Melatonin: Countering Chaotic Time Cues

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Last year melatonin was 60 years old, or at least its discovery was 60 years ago. The molecule itself may well be almost as old as life itself. So it is time to take yet another perspective on our understanding of its functions, effects and clinical uses. This is not a formal review—there is already a multitude of systematic reviews, narrative reviews, meta-analyses and even reviews of reviews. In view of the extraordinary variety of effects attributed to melatonin in the last 25 years, it is more of an attempt to sort out some areas where a consensus opinion exists, and where placebo controlled, randomized, clinical trials have confirmed early observations on therapeutic uses. The current upsurge of concern about the multiple health problems associated with disturbed circadian rhythms has generated interest in related therapeutic interventions, of which melatonin is one. The present text will consider the physiological role of endogenous melatonin, and the mostly pharmacological effects of exogenous treatment, on the assumption that normal circulating concentrations represent endogenous pineal production. It will concentrate mainly on the most researched, and accepted area of therapeutic use and potential use of melatonin—its undoubted ability to realign circadian rhythms and sleep—since this is the author’s bias. It will touch briefly upon some other systems with prominent rhythmic attributes including certain cancers, the cardiovascular system, the entero-insular axis and metabolism together with the use of melatonin to assess circadian status. Many of the ills of the developed world relate to deranged rhythms—and everything is rhythmic unless proved otherwise.

Keywords: melatonin, circadian, seasonal, health, sleep, light, desynchrony

BACKGROUND

The essential physiological role of the pineal hormone melatonin is to provide information on photoperiod (day length) for the organization of seasonal physiology (1). It does not appear to have an essential function in the circadian system but has clear modulatory effects. These functions depend primarily upon G-protein linked membrane receptors MT1 and MT2 (2, 3). It may also be concerned with periodicities other than circadian and seasonal but as yet this is an emerging field (4–6). Its profile of secretion reflects the length of the scotoperiod (night). Even humans with ubiquitous artificial light, can show this change in suitable conditions (7). It was originally called a photo-neuroendocrine transducer molecule and subsequently, informally, a darkness hormone. Most if not all vertebrate photoperiodic species depend on this signal to time seasonal breeding (1), but see (8).

Melatonin is synthesized from tryptophan via 5-hydroxytryptophan and 5-hydroxytryptamine (serotonin). Then N-acetylation of serotonin by N-acetyl transferase (arylalkylamine N-acetyl

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transferase, AA-NAT) to N-acetylserotonin (NAT) and O-
methylation by acetylserotonin O-methyltransferase (ASMT),
[previously known as hydroxyindole-O-methyltransferase
(HIOMT)] to melatonin (N-acetyl-5-methoxytryptamine).
A major increase (7–150 fold) in the activity of AA-NAT at
night is usually rate limiting in melatonin production. The
rhythm of production is endogenous, being generated by clock
genes in the suprachiasmatic nuclei (SCN), the major central
rhythm-generating system or “clock” in mammals (9, 10). The
rhythm, as for the circadian system in general, is synchronized
to 24 h primarily by the light–dark cycle acting via the retina and
the retinohypothalamic projection to the SCN (9).

Light of suitable intensity and spectral composition can
phase shift and entrain circadian rhythms. Light also suppresses
melatonin production at night (11). The amount of light required
for suppression varies from species to species, with time of night,
with spectral composition and with previous light exposure. In
humans, ∼2,000 lux full spectrum light (domestic light is around
50 to 500 lux) is required for complete suppression at night.
However, much lower intensities will partially suppress and shift
the rhythm (12, 13). A non-image forming photoreceptor system
of light sensitive retinal ganglion cells is implicated in these
effects, with a pivotal role of the photopigment melanopsin,
although in normal circumstances input from rods and cones
is also used (14, 15). In humans maximum suppression and
phase shifting for equal numbers of photons is given by blue
light (460–480 nm).

In humans melatonin is metabolized, ∼70% to
6-sulphatoxy melatonin (aMT6s), primarily within the liver,
by 6-hydroxylation, followed by sulfate conjugation (with
some species variations). A number of minor metabolites
are also formed, including the glucuronide conjugate.
N1-acetyl-N2-formyl-5-methoxykynuramine and N1-acetyl-
5-methoxy-kynuramine, were initially reported as brain
metabolites (1, 16) but have proved difficult to detect in plasma
or urine except after administration of exogenous melatonin
(17). Exogenous oral fast release or intravenous melatonin has
a short metabolic half-life (20 to 60 min, depending on author
and species), with a large hepatic first pass effect and a biphasic
elimination pattern (18). Slow release/prolonged release/surge
sustained preparations are of course designed to extend the
time of high circulating melatonin [e.g., (19)]. It has low
bioavailability in general although transmucosal administration
increases bioavailability (20). A critical feature of exogenous
melatonin with regard to its clinical uses is its very low toxicity
and lack of addictive properties (21, 22).

