Annals of Medicine

ISSN: 0785-3890 (Print) 1365-2060 (Online) Journal homepage: https://www.tandfonline.com/loi/iann20

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Robert L Sack, Alfred J Lewy & Rod J Hughes

To cite this article: Robert L Sack, Alfred J Lewy & Rod J Hughes (1998) Use of melatonin for sleep and circadian rhythm disorders, Annals of Medicine, 30:1, 115-121, DOI: 10.3109/07853899808999393

To link to this article: https://doi.org/10.3109/07853899808999393

Published online: 08 Jul 2009.

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Although not licensed as a drug, melatonin is widely sold as a nutritional supplement in the USA for its purported sleep-promoting and antiageing properties. In this article, we provide some guidelines for its use in sleep disorders medicine. In brief, melatonin appears to promote sleep by producing corrective circadian phase shifts, thereby improving the alignment of the endogenous sleep propensity rhythm with the desired sleep schedule. Melatonin may also have a direct soporific effect, especially when administered during the day. We suggest that the direct soporific action results from the release of accumulated sleep drive by melatonin's attenuation of the circadian alerting signal. Melatonin has not been proven safe by the usual clinical trial criteria, but to date no catastrophes have been related to its use. Also, there is little information about the safety and efficacy of chronic administration.

Key words: insomnia; jet lag; melatonin; shift work; sleep.

Ann Med 1998; 30: 115–121

Status of melatonin

In a strict sense, one cannot 'prescribe' melatonin because its indications for use are not currently established. However, it is classified as a nutritional supplement in the USA and widely marketed in health food stores. Because it is not licensed as a drug, no direct therapeutic claims can be made, but the popular literature and product labelling typically suggest sleep-promoting and antiageing effects. In the UK, it was available for a while but was then withdrawn, which was apparently related to hypothetical safety concerns, not because of any specific report of toxicity. Melatonin itself (its 'composition of matter' – a legal term) cannot be patented because it is a naturally occurring compound; however, several patents concerning methods of use have been issued in the USA and Europe. It remains to be seen whether 'use patents' provide sufficient proprietary incentives to induce a pharmaceutical firm to undergo the costly process necessary to apply for a drug licence; if not, the safety and efficacy of melatonin may never be defined through this formal process.

Even though melatonin is readily available in the USA, its use remains controversial (see recent reviews (1–3)). A recent melatonin fad generated inflated and sometimes outrageous claims which occasionally overshadowed the solid scientific progress in understanding this remarkable hormone. In this article, we provide some guidelines for the clinical application of melatonin to circadian sleep disorders, based upon available research in humans and animals. It should be emphasized that this is not a critical review of the literature. Rather, it is meant to provide some practical recommendations to the practising clinician, given the current state of knowledge. With this goal in mind, the bibliography is selective and limited.

From the Sleep and Mood Disorders Laboratory, Department of Psychiatry, School of Medicine, Oregon Health Sciences University, Portland, OR, USA.

Correspondence: Robert L Sack, MD, Mail Code L-469, Oregon Health Sciences University, Portland, OR 97201, USA. E-mail: sackr@ohsu.edu, Fax: +1 503 4945329.

Doses, pharmacokinetics and formulations

Melatonin has been administered to human research subjects in doses ranging from 0.1 mg to 2000 mg.

This remarkable range of tolerated doses is consistent with the animal literature indicating low toxicity. It should be emphasized that doses above 0.5 mg produce blood levels that are definitely in the pharmacological range (above the usual peak endogenous blood levels).

Oral melatonin formulated in an ordinary gelatin capsule or tablet is absorbed within 30 min (4). It is quickly metabolized in the liver primarily to the water-soluble hydroxy derivative, resulting in a half-life for plasma concentrations of about 45 min. Thus, the typical 3-mg melatonin tablet sold in the USA usually produces a 'spike' in plasma melatonin levels that can be over 50 times the physiological blood concentration, although there are large individual differences. This dose is cleared in about 10 h.

More refined formulations of melatonin have been developed in an attempt to deliver melatonin in ways that will mimic the overnight plasma profile of endogenously produced melatonin. For example, Lee et al (5) developed an oral slow-release formulation that approximates the endogenous profile, although some patients may continue to have elevated levels into the following day. Application of a transmucosal (gingival) patch is a very accurate way to mimic melatonin blood levels, but is not currently available for general use. Lee et al also developed a skin patch (6), but because melatonin is quite lipid soluble, it tends to be trapped in the fatty layers of the dermis, and the transit time across the skin is quite slow. Although it may be highly desirable to mimic the endogenous melatonin profile in studies that seek to understand the function of endogenously secreted melatonin, there are no studies to date that demonstrate an enhanced clinical outcome of one formulation compared to another.

