjects suggesting that owls need greater phase shifts than larks to remain entrained). Another factor, difficult to evaluate in field studies, is the effect of non-photic time cues such as exercise, scheduled sleep/activity, meal times and content.[50] It is likely that entrainment by melatonin is reinforced in some subjects and not others, by such time cues. However, with a small number of subjects studied to date, these questions remain to be resolved.

Therapeutic applications of the chronobiotic properties of melatonin

Phase shift conditions: jet lag and shift work

Melatonin administered from about 6 h before to about 4 h after the initial onset of endogenous secretion will normally induce an advance shift of

sleep, cBT and the endogenous melatonin rhythm. Delays occur when melatonin is given on the declining phase of the endogenous rhythm such as to extend high levels into the morning hours. There are minor differences between authors and rather large individual differences. The scatter of data is such[20] that it is difficult to determine precise times when only advances or only delays occur (Fig. 3). In subjects entrained to a normal 24 h environment, the timing of melatonin to achieve the desired phase shifts is relatively simple and can to some extent be judged by habitual sleep times, which occur approximately 2 h after the evening melatonin rise. Optimal timing however is not so simple after time zone travel (Fig. 7), in shift workers, and in blind subjects unless circadian phase is determined prior to treatment. This is an onerous undertaking and impractical (at present) in clinical use. In fact most clinical reports of the therapeutic use of melatonin have used subjective measures of benefit (e.g. improved sleep). Reported effects on circadian phase are sparse and the clinical importance attached to optimal circadian timing as a study outcome is evidently not great.

A number of studies have addressed the ability of melatonin to hasten circadian adaptation to simulated phase shift. In environmental isolation, studies using advanced phase shift and suitably timed melatonin treatment (5 mg) have shown an increase in the rate of re-entrainment of temperature, hormonal, and electrolyte rhythms but with inconsistent effects on sleep.[51] Of particular note was the observation that melatonin was able to specify the direction of re-entrainment to advance rather than delay,[51] consistent with very early observations in rats. After a simulated rapid 9-h phase advance, we investigated the ability of melatonin with or without conflicting bright light treatment to hasten adaptation.[52] Melatonin (5 mg fast release) or placebo was taken at 23:00 h on the first night after the shift and for two subsequent nights at the same time. Conflicting light (white, 1200 lux) exposure occurred from 08:00 to 12:00 h during the first 3 days after the shift. Melatonin treatment was (theoretically) timed to be just within a phase advance window, and light treatment was timed to phase delay. Melatonin consistently improved sleep (quality, duration, and night awakenings) compared with placebo even in the presence of inappropriate light, and this appeared to be independent of the direction of phase shift. Daily mean alertness and performance efficiency were higher for melatonin treatment compared with placebo. The effects of melatonin were