**Source of Endogenous Melatonin**
The pineal gland is the source of the vast majority of circulating
melatonin in mammals [e.g., (23–25)]. Its synthesis and presence
has been described in a large number of other structures, but
they do not appear to contribute significantly to blood
levels in, for example, humans and rodents, except following
specific manipulations of synthesis such as provision of excess
precursor (26, 27). Pinealectomy leads to loss of the rhythm
and usually undetectable amounts of circulating melatonin in
mammals although with high sensitivity assays traces may
be found. This is curious in view of reported non-pineal
melatonin synthesis, sometimes in very large amounts, and
the highly lipophilic/amphipathic nature of the molecule which
penetrates all compartments rapidly (28, 29). Superior cervical
ganglionectomy (derervation of the pineal) also abolishes the
rhythm (30). Retinal melatonin is of major interest [e.g., (31, 32)]
but beyond the scope of this text.

Non-pineal melatonin has been considered to act locally (29).
Local effects have been invoked with regard to metabolism,
immune function, gut function, inflammation, membrane
fluidity, mitochondrial function, apoptosis (both stimulation and
inhibition), free radical scavenging, direct anti-oxidant activity,
influence on anti-oxidant enzymes, redox status, radioprotection,
and others (33). Protective therapeutic effects are reported with
regard to many various systems but notably neural, oncological
and cardiovascular. Some of these effects are thought not to
require receptor signaling, although melatonin receptors are now
found widely distributed.

Very recently it has been demonstrated that in the mouse
brain melatonin is exclusively synthesized in the mitochondrial
matrix. It is released to the cytoplasm, thereby activating a
mitochondrial MT1 signal-transduction pathway which inhibits
stress-mediated cytochrome c release and caspase activation:
these are preludes to cell death and inflammation. This is a
new mechanism whereby locally synthesized melatonin protects
against neurodegeneration. It is referred to as automitocrine
signaling (34). Another recent addition to our understanding
is the observation that a gut bacterium, Enterobacter aerogenes,
expresses an endogenous circadian clock that is responsive to
signals from the host’s circadian system, the hormone melatonin,
and changes in temperature. This establishes a prospective link
between melatonin as a peripheral circadian zeitgeber (time cue),
and the gut (35).

Peripherally administered exogenous melatonin (sometimes
in very high pharmacological doses) can presumably access the
various structures involved in local effects even though the non-
 pineal endogenously synthesized melatonin does not apparently
generate the gut. The gut is reported to contain several 100 fold more
melatonin than the pineal gland, but does not contribute to the
circulating rhythm of melatonin. It is said to sustain the (very
low) day time plasma levels (27). Although melatonin is present
in some foodstuffs (36), in the authors experience it is hard to
show an increase in plasma melatonin after a normal meal. This
area has been extensively reviewed by others and will also feature
in this volume.

In principle the established role of melatonin in rhythmic
function is not necessarily incompatible with the use of high
doses for ‘protective’ effects. Unless desensitization of the
melatonin membrane receptors occurs as a result of continuous
high circulating concentrations (37, 38) and compromises
functions responsive to low levels of melatonin such as sleep and
circadian phase.

**Melatonin Physiology**
**Seasonal Rhythms**
A truly distinct physiological role for melatonin was initially
indicated by the fact that pinealectomy or ganglionectomy (which
abolished the rhythm of circulating melatonin) abolished the ability of photoperiodic mammals to time seasonal physiology according to the day length (with very rare exceptions) (39, 40). Melatonin secretion, long in long nights, short in short nights provided the information, via photoneurotransduction, to body physiology for the organization and timing of seasonally rhythmic functions such as reproduction and coat growth. Replacement of the endogenous melatonin signal by long or short profiles of exogenous melatonin at the same plasma concentration as the endogenous signal was equipotent with day length for control of seasonal timing. The downstream events have now been investigated in considerable detail [e.g., (41, 42)] and melatonin treatment to shift the timing of seasonal breeding in domestic species such as sheep, mink, and goats to maximize profit is now commercialized (43).

Humans have residual seasonality as evidenced by numerous physiological variables, and particularly by the existence of seasonal affective disorder and its treatment by suitable light exposure (and on occasion by melatonin as a chronobiotic) (44, 45). So for the therapeutic use of melatonin in humans it should never be forgotten that this hormone has profound effects on animal seasonal functions. The evidence for anti- gonadotrophic effects of high amounts in humans is quite substantial (46–49), and an influence on pubertal development is possible but not demonstrated. For example photoperiod, via melatonin profile, times puberty in sheep (50), melatonin inhibits LHRRH stimulation of LH in the neonatal rat pituitary (46, 51), and in a case report of successful treatment of delayed puberty in a young woman, her production of melatonin declined dramatically (52). A serious attempt to develop it as a contraceptive was made some 25 years ago (53).