Pharmacological doses of melatonin (above 0.5 mg) may have actions that are different from physiological doses. The mechanisms may involve 'crosstalk' with other receptor systems, such as the GABA inhibitory neurones, which may account for a weak benzodiazepine-like effect. These actions may be of clinical use but cannot be assumed to reflect the function of endogenous melatonin.

Biological actions of melatonin

In order to discuss the rational use of melatonin in clinical practice, it is necessary to review briefly some of its well-established biological actions. Melatonin is a phylogenetically ancient hormone. In vertebrates, it is produced by the pineal gland. In all species, elevated melatonin levels are associated with night-time darkness. In mammals, the nocturnal rise in melatonin secretion is triggered by the endogenous circadian pacemaker in the suprachiasmatic nucleus of the hypothalamus (SCN), but the overall profile is also shaped by the suppressive effects of light. Bright light at dawn and dusk bracket the duration of melatonin secretion, producing a signal that varies according to the time of year (7). Seasonally breeding species such as hamsters and sheep use the duration of melatonin production to regulate annual reproductive cycles. A long duration of melatonin secretion stimulates reproductive physiology and behaviour in sheep (who breed in the fall), but inhibits it in rodents (who breed in the spring) (8). The regulation of seasonal breeding, so well documented in other mammals, appears to be vestigial in humans, perhaps because melatonin receptors are absent from the critical areas of the hypothalamus in humans. Because this is such an important role for melatonin in other species, it has raised concerns that melatonin administration to humans may have adverse effects on reproductive physiology; however, to date none have been observed.

Melatonin may have some role in modulating the circadian time-keeping mechanism in mammals, including humans. Evidence for this role includes the presence of specific melatonin receptors in the SCN (the circadian pacemaker) (9). These receptors provide a critical link for a functional feedback loop whereby circulating melatonin can influence the circadian pacemaker, which in turn controls the timing of its secretion. Furthermore, exogenous melatonin (even in physiological doses) can shift the phase of the circadian pacemaker, both in rodents and humans (see below) (10–12). On the other hand, pinealectomy in either rodents (13) or humans (RL Sack, unpublished observations) does not produce profound changes in circadian rhythms, so that the effects of endogenous melatonin on the circadian system appear to be subtle.

Early observations of melatonin-induced sleepiness (high pharmacological doses), coupled with the finding that melatonin is produced only at night, suggested to early investigators that it might be a 'sleep hormone' (14–16). However, in nocturnal species, melatonin is associated with wake and activity. So while it is possible that melatonin has been recruited as a sleep hormone in diurnal mammals, from a broader biological perspective, melatonin is more accurately considered a 'darkness hormone' rather than a sleep hormone. Clinical trials regarding a soporific action of melatonin are reviewed below.

Sleep-promoting actions

Melatonin may impact sleep by two mechanisms:

1. Melatonin might improve sleep by producing corrective circadian phase shifts, thereby improving the alignment of the endogenous sleep propensity rhythm with the desired sleep schedule. These phase-shifting effects of melatonin are critically