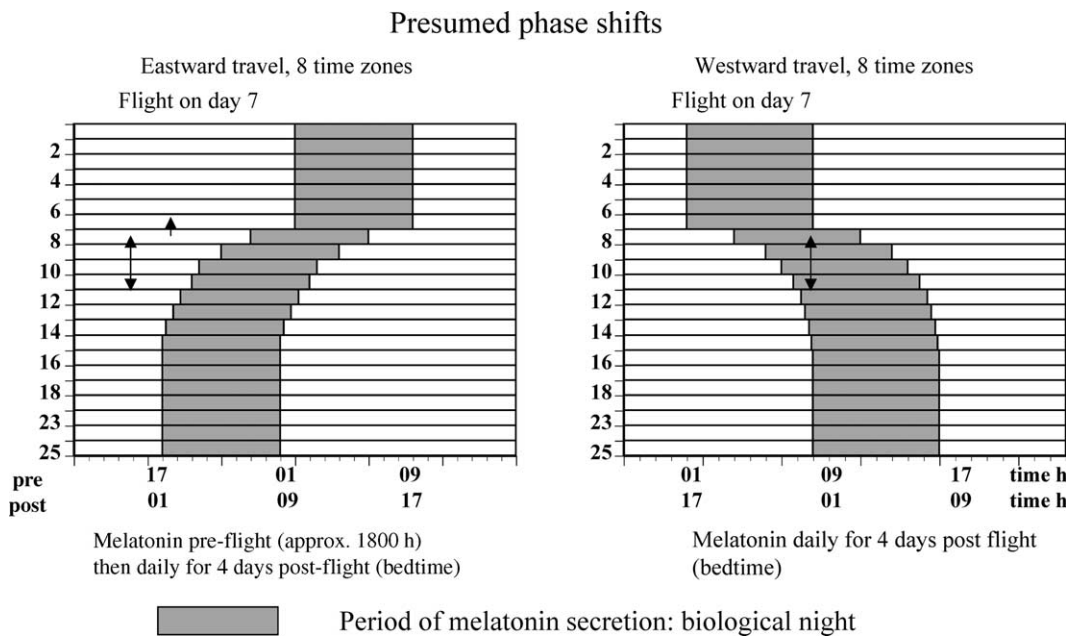

Figure 7. Diagram to illustrate the timing of melatonin (arrows) to hasten adjustment to flights over eight time zones East and West, assuming greater phase shifts during initial adaptation. Eastward melatonin may be taken on departure day at approximately 1800 h to initiate a phase advance, and then at bedtime in the new time zone, to reinforce phase advances and the soporific effects. Westward melatonin may be taken at bedtime in the new time zone initially to phase delay, but primarily using soporific effects. Note that for short stopovers, long haul pilots and aircrew, timing relative to circadian phase is almost impossible to judge and there is no evidence for effectiveness in these circumstances.

immediately evident even before phase adaptation had occurred. They appear to be related to its acute effects on behaviour and temperature reinforced by a hastening of phase adaptation. The latter, however, did not appear to play a major role, at least during the first post-phase shift days. In a recent crossover study of simulated phase shift, timed melatonin (1.8 mg sustained release) appeared to be effective in hastening circadian adaptation to the new schedule.[53]

At least 14 placebo-controlled field studies have reported the use of melatonin to alleviate perceived jet lag (primarily sleep disturbance) (reviewed in Ref. 54). Of these, 11 were successful in the sense that some measures of subjective jet lag, sleep and alertness improved compared with placebo. The first study (Eastward, 8 time zones) used objective and subjective measures and a time sequence designed to initiate an eastward (advance) phase shift before departure with 5 mg, fast release melatonin at 18:00 h for 3 days before flight and a reinforcement of the advance by bedtime (23:00 h) administration on arrival for 4 days.[55] The results indicated that both subjective and objective parameters (including endogenous melatonin and cortisol rhythms) showed more rapid adaptation in the melatonin-treated group ($n = 8$) than in the placebo group ($n = 9$). Over 6–11 time zones eastward or westward, 5 mg melatonin at bedtime accelerated adaptation of the cortisol rhythm with a consistent, but not significant, improvement of subjective jet lag in 36 subjects.[54] A very small recent study (six subjects), used complete plasma melatonin profiles to determine phase, and reported faster resynchronisation with melatonin at 23:00 h after travel from Tokyo to Los Angeles, in spite of uncontrolled exposure to natural light.[56]

Several studies using only subjective measures have reported positive outcomes,[54] however positive reports are in contrast to the results of three other studies, none of which assessed circadian phase. The successful studies involved subjects demonstrably or probably synchronised to the local environment prior to melatonin treatment. With short stopovers and with long-haul aircrew, difficulties with timing the treatment arise and there is no evidence for efficacy in these cases.[54] One unsuccessful study on athletes travelling to Australia from the UK, apparently used phase delay timing of treatment when an advance would have been preferable.[57] A method suitable for use in field situations for rapid assessment of circadian phase would be highly desirable.

In both controlled and uncontrolled field studies on the travelling public since 1986 we have observed an overall 50% reduction in subjective assessment of jet lag symptoms ($n = 474$) using 5 mg fast-release melatonin and specific instructions for timing the treatment[44] (examples are shown in Fig. 7). A meta analysis of those studies considered suitable for analysis has been published.[58] The authors concluded that melatonin was indeed effective at alleviating jet lag. There is a need to explore the limitations of the treatment and to make further comparisons with for example, benzodiazepine hypnotics and caffeine.