Circadian Rhythms

By contrast it is quite difficult to show major effects of pinealectomy on circadian rhythms and even on sleep. Initial investigations on pinealectomized rats showed little effect on activity rest cycles (54). These have been reinforced by a very recent study, again indicating that removal of the pineal has no effect on rodent sleep (55). However, if animals were subjected to an abrupt phase shift (as in jet lag), they adapted faster to the new schedule without a pineal gland (56, 57). This suggested that the pineal, and by inference melatonin, acted as a brake on abrupt changes of phase, these being undesirable in a natural environment. This possibility is reinforced by the fact that suppression of melatonin production by the beta blocker atenolol leads to faster adaptation to light-induced phase-shifts in humans (58). Ironically therefore whilst exogenous melatonin is used to hasten adaptation, it is possible that a function of endogenous production is to do the opposite.

Further support for a modulatory role in the circadian system is evident from the fact that in constant bright light pinealectomized animals, in comparison to sham operated animals, show more disrupted rhythms in wheel running, general activity, body temperature, and heart rate (54). Several authors have suggested that a function of the pineal and melatonin is to act as a coupling agent with regard to rhythmic systems (“circadian glue”). This would fit with the suggested role of maintaining the status quo (Figure 1). It could also be considered with respect to any effects on other periodicities.

Since melatonin is constantly referred to as the sleep hormone in the media, it is worth stating that it is not essential to sleep although we sleep better when in phase with rhythmic circulating melatonin and the rest of the circadian system (59). It is, to say the least, difficult to study pinealectomized humans before and after pinealectomy. However, this has been done prospectively with pre and post-operative polysomnography, the so-called gold standard for sleep measures. No effects of the missing pineal on sleep were seen (60). This was a small but careful and exceedingly rare study, it merits serious attention. The final comment on melatonin as a “sleep hormone” is that it most certainly is not so in nocturnal rodents—it is a darkness hormone not a sleep hormone.

COUNTERING CHANGES IN TIME CUES

The accumulated knowledge on the deleterious effects of abruptly changing time cues in for example shift work and jet lag [e.g., (61–67)] lead to the suggestion that one function of endogenous melatonin is to protect against abrupt short term changes of phase by maintenance of the circadian status quo.

Effects on Circadian Rhythms

Early work indicated that timed exogenous melatonin treatment, pharmacological in rats, close to, but still usually supra-physiological in humans, could entrain activity rest cycles in rats, shift circadian phase, assessed using endogenous melatonin as a marker rhythm, and synchronize free-running rhythms in humans. For references see (68). The most obvious manifestation in humans is the timing of the sleep-wake cycle. Phase shifts and entrainment after timed low dose melatonin treatment were evident initially in the rhythm of sleep and of melatonin itself and then in the timing of all the circadian rhythms observed.
Arendt Melatonin and Rhythms

**FIGURE 2** | Melatonin phase shifts all measured rhythms in humans. 1.5 mg surge sustained release at 1600 h daily for 8 days, recumbent, <5 lux, 1600–0800 h, evaluated in constant routine. Data derived and redrawn from Rajaratnam et al. (19), Middleton et al. (69), and Vandewalle et al. (71). CR1, 1st constant routine; CR2, 2nd constant routine; TSH, thyroid-stimulating hormone; HRV-SDNN, heart rate variability - standard deviation of the interbeat interval of normal sinus beats.

(19, 69, 70) (Figure 2). Both phase advances and phase delays can be induced dependent on the time of treatment (72) which can be expressed as a Phase Response Curve or PRC. The melatonin PRC is approximately the opposite of that to light pulses and for maximum effect the two treatments can be combined with careful timing (73, 74). If the period of melatonin secretion is considered to be “biological night” then low dose (0.5–5 mg) treatment in the late afternoon will advance circadian phase and sleep (75), whereas treatment in the early ‘biological morning’ will cause phase delays. Thus, it is important to know or predict circadian phase in order to time treatment correctly. The clearest demonstration of entrainment could be seen in free-running blind subjects (76, 77) and in sighted subjects kept in a time free environment (78).

Melatonin clearly has both a direct sleep inducing effect coupled with a circadian phase shift (70). Importantly it was shown to act directly at the level of the suprachiasmatic nucleus (79) to modify its rhythmic activity, amplitude and phase, via G-protein linked membrane receptors now extensively characterized as MT1 and MT2 (MTR1A/Mel1a, Mel1b/MTR1B) (2, 3, 79–81). MT1 was associated with suppression of SCN electrical activity and MT2 with phase shifts, with some redundancy and cooperation between these subtypes. However, a recent report describes a lack of overlap in mouse brain structures showing one or other of these receptors. The authors state that “the expression and distribution of MT2 receptors are much more widespread than previously thought, and there is virtually no correspondence between MT1 and MT2 cellular expression” (82). A third receptor MT1c is not found in mammals but a related G-protein coupled receptor GPR50 has 45% identity in amino-acid sequence with MT1 and MT2 and is thought to be the ortholog of Mel1c in mammals (83). It may have a role in
glucocorticoid receptor signaling with implications for peripheral control of circadian rhythms (84). Melatonin may also directly affect clock genes in the SCN [e.g., (85)].