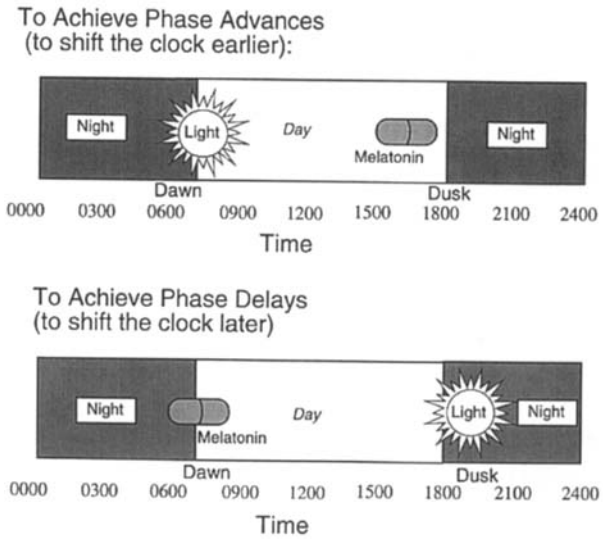

Figure 1. The strategy for using melatonin and light to shift circadian rhythms according the their respective phase response curves (PRCs) shown schematically. As shown in the upper panel, melatonin in the evening (or light in the morning) will shift circadian rhythms earlier (cause a phase advance). As shown in the lower panel, melatonin in the morning (or light in the evening) will shift circadian rhythms later (cause a phase delay). The most critical times for phase shifting in nature are dawn and dusk. Melatonin given in the middle of the night and light exposure in the middle of the day (the so-called 'dead zones' of the PRCs), have minimal phase-shifting effects. (Adapted from (17) with permission.)

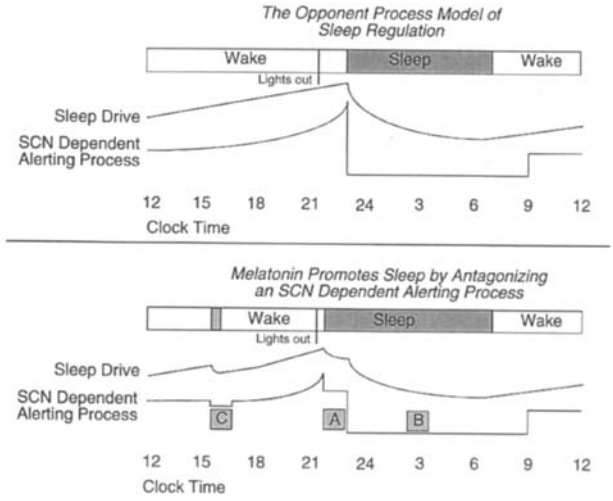

Figure 2. The hypothesized effects of melatonin on the suprachiasmatic nucleus (SCN)-alerting process shown schematically. The upper panel illustrates the dynamics of the opponent process of sleep regulation. According to the model, sleep drive builds up during the waking hours and is discharged at night. However, the build-up of daytime sleep drive is usually unexpressed because it is opposed by an alerting process generated in the SCN. At bedtime, there is a rather sudden transition to sleepiness (called the 'sleep gate') which coincides with the abrupt diminution in the SCN-dependent alerting process. As shown in the lower panel, we have hypothesized that melatonin promotes sleep by attenuating the SCN-dependent alerting process, thereby releasing the build-up in sleep drive. If melatonin is given just prior to bedtime (A), this action will shorten sleep latency. If given in the middle of the night (B), there will be little effect on sleep because sleep drive is in the process of discharging and the alerting process is quiescent (the 'sleep gate' is already open). According to the model, melatonin can promote daytime naps (C) depending on the amount of underlying sleep drive.

dependent on the timing of administration (Fig 1). If given a few hours prior to the onset of endogenous production (for example, the late subjective day), melatonin will shift the circadian pacemaker to an earlier time (cause a phase advance). If given around the time of the melatonin offset (early subjective day), it will shift the circadian pacemaker to a later time (cause a phase delay). If administration occurs within the time of endogenous secretion little, if any, shifting occurs.

2. Melatonin might also improve sleep by attenuating the daytime alerting process generated by the SCN (18) (Fig 2). We postulated that this sleep-promoting effect of melatonin is dependent on the daytime build-up of sleep drive that is normally held in check by a daytime alerting signal. By attenuating this alerting signal, melatonin releases or unmasks sleep propensity (it does not generate it). According to this model, the sleep-promoting effects of melatonin are most robust when administered during the daytime to subjects who have some accumulated 'sleep debt.' During the night, when sleep drive is partially discharged, and the alerting signal from the SCN is quiescent, melatonin may have little effect on sleep. Shochat and colleagues have proposed a similar model (19).

There are several implications of these models that are worth emphasizing. Taking melatonin for its soporific effect may induce circadian phase shifting. Conversely, taking melatonin for a phase-shifting effect may induce sleepiness. Both effects may be desirable, but there are situations when one of these actions may be undesirable. For instance, when administering melatonin in the morning to promote a phase delay, there may be some undesirable daytime drowsiness, although our model predicts minimal soporific effects at this time of day if the individual has had adequate night-time sleep. On the other hand, melatonin taken by a night shift worker to promote daytime sleep may induce an unintended shift in the circadian pacemaker. In any event, it is prudent to keep both actions in mind when offering advice regarding the use of melatonin.