Success using melatonin to adapt to night shift has proved to be inconsistent.[54,59] Field studies were usually uncontrolled with respect to confounding variables such as light exposure. The first report used early morning melatonin administration, designed to phase delay, and significantly improved day sleep duration and quality and night shift alertness in a 7 day rotating shift system.[60] In another study (also a 7 day rotation) melatonin improved the synchrony between endogenous circadian rhythms and daytime sleep.[61] Some later studies have shown no significant effects. However, recent simulated and carefully controlled shiftwork studies have shown objective benefits of melatonin treatment.[53,59,62]

In situations (fast rotation) where adaptation is undesirable melatonin may be used in other ways to facilitate 'out of phase' sleep. Taken in the late afternoon just before a period of recumbency and very dim light, it is clearly effective at facilitating sleep.[26,27] Shiftworkers complain that it is difficult to sleep prior to nightwork in the evening, and thereby reduce sleep deprivation. Use of melatonin in this context might well be helpful. Secondly, melatonin can facilitate daytime sleep in the short-term without necessarily shifting circadian phase (although whether or not a 'dead zone' of the PRC to melatonin exists remains to be determined). It is a question of considerable importance whether the use of melatonin is accompanied by consistent changes in work-related performance. However, melatonin clearly shows promise in the context of shiftwork.

Therapeutic benefits in the blind

There is no doubt that melatonin treatment improves sleep in blind subjects suffering from non-24 h sleep–wake disorder.[38,42,44,47] It is probably the treatment of choice in this situation, and may in future be combined with behavioural therapy with regard to reinforcing the treatment by appropriate behaviour, e.g. regular bedtime and

structured daytime activities. In principle entrainment of all circadian rhythms is desirable for optimising the treatment effects. However, sleep improvement has been seen in both entrained and non-entrained individuals.[38,42,44] In one case report, a subject taking melatonin (5 mg daily at bedtime) for more than 10 years showed no evidence of entrainment of endogenous melatonin, cortisol or cBT, but his subjective sleep has been consistently stabilised to 24 h during this time. Moreover, he showed no evidence of any deleterious effects of long-term treatment after 10 years.[44]

A problem may arise if a subject's τ is shortened rather than entrained to 24 h, since this will lengthen the period in which he/she is in a poor sleep phase (but also the period of good sleep).[38,46] The worst outcome is probably synchronisation to 24 h but with an abnormal phase, for example the peak of endogenous melatonin occurring persistently during the daytime. This phenomenon has not so far been reported in blind subjects treated with melatonin. To date there are no reports of subjects developing tolerance to treatment. However non-24 h sleep–wake disorder of the blind is a lifetime problem requiring lifetime treatment. It is essential therefore that long-term safety of melatonin is evaluated and the lowest possible dose used.

Elderly

Age-related changes in the human circadian system are well documented. The most commonly described characteristics include reduced amplitude and advanced timing of melatonin, cortisol and cBT rhythm.[63–65] The causes of these changes are less well known and are likely to be a combination of endogenous and exogenous factors. Ageing of the retina, the SCN oscillator, the SCN afferent and efferent neural connections or the downstream target nuclei or glands such as the pineal gland are possible endogenous factors,[65] while changes in environmental light exposure such as reduced daytime illumination or changes in behaviour including early morning awakening or daytime napping are some exogenous factors. Age-related sleep changes: increased sleep latency, reduced sleep efficiency, increased night awakenings, increase in early morning awakenings and difficulty falling asleep again (review[66]) may in part be associated with the age-related changes in the circadian system. This possible relationship has justified the assessment of exogenous melatonin in the treatment of insomnia in the elderly.

The decline in melatonin production with ageing has led to the so-called 'melatonin replacement' hypothesis and melatonin replacement studies have been conducted in older people with insomnia (reviews[13,67]). Melatonin in a range of doses (0.5–6 mg) in different formulations (fast and slow release) given at different times before bedtime (0.5–2 h) has been shown to improve some subjective and objective sleep parameters (measured by actigraphy or polysomnography) in some studies, but conflicting data exist.[13,67] As few of these studies have performed circadian phase assessments, it is not clear whether melatonin's beneficial effect is a result of its soporific or phase shifting effect or both.