Others will report in this volume in detail concerning receptors and downstream signaling events. It is just noted here that a recently reported signaling by melatonin receptors in the SCN appears to require G-protein-coupled inwardly rectifying potassium (GIRK) channels: a widely distributed physiological neural communication system (86). The authors propose this as some of the explanation for the variety of reported effects of this hormone in mood and other neurological disorders.

In addition to effects on the central rhythm generating system, melatonin also influences peripheral oscillators for example in the pars tuberalis, the cardiovascular system, the skin, the adrenal (87–90), various primate fetal tissues (91) and possibly the expression of sirtuin 1 (a histone deacetylase) which is thought to enhance circadian amplitudes and may prolong survival (92). Melatonin clearly has the potential to influence all rhythmic function by virtue of its universal distribution, however very recent data indicates a major role for glucocorticoids in entraining/synchronizing peripheral clocks (84). It is clear that melatonin can manipulate the circadian system. It may well be that a combination of melatonin, light and glucocorticoids could provide the most efficient realignment of both centrally generated and peripheral clocks.

**Circadian Desynchrony**

In a natural environment, changes in circadian rhythms occur due to seasonal influences, notably changes in photoperiod leading to shorter or longer melatonin secretion profiles (93). In humans a seasonal effect is more commonly seen as delayed rhythms in winter (94) especially in polar regions with no sunlight for long periods of the year (95). A duration change in melatonin profiles is rarely seen in humans in temperate zones but can be elicited with artificial light/darkness (7). One explanation is that the onset of secretion is delayed in winter, but the subject is required to get up to work in the morning. Thus, the full expression of the profile is curtailed by artificial light suppression both in the evening and in the morning. In the urban environment of today artificial light is everywhere leading to changes in sleep. It is interesting to compare sleep in similar rural communities with and without artificial light. Artificial light clearly impacts the timing and duration of sleep (96).

The abrupt changes in the light dark cycle and consequent desynchrony experienced by shift workers and time zone travelers are now known to be associated with increased risk of accidents, sleep deficits, lowered alertness and performance, gut problems, lowered fertility, perhaps psychiatric problems, and increased risk of major disease such as cancer, diabetes, metabolic syndrome and heart disease (67, 97).

The central pacemaker of the SCN adapts slowly to these abrupt changes and peripheral oscillators adapt at different rates, such that the body is in a state of both internal and external desynchrony (63, 65, 98–103). Melatonin (and other rhythms being driven by the SCN) is slow to adapt, endeavoring to maintain the circadian status quo. It is out of phase during adaptation and may be partly suppressed by sufficient light at night (LAN), e.g., in shift workers, although not all studies concur. This is thought to be a causal factor in the increased risk of, for example, breast cancer by some authors and will be discussed later (97, 104, 105). However, the entire circadian system is disturbed in these circumstances, not just melatonin.

Out of phase rhythms with or without suppressed melatonin may well be involved in the deleterious effects of shift work (63, 104, 106, 107). As yet there is no definitive linkage between a particular degree of melatonin suppression and any deleterious effects. Some people appear to lead perfectly normal lives with very low or even undetectable melatonin. But there is no long term information on disease risk in these low melatonin secretors. Certainly desynchrony will be one cause of disordered sleep, since we sleep better when in an appropriate phase relationship with the melatonin rhythm. But when the entire circadian system is dysregulated numerous other effects and potential causes can be invoked.

**SLEEP**

Melatonin itself and its agonists have been developed primarily to treat sleep disturbance (108) but with currently expanding possibilities for clinical therapeutics. Its immediate effects on sleep were initially investigated long ago, first by Aaron Lerner who identified melatonin. Its immediate effects on sleepiness/sleep are accomplished by a dose-dependent lowering of core body temperature in near physiological doses (75, 109), and this has been invoked as part of the mechanism of action. This phenomenon has been linked to sleep induction in a series of careful trials (110, 111). Melatonin has clear, time-dependent direct (soporific) and phase shifting effects on human sleep in near physiological/low pharmacological doses (70, 112) (see Figure 3). Its rhythm is closely associated with the timing of sleep and sleep propensity, and inversely with that of core temperature (113).