Melatonin as a phase-shifting (clock-resetting) agent

In this section, we review the clinical use of melatonin to reset the phase (timing) of the circadian system.

Phase-shifting effects of melatonin may be useful in treating circadian rhythm sleep disorders. These disorders have a common underlying pathophysiology; namely, a desynchrony between the timing of endogenous circadian rhythms and the timing of the environmental day–night cycle and/or the timing of the desired sleep–wake schedule – in some cases, sleep is desired at an atypical time, eg during the day in night workers. Other examples include 'jet lag,' delayed sleep phase syndrome (DSPS), recurrent insomnia in the totally blind, as well as some other less common sleep disorders. Certain mood disorders, especially winter depression, may also involve circadian rhythm disturbances.

Jet lag is a prototypical circadian rhythm sleep disorder. After rapid travel across time zones, there is a period lasting for several days during which endogenous circadian rhythms are out of phase with local time. Symptoms include daytime sleepiness, night-time insomnia, gastrointestinal disturbances, difficulties in maintaining concentration, and intense fatigue. These symptoms gradually resolve as the internal body clock 'catches up' to local time and circadian harmony is restored.

A more persistent form of circadian desynchrony underlies night shift work maladaptation. Commonly, the night worker is trying to sleep when the clock is promoting wakefulness, and trying to stay alert when the circadian clock is cueing sleep. Sleep bouts are typically short, and a cumulative 'sleep debt' may build so that maintaining night-time alertness is an even greater challenge.

DSPS is another common sleep schedule disorder, and many young people have a tendency towards DSPS even if they do not meet criteria for the syndrome (20). DSPS patients would greatly prefer to stay awake late into the night and wake up at mid-day. This difficulty in conforming to conventional sleep times produces conflicts with employment or school schedules. It has been suggested that DSPS results from a circadian pacemaker with an intrinsic period much longer than the average (eg 25–26 h). This would explain why DSPS patients are always tending to lengthen their day. Although an attractive hypothesis, it has been difficult to prove, and some patients with DSPS (especially adolescents) may have a sleep pattern that may be more related to behavioural issues, such as school avoidance.

Advanced sleep phase syndrome (ASPS) is rare (20), but a tendency for an advanced sleep schedule is quite common in older people who doze off in the evenings and awaken too early in the morning. Totally blind patients often have a non-24-hour sleep cycle that reflects the intrinsic rhythm of the circadian pacemaker, when not entrained by light (21). Periodic insomnia and daytime sleepiness occur when the internal clock is desynchronized from the solar and social 24-hour day.

The general approach to the treatment of circadian sleep disorders is to resynchronize the circadian pacemaker with the desired sleep–wake schedule. It is rarely useful to adjust the hours of sleep to match the phase of the pacemaker, but more often it is necessary to adjust the circadian sleep propensity to match the desired sleep time. Both interventions are aimed at improving the congruence between the circadian signal and the timing of sleep and wake.

Bright-light exposure was the first clinically used phase-shifting technique. In order to reset the pacemaker, light needs to be administered according to the light phase response curve (PRC). Light in the morning shifts the clock earlier (advances the phase), and light in the evening shifts it later (delays the phase). There is a crossover point in the middle of the night between advance and delay responses.

We (22) subsequently documented a PRC for melatonin administration, which is 180 degrees out of phase with the light PRC. This PRC is consistent with the role of melatonin as a darkness signal. Thus, melatonin in the morning shifts the clock later (delays the phase) while melatonin in the evening shifts the clock earlier (advances the phase) (see Fig 1). Because of the complementary shapes of the light and melatonin PRCs, applying the two treatments in a 'push–pull' manner may be synergistic, although this has not been documented experimentally.

The optimal time of day to administer melatonin to produce a phase advance is 4–8 h prior to the onset of endogenous melatonin (at about 17.00 for people on a conventional schedule). The optimal time to produce a phase delay is near the offset of endogenous secretion (at about 07.00). These times may be especially favourable if melatonin administration produces a profile that is continuous with the endogenous profile (23). In the treatment of circadian rhythm sleep disorders, the benefits may not become robust until the rhythms are realigned. Therefore, a sedative agent may be necessary to promote sleep until circadian synchrony has been achieved. Table 1 provides a model for the treatment of jet lag that combines melatonin with the use of a hypnotic drug.

The treatment of DSPS has many similarities to the treatment of jet lag. Table 2 outlines the protocol used in our clinic.