Delayed sleep phase syndrome

The ability of exogenous melatonin to phase advance circadian rhythms suggests that it will be effective in the treatment of instrinsic DSPS. In the first placebo controlled crossover study, melatonin (5 mg fast release) was given at 22:00 h (5 h before sleep onset) to eight men with DSPS.[68] Compared to placebo, melatonin advanced sleep onset and wake time ($P < 0.01$). Later studies using 5 mg melatonin have agreed with the first report.[69–71] Nagtegaal et al.[70] demonstrated beneficial effects of melatonin in 25 DSPS patients when melatonin (5 mg) was given earlier (5 h before melatonin onset $\cong$ 7 h before sleep onset). Lower melatonin doses (0.3–1.0 mg) at 1, 3 and 5 h before sleep onset have also been assessed.[72]

In the above studies melatonin was given at the same clock time for 2–6 weeks. A more effective treatment regimen may be to 'stagger' the timing of melatonin administration in order to utilise the phase shifting effect of each melatonin dose. This protocol has been successfully tried in a single blind subject with delayed circadian rhythms (peak time of 6-sulphatoxymelatonin at 14 h 18 min). The first dose of melatonin was administered at 02:00 h (CT9) and then given an hour earlier each day for 5 days after which the time of administration was held constant at 22:00 h for 23 days. This melatonin dosing schedule significantly advanced the onset of sleep, delayed wake up time, increased sleep duration and reduced daytime napping compared to a similar placebo dosing schedule.[73] More studies of this nature are required to determine the optimum dosing schedules (set or staggered) for phase shifting.

Future

There is no doubt that melatonin has chronobiotic properties, as well as the ability to induce transient sleepiness or sleep. Very few reports of deleterious effects exist, however the vast majority of subjects have been normal healthy volunteers and experimenters use rigorous exclusion criteria. The safety of melatonin in long-term use has still not been evaluated. Little is known of possible drug interactions with melatonin. In virtually all of the applications described here the dose, formulation, timing and duration of treatment require optimisation. Most progress has been made with these factors in studies of blind subjects and hopefully a consensus will be reached in the near future. It is likely in view of the individual pharmacokinetic differences that treatment will have to be adjusted on an individual basis in order to use the lowest effective dose.

Although melatonin appears to be well tolerated and an effective treatment for a number of sleep disorders related to circadian rhythm disturbance, it is possible that more effective melatonin analogues will emerge, with proper safety and efficacy assessments. In the meantime many countries (but not the USA) regard it as a drug requiring registration. A priority is to make melatonin available on prescription as a registered medication in these countries.

Practice points

- Sleep disorder which is related to underlying circadian rhythm disorder is probably often not identified and consequently inappropriately treated: diagnosis by actigraphy may be of use.
- Melatonin timing measured in saliva or plasma, or 6-sulphatoxymelatonin in urine provides the most accurate but labour intensive assessment of circadian timing.
- Treatment with melatonin for circadian rhythm disorders should be timed to maximise phase shifting and soporific effects.
- Use the lowest effective dose.
- Use a licensed preparation with guaranteed purity.
- Be aware that no long-term safety data exists.

Research agenda

- Optimise dose, timing and formulation of melatonin for all applications.
- Construct a single dose PRC for melatonin in free-running conditions.
- Assess power of combined melatonin, and light in sighted individuals.
- Assess power of combined melatonin and non-photic zeitgebers in blind individuals.
- Develop a rapid simple and cheap method for assessing circadian timing.
- Produce advice for clinicians on diagnosis and treatment of circadian rhythm disorder.

Acknowledgements

This review was written during the tenure of grants from the Health and Safety Executive (UK), the Institute of Petroleum (UK), the Antarctic Funding Initiative, the BBSRC, the European Union Framework 5 (QLK6-CT-2000-00499) and the National Grid plc (UK).

References

1. Arendt J. *Melatonin and the mammalian pineal gland*. London: Chapman & Hall 1995.
2. Brainard GC, Hanifin JP, Greeson JM et al. Action spectrum for melatonin regulation in humans: evidence for a novel circadian photoreceptor. *J Neurosci* 2001; **21**: 6405—6412.
3. Thapan K, Arendt J, Skene DJ. An action spectrum for melatonin suppression: evidence for a novel non-rod, non-cone photoreceptor system in humans. *J Physiol* 2001; **535**: 261—267.
4. Macchi MM, Bruce JA, Boulos Z et al. Sleep, chronotype and seasonality after pineal resection in humans. *Soc Res Biol Rhythms Abstr* 2002; **9**: 157.
5. Deacon S, English J, Tate J et al. Atenolol facilitates light-induced phase shifts in humans. *Neurosci Lett* 1998; **242**: 53—56.
6. Dijk DJ, Cajochen C. Melatonin and the circadian regulation of sleep initiation, consolidation, structure, and the sleep EEG. *J Biol Rhythms* 1997; **12**: 627—635.
7. Wehr TA, Aeschbach D, Duncan Jr WC. Evidence for a biological dawn and dusk in the human circadian timing system. *J Physiol* 2001; **535**: 937—951.
8. Lockley SW, Skene DJ, Tabandeh H et al. Relationship between napping and melatonin in the blind. *J Biol Rhythms* 1997; **12**: 16—25.
9. Strassman RJ, Qualls CR, Lisansky EJ et al. Elevated rectal temperature produced by all-night bright light is reversed by