When treatment with melatonin is related to the so-called circadian rhythm sleep disorders (CRSDs) it is a logical development exploiting both the direct and phase shifting properties (68). CRSDs include delayed sleep phase, advanced sleep phase, free-running sleep, and the sleep detriments of jet lag and shift work. Although the endogenous central pacemaker has a major role in timing sleep, humans exercise choice according to desire or necessity, as to when they try to sleep. This means that sleep rhythms are not a pure manifestation of the circadian system. True circadian phase shift and/or entrainment requires a demonstration that a marker rhythm such as melatonin, cortisol or core temperature is entrained. If treatment is timed to maximize the phase shifting and direct sleep inducing effects of melatonin it can be very successful, particularly with respect to mistimed sleep.

**Delayed Sleep Phase Syndrome (DSPS)**

Typically a subject reports inability to sleep before 2 to 6 a.m. When not required to maintain their schedule—i.e., weekends, holidays, etc.—they sleep without difficulty, and will awaken spontaneously after a sleep period of normal length. Severe cases of DSPS are relatively common in adults (114). The incidence
of clinically important DSPS in students/adolescents may well be as high as 7%. An early meta-analysis (115) concluded that there was no evidence for efficiency of melatonin in treating secondary sleep disorders and sleep disorders associated with sleep restriction. Sadly they did not specifically select publications which gave treatment at the correct time but they did conclude that DSPS was an area where melatonin could be useful. The British Medical Journal published some “rapid responses” to this publication which were highly critical of the summary and conclusions. Some very careful work has been carried out in adults and children with DSPS, measuring circadian phase and timing treatment to 5 h before melatonin onset for maximum phase advance. Sleep timing was advanced, criteria of general health were improved, there were no later effects on reproductive health and in some cases treatment could eventually be withdrawn. A meta-analysis (116) describes the quality studies in both children and adults published up to 2010 and concludes that melatonin treatment induced an earlier phase (melatonin onset, 1.18 h) reduced sleep latency of 23 min and earlier clock onset of sleep by 0.67 h. Timed melatonin treatment was recommended for DSPS by the American Academy of Sleep Medicine (117). More recent well-controlled trials have strongly supported the use of timed melatonin with or without timed light exposure for DSPS (118, 119). However, by no means all diagnosed DSPS patients have a circadian delay as well as a sleep delay (120).

For Advanced sleep phase syndrome (ASPS), there is little information on melatonin treatment. **Shift Work**

Another common situation with temporarily displaced sleep is that of shift work. There is sparse evidence that melatonin can help day time sleep during real life night shift and night time sleep after return to day work, although anecdotally melatonin is used. An early real life study reported greater day sleep duration after night shift when subjects left work early (6 am, before conflicting bright light) and took melatonin (5 mg) before day sleep (121). A later real life timed study addressed both day and night time sleep and was successful in its carefully timed use of melatonin (3 mg) 1 h before bedtime (122). An increase in sleep duration of 15–20 min was obtained and a reduction in sleepiness at work (subjective measures). In a series of simulation shift work studies Eastman and colleagues have clearly shown that timed melatonin (1.8 mg sustained release) and bright light exposure will partially shift phase, such that day sleep is improved when working nights and subjects rapidly readapt on return to day work (73, 123, 124). Data from real life shift work studies were positive in one review (125) and the American Academy of Sleep Medicine approves its use in shift work sleep disorder (117).

**Jet Lag**

There are now so many reviews of the use of melatonin in jet lag, its dependence on timing and concomitant light exposure that it is pointless to write another here, see for example (98). In summary, successful studies used timed melatonin correctly, unsuccessful studies [e.g., (126)] did not. The latter in particular used a cohort who had flown from Norway to New York, stayed 4 days and then were studied on the flight back to Norway. One can predict that their study population was unadapted to New York time, phase shifted from Norwegian time, internally and externally desynchronized, and individually different since individual response to abrupt change of time cues is variable. Their lack of useful effect is not surprising since this situation was not taken into account.
In 2006 a Cochrane Database review concluded that melatonin was useful for jet lag (127). It is updated regularly. Timed melatonin treatment is recommended for jetlag by the American Academy of Sleep Medicine (128). Advice on how to time melatonin and light exposure can be found in reference (98) and elsewhere.

**Sleep in the Elderly**
Sleep problems in the elderly may be due to many factors one of which may be disturbed circadian rhythms. Prolonged release melatonin “circadin” is registered for use in sleep disorder of the over 55s. From the European Medicines Agency Website: “Circadin was more effective than placebo at improving quality of sleep and the patients’ ability to function normally on the following day. When the results of all three studies were looked at together, 32% of the patients taking Circadin (86 out of 265) reported a significant improvement in symptoms after 3 weeks, compared with 19% of those taking placebo (51 out of 272).” The CHMP decided that, although Circadin has only been shown to have a small effect in a relatively small number of patients, its benefits are greater than its risks, “https://www.ema.europa.eu/en/medicines/human/EPAR/circadin.”

Use of melatonin in the very elderly, particularly suffering from dementia, has been advocated but proved to have adverse effects in some studies (129).