Melatonin as a sleep-promoting agent

A popular and reasonable hypothesis suggests that melatonin might be particularly effective for people with low endogenous levels – a frequent finding in the elderly. However, doses of melatonin designed to restore youthful overnight concentrations did not improve total sleep time in our study of elderly subjects selected for sleep maintenance insomnia (4). Moreover, a trial with a pharmacological dose (10 mg)

Table 1. Patient recommendations for a long eastward flight. Example: a flight from New York to Helsinki.

To advance the body clock

1. On the day of departure, take melatonin at 16.00 local time.
2. On arrival, calculate the time for taking melatonin by adding the number of time zones crossed to 17.00. For example, on arriving in Helsinki (6 time zones from New York), melatonin would ideally be taken at 23.00 local time the first night.
3. On the subsequent 3 or 4 nights, melatonin can be taken an hour or two earlier each day. For example, at 22.00 on day 2, then at 21.00 on day 3, etc, until you feel you have adjusted to local time; then stop taking melatonin.

To prevent sleep deprivation

1. A sleeping pill is recommended when flying overnight to get to sleep at an earlier hour (remember your day is short!) and to allow you to sleep in an uncomfortable airplane seat.
2. Have dinner on the plane, then put on the eye-mask and take your sleeping pill (don't watch the movie!).
3. Sleeping medication (eg Zolpidem) is also helpful for the first 3–5 nights after you arrive at your destination, until your body clock has caught up to local time.
4. With any sleeping pill, alcohol intake should by quite conservative (we think no more than one drink!).

Table 2. Protocol for treating delayed sleep phase syndrome

1. Keep a sleep diary throughout the treatment period.
2. First, concentrate on developing a consistent sleep schedule. Maintain the same sleep times on weekends and week days. Obtain help from family or friends in getting up at the same time each day.
3. Obtain exposure to bright light promptly on awakening. If the sun is up, go outside for at least 30 min (but don't look directly into the sun), or if it is dark, sit in front of a bright-light source (2500 lux light box).
4. Assuming you require about 7.5 h of sleep per night, determine the time for your ideal 'lights out' by subtracting your sleep time from your current wake-up time.
5. Take 0.5–3.0 mg of melatonin 3 h prior to your current bedtime.
6. If you are not sleepy at your targeted bedtime, take a safe and effective sleeping pill (eg Zolpidem sleeping pills are safe and effective on a short-term basis). Even if you do not get to sleep promptly at your targeted bedtime, maintain a consistent wake-up time (you may have to tolerate a certain amount of daytime sleepiness until you establish a good sleep rhythm).
7. After you have adapted to this routine for at least 2 or 3 days, move your whole schedule 15 min earlier (ie the timing of the melatonin dose, your bedtime and your wake-up time). Mark it on a calendar. Continue to move your whole schedule 15 min earlier every 2–3 days. If you are not adapting, hold the schedule until you do.
8. When you are sleeping at the desired time, taper off the sleeping medication at your doctor's direction, but continue to use the light and melatonin to stabilize your daily schedule.
9. Relapses are less likely to occur if you maintain a consistent schedule. If you get off schedule, back up, and repeat the process described above.

Table 3. The use of melatonin for elderly or insomniac patients.

1. Maintain a daily diary for 2 weeks before starting melatonin, and for 2 weeks after starting treatment.
2. Take melatonin about 1 h before turning out the lights.
3. Use the principles of sleep hygiene to promote good sleep.
4. If melatonin appears to be helping, you may continue to take it, but see your doctor if medical problems arise.
5. Remember, there is no information on the long-term effects of chronic melatonin administration.

in a similar elderly population (not necessarily selected for insomnia) also failed to produce robust findings (RL Sack, RJ Hughes, C Singer et al, unpublished observation). On the other hand, within these relatively small groups of subjects, there appeared to be a few specific responders. Other investigators have reported more favourable results (24–26). Currently, a large multicentre trial has begun testing melatonin in elderly demented patients.

Clinical insomnia in younger subjects has been another target for melatonin treatment, but the evidence for efficacy is either negative or meager (27, 28). Because insomnia is such a broad categorization that may involve anxiety, depression or physiological abnormalities, it is possible that a more refined subgroup might respond.

In light of the possibility that some elderly or insomnia patients might respond to the soporific effects of melatonin, we offer the guidelines outlined in Table 3.