*The most important references are denoted by an asterisk.

melatonin infusion in men. *J Appl Physiol* 1991; **71**: 2178—2182.
10. Cagnacci A, Krauchi K, Wirz-Justice A et al. Homeostatic versus circadian effects of melatonin on core body temperature in humans. *J Biol Rhythms* 1997; **12**: 509—517.
11. Arendt J. Biological Rhythms. *Int Med* 1983; **3**: 6—9.
12. Lerner AB, Nordlund JJ. Melatonin: clinical pharmacology. *J Neural Transm Suppl* 1978; : 339—347.
13. Zhdanova IV, Lynch HJ, Wurtman RJ. Melatonin: a sleep-promoting hormone. *Sleep* 1997; **20**: 899—907.
*14. Redman J, Armstrong S, Ng KT. Free-running activity rhythms in the rat: entrainment by melatonin. *Science* 1983; **219**: 1089—1091.
15. Murakami N, Hayafuji C, Sasaki Y et al. Melatonin accelerates the reentrainment of the circadian adrenocortical rhythm in inverted illumination cycle. *Neuroendocrinology* 1983; **36**: 385—391.
16. Arendt J, Borbely AA, Franey C et al. The effects of chronic, small doses of melatonin given in the late afternoon on fatigue in man: a preliminary study. *Neurosci Lett* 1984; **45**: 317—321.
*17. Arendt J, Bojkowski C, Folkard S et al. Some effects of melatonin and the control of its secretion in humans. *Ciba Found Symp* 1985; **117**: 266—283.
18. In: JCLJ Dunlap, PJ Decoursey (eds.) *Chronobiology: biological timekeeping*. Massachusetts: Sinauer Associates, Inc 2003.
*19. Lewy AJ, Ahmed S, Jackson JM et al. Melatonin shifts human circadian rhythms according to a phase-response curve. *Chronobiol Int* 1992; **9**: 380—392.
20. Lewy AJ, Bauer VK, Ahmed S et al. The human phase response curve (PRC) to melatonin is about 12 hours out of phase with the PRC to light. *Chronobiol Int* 1998; **15**: 71—83.
21. Zaidan R, Geoffriau M, Brun J et al. Melatonin is able to influence its secretion in humans: description of a phase-response curve. *Neuroendocrinology* 1994; **60**: 105—112.
22. Middleton B, Arendt J, Stone BM. Complex effects of melatonin on human circadian rhythms in constant dim light. *J Biol Rhythms* 1997; **12**: 467—477.
23. Wirz-Justice A, Werth E, Renz C et al. No evidence for a phase delay in human circadian rhythms after a single morning melatonin administration. *J Pineal Res* 2002; **32**: 1—5.
*24. Deacon S, Arendt J. Melatonin-induced temperature suppression and its acute phase-shifting effects correlate in a dose-dependent manner in humans. *Brain Res* 1995; **688**: 77—85.
25. Dollins AB, Zhdanova IV, Wurtman RJ et al. Effect of inducing nocturnal serum melatonin concentrations in daytime on sleep, mood, body temperature, and performance. *Proc Natl Acad Sci USA* 1994; **91**: 1824—1828.
26. Rajaratnam SM, Dijk DJ, Middleton B et al. Melatonin phase-shifts human circadian rhythms with no evidence of changes in the duration of endogenous melatonin secretion or the 24-hour production of reproductive hormones. *J Clin Endocrinol Metab* 2003; **88**: 4303—4309.
27. Rajaratnam SMW, Dijk D-J, Middleton B et al. Rapid and persistent phase advance of human sleep and biological rhythms by melatonin in a 16-h night/8-h day protocol (Abstract). *Sleep* 2002; **Suppl 25**: A188—A189.
28. Vondrasova-Jelinkova D, Hajek I, Illnerova H. Adjustment of the human melatonin and cortisol rhythms to shortening of the natural summer photoperiod. *Brain Res* 1999; **816**: 249—253.
29. Borbely AA, Tobler I. Sleep regulation: relation to photoperiod, sleep duration, waking activity, and torpor. *Prog Brain Res* 1996; **111**: 343—348.