**Sleep in Children**
There has been considerable interest in the pediatric use of melatonin for sleep disorder, initially in children with neurodevelopmental disorders, in spite of the possible adverse effects on reproductive function. A large multi-center RCT has been conducted in the UK— the MENDS study (130). Escalating doses from 0.5 to 12 mg 45 min before bedtime were used. The primary outcome was sleep duration by diaries, and objective measures (actigraphy) were also used. They were able to show (130, 131) 23 min longer sleep and shortened sleep latency by 45 min. Evidently this success has inspired further treatment. Pediatric use of melatonin for sleep problems has covered autism, ADHD and intellectual disability (ID) (132) and now has expanded hugely to more general use. According to a serious UK newspaper- The Guardian- there are safety concerns: Despite the fact it is not licensed for use by any other age group, (other than over 55s) 117,085 people under 18 were given melatonin “off label”—the term used for when a drug is given for an unapproved indication or in an unapproved age group—to aid sleep in the 2017–18 financial year. (https://www.theguardian.com/society/2018/nov/02/rise-in-melatonin-use-to-help-children-sleep-leads-to-safety-warning).

**Non 24 h Sleep Wake Cycle (Irregular Sleep Wake Cycle, Free-Running Sleep-Wake or Non-24)**
This condition is the least numerous of the CRSDs but the most interesting. It is the expression of an individual circadian clock periodicity. Each person has their own periodicity usually slightly longer than 24 h (hence the tendency to delay over the weekend) which manifests itself in the absence of strong time cues, primarily the light dark cycle. Many blind people with no conscious or unconscious light perception cannot properly synchronize to the 24 h day (133–136). In expressing their own periodicity they drift away from normal clock time such that intermittently they will be in “night” phase during the day (e.g., secretion of melatonin, low alertness and performance) and day phase during the night (low melatonin, poor sleep). It has been described as a lifetime’s intermittent jet lag.

Melatonin (usually 0.5–5 mg daily, lower doses than 3 mg are often better) is able to synchronize this non-24 h sleep wake cycle to 24 h in the vast majority of patients (76, 137) (Figure 4). Until a registered melatonin preparation became available in the UK (circadin) (138), patients had to obtain melatonin on a named patient basis. It is prescribed by Moorfields Eye Hospital (premier eye hospital in the UK). Unfortunately the completely blind do not often appear before a specialist, the condition is not correctly diagnosed, and is often treated with straight hypnotics (which do not work). A survey in New Zealand reported very little use of melatonin to correct this cyclic sleep disorder (139).

In 1986 a blind man rang me up, said he had non 24 h sleep wake disorder, and could he have some melatonin? He had seen my jet lag studies and worked it out for himself. After a very successful double blind placebo controlled cross over study [5 mg melatonin, (134)] he took this dose, prescribed on a named patient basis by his GP, for the rest of his life. He died 8 years ago, of prostate cancer at 83 years old, after 24 years use, refusing to lower the dose. We checked his biochemistry and hematology after 10 years treatment and all was normal for age. Since then quite a number of similar studies have found the same synchronizing effect on sleep, and from the year 2000 synchronization of the underlying circadian pacemaker was shown in most, but not all patients. The tendency is to start with very low doses and if necessary increase (or in one

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**FIGURE 4** | Diagram of melatonin-induced entrainment by phase advance of a free-running sleep wake cycle and circadian phase, for example in a blind subject with no conscious or unconscious light perception. Treatment is best initiated in a period of good sleep prior to desired sleep time in the “biological dusk” before onset of melatonin secretion.
publication decrease) the dose until it is effective. We recommend starting treatment about an hour before bedtime when in a ‘good’ sleep phase. Even without full circadian entrainment sleep can be improved.

Non-specific Insomnia
As a treatment for non-specified insomnia melatonin also appears to be quite useful. Some 3,000,000 Americans also used melatonin last year according to the following website (https://nccih.nih.gov/research/statistics/NHIS/2012/natural-products/melatonin), presumably for jet lag or for “poor sleep.” In the case of non-specific “poor sleep” this is likely related in many cases to the fact that our circadian rhythms are frequently not in optimal phase in a “urban normal environment” (140) with insufficient time cues or zeitgebers to maintain optimum circadian phase. In these circumstances most people will delay the circadian system, particularly over the weekend if there is no requirement to get up in the morning. In this way the social need for sleep is in advance of the circadian optimum time and melatonin secretion in particular, and sleep suffers. The discrepancy has been referred to as “social” jet lag (141). Popping a melatonin pill in the evening has a good chance of advancing circadian phase to a more appropriate time and thus better sleep.