Employing the dual action of melatonin

Melatonin is most likely to promote sleep during the daytime hours (2). This includes the late evening at which time melatonin may be able to shorten the latency to sleep onset. Any benefits for night-time sleep, including an increase in total sleep time, or an improvement in sleep continuity, have been modest. In contrast, melatonin given to younger subjects (usually college students) during the day tends to shorten sleep latency and extend the duration of daytime naps (29, 30). Some of these subjects may have had some build-up of 'sleep debt' as judged by the short sleep latencies under the placebo condition.

Because they sleep during the day, night shift workers could be a reasonable target population for melatonin treatment. It could help by both phase-shifting and direct soporific actions. However, making specific recommendations for the treatment of night shift workers is a rather complicated matter. First, there are many shift schedules. For example, there are 1) 'permanent' night shifts (which are not really permanent because workers resume a conventional schedule on their days off); 2) slowly rotating night shifts, involving changing from 'days' to 'evenings' to

'nights' every few weeks; and 3) rapidly rotating night shifts, lasting just a few days. Finally, there are highly irregular working hours; for example, according to regulations in the USA, a train driver can be called to work at any time of the day as long as he has had 8 h off since his last run.

Furthermore, there appears to be a great deal of variation among workers in their tendency to shift their rhythms. Our studies involving subjects working a '7–70' shift (seven consecutive 10-hour shifts followed by 10 days off), found that approximately a third of the subjects showed no change in their circadian rhythms after a week of work, and a third showed a complete inversion of their circadian cycle (the rest had intermediate responses) (31). Eastman has shown that the amount of light exposure, particularly during the morning commute, may explain much of the variability in phase-shifting response (32).

Perhaps the place to start with the shift worker is to decide whether clock resetting is desirable or not. On a rapidly rotating shift, it may be better to maintain a stable conventional circadian phase. If circadian shifting occurs, it means that the individual must reverse the process on his/her days off. On the other hand, when longer runs of night work are involved, facilitating circadian adaptation may be well worth it. In summary, melatonin may be inadvisable for night workers who work for just two to three nights in a row. If the run is five to seven nights, a trial of melatonin might be tried.

If phase shifting is desired, it is usually best to aim for a delay, because this direction is consistent with the natural tendency of the clock. For example, if a night worker goes to bed soon after getting off work (eg 08.30), a dose of melatonin at this hour would be predicted to facilitate an adaptive phase delay. Also, as explained above, it might counteract the alerting signal from the circadian pacemaker, permitting longer or better daytime sleep. Short-term use of a sedative hypnotic could be considered in some situations.

Safety issues

As mentioned above, the standard clinical trial methodologies used by the Food and Drug Administration (FDA) for judging the safety of a drug have not been applied to melatonin. Therefore, judgments must be made based on unsystematic observations. Huge doses have been administered to humans and animals without toxic effects. Also, individuals in the USA have taken melatonin nightly for months or even years without apparent adverse effects. Because of the known effects of melatonin in seasonally breeding species, concerns have been raised about possible reproductive effects in humans, but most studies have shown little or no effect on reproductive hormones. More recently, melatonin-mediated vasoconstriction of the tail artery of the rat has been reported (33), which raises questions regarding possible adverse vascular effects in humans. Although there is no systematic surveillance system in place, there have been no reports of proven toxicity. Table 4 suggests a statement that might be made to a patient regarding issues of safety.

Table 4. Is melatonin safe?

1. Melatonin
   - has not been approved as a drug (by the FDA).
   - is officially considered as a nutritional supplement (in the USA).
2. No serious adverse effects from taking it are known, but it is always possible that these will become known in the future.
3. Information regarding the safety of long-term use (weeks to months) is especially lacking.
4. We cannot officially prescribe melatonin (in the USA). We can recommend its use, and advise you about taking it. If you feel at all uncomfortable taking a substance that has not been rigorously tested for safety and efficacy (by the FDA), you should not take it.

Conclusions

Although melatonin is not approved as a drug, it is widely used in the USA for purported medicinal properties. It remains to be seen whether its status will change in the USA, and whether it will become available in other countries. Meanwhile, physicians can advise patients on its biological actions, appropriate uses and potential risks based on the available research. In regard to sleep and circadian rhythms, the research is quite extensive, and although controversies continue, a consensus on basic issues is building up. Finally, the recommendations in this paper should be considered interim as our ideas on the uses of melatonin continue to be refined (see for example (23)).

This work has been supported by a NIH grant AG 10794.

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