30. Wehr TA, Moul DE, Barbato G et al. Conservation of photoperiod-responsive mechanisms in humans. *Am J Physiol* 1993; **265**: R846—R857.
31. Wright J, Aldhous M, Franey C et al. The effects of exogenous melatonin on endocrine function in man. *Clin Endocrinol (Oxf)* 1986; **24**: 375—382.
32. Campbell SS, Dawson D, Zulley J. When the human circadian system is caught napping: evidence for endogenous rhythms close to 24 hours. *Sleep* 1993; **16**: 638—640.
33. Czeisler CA, Duffy JF, Shanahan TL et al. Stability, precision, and near-24-hour period of the human circadian pacemaker. *Science* 1999; **284**: 2177—2181.
34. Gibertini M, Graham C, Cook MR. Self-report of circadian type reflects the phase of the melatonin rhythm. *Biol Psychol* 1999; **50**: 19—33.
35. Duffy JF, Rimmer DW, Czeisler CA. Association of intrinsic circadian period with morningness-eveningness, usual wake time, and circadian phase. *Behav Neurosci* 2001; **115**: 895—899.
36. Archer SN, Robilliard DL, Skene DJ et al. length polymorphism in the circadian clock gene Per3 is linked to delayed sleep phase syndrome and extreme diurnal preference. *Sleep* 2003; **26**: 413—415.
37. Skene DJ, Lockley SW, Thapan K et al. Effects of light on human circadian rhythms. *Reprod Nutr Dev* 1999; **39**: 295—304.
38. Hack LM, Lockley SW, Arendt J et al. The effects of low-dose 0.5-mg melatonin on the free-running circadian rhythms of blind subjects. *J Biol Rhythms* 2003; **18**: 420—429.
39. Broadway J, Arendt J, Folkard S. Bright light phase shifts the human melatonin rhythm during the Antarctic winter. *Neurosci Lett* 1987; **79**: 185—189.
40. Kennaway DJ, Van Dorp CF. Free-running rhythms of melatonin, cortisol, electrolytes, and sleep in humans in Antarctica. *Am J Physiol* 1991; **260**: R1137—R1144.
41. Krauchi K, Cajochen C, Mori D et al. Early evening melatonin and S-20098 advance circadian phase and nocturnal regulation of core body temperature. *Am J Physiol* 1997; **272**: R1178—R1188.
42. Arendt J, Aldhous M, Wright J. Synchronisation of a disturbed sleep—wake cycle in a blind man by melatonin treatment. *Lancet* 1988; **1**: 772—773.
43. Aldhous ME, Arendt J. Assessment of melatonin rhythms and the sleep wake cycle in blind subjects. In: J Arendt, P Pevet (eds.) *Advances in pineal research*. 1991; 307—311.
*44. Arendt J, Skene DJ, Middleton B et al. Efficacy of melatonin treatment in jet lag, shift work, and blindness. *J Biol Rhythms* 1997; **12**: 604—617.
45. Sack RL, Lewy AJ, Blood ML et al. Melatonin administration to blind people: phase advances and entrainment. *J Biol Rhythms* 1991; **6**: 249—261.
*46. Lockley SW, Skene DJ, James K et al. Melatonin administration can entrain the free-running circadian system of blind subjects. *J Endocrinol* 2000; **164**: R1—R6.
*47. Sack RL, Brandes RW, Kendall AR et al. Entrainment of free-running circadian rhythms by melatonin in blind people. *N Engl J Med* 2000; **343**: 1070—1077.
48. Lewy AJ, Bauer VK, Hasler BP et al. Capturing the circadian rhythms of free-running blind people with 0.5 mg melatonin. *Brain Res* 2001; **918**: 96—100.
49. Lewy AJ, Emens JS, Bernert RA et al. Eventual entrainment of the human circadian pacemaker by melatonin is independent of the circadian phase of treatment initiation: clinical implications. *J Biol Rhythms* 2004; **19**: 68—75.