Melatonin and Cancer
Animal experiments have shown clearly the increased risk of cancer with abrupt phase shifts (97, 142, 143). In 2006 the World Health Organization in Lyon, France held a week-long meeting in which, on the basis largely of animal experiments, decided that shift work was a probable carcinogen (97, 144). A large proportion of the population of developed countries (15–20%) works shifts and thus this is of major health interest.

An association of the pineal gland with anti-cancer activity has a very long history (145). Early work suggested that the gland contained oncostatic activity initially not specified as melatonin. Important evidence of the association included for example that pinealectomy of rats led to much shorter survival times from DMBA-induced cancer and secondly that exogenous melatonin could substantially increase survival times (146). In the 1970s melatonin treatment (very large doses 80–300 mg pd) to young women was proposed for avoidance (prophylactic) of breast cancer (48, 53), and development proceeded to clinical trials in combination with a progestagen. These trials were not successful. But the subject continued of interest when light at night, thought to suppress melatonin (at least partially) (147–149), was invoked as the reason for an excess of breast cancer in nurses, working rotating long term night shifts (104, 144, 150), and subsequently other shift workers.

There is good reason to consider melatonin firstly as a prophylactic, in the case of suppression by light during night work, secondly to hasten adaptation of the circadian system to abrupt phase shift when this is desirable. Thirdly it has been very extensively researched with regard to its anti-cancer activity in breast cancer and other neoplasms (151, 152). Some of the most convincing data linking physiological levels of melatonin with anti-cancer growth concerns human breast cancer-mouse xenograft studies. In a series of experiments Blask et al. could show the protective effects of exogenous and endogenous melatonin and the deleterious effects of extra light (153–156). The xenograft approach is being applied to other cancers.

Most epidemiology agrees that there is an increased risk of developing various cancers as a function of long term night shift work (97, 150). Melatonin has been used as adjuvant therapy in various cancers for nearly 20 years notably by Lissoni et al. in very advanced cancer [e.g., (157)] with positive effects but not usually significant results. With all the suggestive background, several clinical trials in different cancers using melatonin, usually as an adjunct to conventional treatment, have now been conducted (33)—but not enough. The results are quite positive in several domains- survival time, progression of the disease, reduced toxicity of treatment and in general well-being. An important question is to what extent the effects are due to rhythm optimization and/or improved sleep?

METABOLISM
A substantial early clinical literature exists concerning diurnal and ultradian rhythms in metabolic function [e.g., (158)]. With the application of constant routine technology it became possible to identify endogenously generated (i.e., circadian) rhythms from those derived from the external environment, meal times etc. (159–161). This has now been extended to metabolomics. For example simultaneous evaluation of many metabolites in constant routine has shown that of 132 circulating metabolites nearly half showed a 24 h rhythmicity (162). Following sleep deprivation it was clear that many metabolites desynchronized amongst themselves (163, 164). With sequencing of the human genome, this approach has now devolved to the level of genes (67). Melatonin has been invoked as a supplementary treatment for avoidance or reversal of metabolic syndrome but without substantial evidence of efficacy [e.g., (165)].

The Entero-Insular Axis and Diabetes
The importance of rhythms to the entero-insular axis was also evident early on, with variations in glucose tolerance and insulin sensitivity (166). The subject has been very recently reviewed (161). The circadian, SCN-driven nature of these rhythms is now well established alongside the “masking” effects of mealtimes, meal content and other external inputs (167, 168). Triacylglycerol (TAG) has a particularly marked circadian rhythm in constant routine (167). During both simulated and real shift work, standard meals taken at inappropriate times at night—biological night when melatonin secretion is high—lead to evidence of insulin resistance/glucose intolerance and higher TAG, both risk factors for heart disease (167, 169). This is therefore one possible mechanism underlying the epidemiological data showing higher risk of these major diseases.

Circadian re-adaptation in real shift workers resolves some metabolic risk factors (169) (and see Gibbs M, Hampton SH, Morgan L, Arendt J. Effect of shift schedule on offshore shift workers’ circadian rhythms and health, 2004. http://www.hse.gov.uk/research/rrhtm/rr318.htm). So there is good reason to use the chronobiotic properties of melatonin (and timed light exposure) to manipulate circadian phase. It remains to be
determined to what extent central and peripheral oscillators remain in synchrony/coupled in these circumstances.

Melatonin clearly influences glucose concentrations—pinealectomy leads to increased glucose in nocturnal rats (170). In MT1 and MT2 receptor knockout mice the SCN-driven glucose rhythm is abolished independently of peripheral oscillators in muscle, adipose tissue and liver (171). In humans in one study, the decrease in glucose tolerance from morning to evening was mostly influenced by the endogenous circadian system compared to the sleep-wake cycle. However, in apparent contrast to pinealectomy effects in animals, melatonin administered during day time just prior to a glucose tolerance test in healthy adults clearly impaired glucose tolerance both in the morning and the evening (172, 173), an effect that was dependent on a common gain-of-function variant of the melatonin receptor gene MTNR1B152 (see below). Melatonin may also acutely decrease insulin secretion in cultured human islets (174). Thus, some controversy exists in the literature especially when comparing results in nocturnal rodents with diurnal humans with both beneficial and detrimental effects of melatonin reported. It is intriguing to note that the rare condition ‘familial insulin resistance’ or Rabden-Mendenhall syndrome is associated with pineal hyperplasia (175, 176).