50. Mistlberger R, Skene DJ. Social influences on mammalian circadian rhythms: animal and human studies. *Biol Rev* 2004; . in press.
51. Samel A, Wegmann HM, Vejvoda M et al. Influence of melatonin treatment on human circadian rhythmicity before and after a simulated 9-hr time shift. *J Biol Rhythms* 1991; **6**: 235—248.
52. Deacon S, Arendt J. Adapting to phase shifts. II. Effects of melatonin and conflicting light treatment. *Physiol Behav* 1996; **59**: 675—682.
53. Sharkey KM, Eastman CI. Melatonin phase shifts human circadian rhythms in a placebo-controlled simulated night-work study. *Am J Physiol* 2002; **282**: R454—R463.
54. Arendt J, Stone B, Skene DJ. Jet lag and sleep disruption. In: FSE Turek, et al. (eds.) *Principles and practice of sleep medicine*. Philadelphia: Saunders 2004; 591—599. in press.
55. Arendt J, Aldhous M, Marks V. Alleviation of jet lag by melatonin: preliminary results of controlled double blind trial. *Br Med J (Clin Res Ed)* 1986; **292**: 1170.
56. Takahashi T, Sasaki M, Itoh H et al. Melatonin alleviates jet lag symptoms caused by an 11-hour eastward flight. *Psychiatry Clin Neurosci* 2002; **56**: 301—302.
57. Edwards BJ, Atkinson G, Waterhouse J et al. Use of melatonin in recovery from jet-lag following an eastward flight across 10 time-zones. *Ergonomics* 2000; **43**: 1501—1513.
*58. Herxheimer A, Petrie KJ. Melatonin for the prevention and treatment of jet lag (Review). In: The Cochrane database of systematic reviews. The Cochrane Library; 2002.
*59. Burgess HJ, Sharkey KM, Eastman CI. Bright light, dark and melatonin can promote circadian adaptation in night shift workers. *Sleep Med Rev* 2002; **6**: 407—420.
60. Folkard S, Arendt J, Clark M. Can melatonin improve shift workers' tolerance of the night shift? Some preliminary findings. *Chronobiol Int* 1993; **10**: 315—320.
61. Sack RL, Lewy AJ. Melatonin as a chronobiotic: treatment of circadian desynchrony in night workers and the blind. *J Biol Rhythms* 1997; **12**: 595—603.
62. Sharkey KM, Fogg LF, Eastman CI. Effects of melatonin administration on daytime sleep after simulated night shift work. *J Sleep Res* 2001; **10**: 181—192.
63. Iguichi H, Kato KI, Ibayashi H. Age-dependent reduction in serum melatonin concentrations in healthy human subjects. *J Clin Endocrinol Metab* 1982; **55**: 27—29.
64. Duffy JF, Dijk DJ, Klerman EB et al. Later endogenous circadian temperature nadir relative to an earlier wake time in older people. *Am J Physiol* 1998; **275**: R1478—R1487.
65. Skene DJ, Swaab DF. Melatonin rhythmicity: effect of age and Alzheimer's disease. *Exp Gerontol* 2003; **38**: 199—206.
66. Feinsilver SH. Sleep in the elderly. What is normal? *Clin Geriatr Med* 2003; **19**: 177—188. see also p. viii.
67. Olde Rikkert MG, Rigaud AS. Melatonin in elderly patients with insomnia. A systematic review. *Z Gerontol Geriatr* 2001; **34**: 491—497.
68. Dahlitz M, Alvarez B, Vignau J et al. Delayed sleep phase syndrome response to melatonin. *Lancet* 1991; **337**: 1121—1124.
69. Dagan Y, Yovel I, Hallis D et al. Evaluating the role of melatonin in the long-term treatment of delayed sleep phase syndrome (DSPS). *Chronobiol Int* 1998; **15**: 181—190.
*70. Nagtegaal JE, Kerkhof GA, Smits MG et al. Delayed sleep phase syndrome: a placebo-controlled cross-over study on the effects of melatonin administered five hours before the individual dim light melatonin onset. *J Sleep Res* 1998; **7**: 135—143.
71. Kayumov L, Brown G, Jindal R et al. A randomized, double-blind, placebo-controlled crossover study of the effect of exogenous melatonin on delayed sleep phase syndrome. *Psychosom Med* 2001; **63**: 40—48.
72. Kamei Y, Hayakawa T, Urata J et al. Melatonin treatment for circadian rhythm sleep disorders. *Psychiatry Clin Neurosci* 2000; **54**: 381—382.
73. Skene DJ, Lockley SW, Arendt J. Melatonin in circadian sleep disorders in the blind. *Biol Signals Recept* 1999; **8**: 90—95.