In view of pre-existing associations of the pineal and melatonin with metabolic function the discovery of related MT1 and MT2 receptor variants aroused enormous interest. A common variant in MTNR1B—MTNR1B rs10830963 is associated with increased risk of type 2 diabetes, increased fasting plasma glucose levels and impaired early insulin secretion (177, 178). Moreover, late dinner, associated with elevated melatonin concentrations (as in night shift workers, above), impaired glucose tolerance in “gain of function” MTNR1B risk allele carriers but not in non-carriers. These data suggest that circulating melatonin is related to the development of Type 2 Diabetes, in a deleterious sense. Of course sleep restriction is also associated with impaired glucose tolerance, increased risk of metabolic syndrome and/or diabetes (179, 180). So that the usefulness of melatonin to address sleep problems may well increase risk of metabolic abnormalities. Some controversies have arisen and have been reviewed (181). The question is not solved.

CARDIOVASCULAR SYSTEM

Rhythmicity is a cardinal feature of the cardiovascular system, with demonstrable involvement of the SCN (182). Considerable attention has been directed at research into the disorders of rhythmic events and the timing of pharmacological interventions e.g., for elevated blood pressure (183). Timing of treatment clinically with anti-hypertensive drugs is accepted and current practice (184). Does melatonin influence the cardiovascular system? A recent review gives a positive report (185) with regard to several cardiovascular effects. In a controlled experiment melatonin was able to shift heart rate variability in company with the major circadian rhythms of cortisol, core body temperature and TSH (71). Evidently this corresponds to an effect on the central circadian clock.

There is certainly some good evidence that melatonin can lower blood pressure at night in patients with essential hypertension and/or metabolic syndrome (186, 187). Possibly the accompanying increased day night amplitude of systolic and diastolic rhythms was equally important and indicative of strengthened function of the SCN. The mechanism involved is not clear. The improved sleep reported in the subjects may well have contributed to the result.

Melatonin has probably had more exposure as a potential cardiovascular protective agent, with respect especially to myocardial ischemia/reperfusion injury. Numerous animal experiments suggest beneficial effects in a meta-analysis, with anti-oxidant effects, free-radical scavenging, anti-apoptosis and/or involvement of MT1 receptor suggested as mechanisms (188). However, a later meta-analysis and experimentation using melatonin in a combination with minocycline and magnesium sulfate did not show efficacy (189). Several clinical trials appear to be ongoing.

USE OF MELATONIN AS A CIRCADIAN “MARKER” RHYTHM, PROVIDING INFORMATION ON THE PHASE AND TIMING OF THE CIRCADIAN SYSTEM FOR BASIC RESEARCH, TIMED TREATMENTS

The rhythmic production of melatonin, normally high during the dark phase in all species studied to date, is linked directly via neural connections to the activity of the central circadian clock or pacemaker in the SCN (9). It was possible to show that the rate limiting synthetic enzyme pineal AA-NAT activity is closely related to the plasma melatonin profile in rats (190), and that the plasma profile is closely related to that of saliva in humans (191). Moreover, the urinary excretion of 6-sulphatoxymelatonin (aMT6s) the major metabolite in rats and humans reflects faithfully the profile of plasma melatonin in humans (192, 193). Thus, the measurable melatonin/aMT6s profiles in plasma, saliva or urine provide a ‘window’ on the clock. The melatonin rhythm has been extensively used to investigate the characteristics of human circadian rhythms. It is considered to be the best circadian marker rhythm, at least for the moment (Figure 5).

The characteristics of melatonin secretion in normal healthy volunteers have been studied for many years with increasing technological sophistication. They have been reviewed previously on numerous occasions. Similarly numerous publications describe abnormalities in melatonin secretion related to pathology. However, what is hardly ever considered is the general circadian status of patients studied. For example if a state of desynchrony exists, then an amplitude reduction in centrally driven and possibly peripheral circadian rhythms is likely (Figure 1) and low melatonin is not a specific symptom but a reflection of rhythm status. Another consideration is whether low (or high) melatonin amplitude is a cause or a consequence of the pathological state.
A change in timing of the rhythm is easier to interpret, not least because there is normally such a vast difference in amplitude between individuals (195). This is probably the feature that has been most exploited clinically— but mostly for research purposes. The complete profile with sampling at hourly intervals or less provides the most information, but the timing of the onset of secretion in the evening in dim light, known as the DLMO (the dim light melatonin onset), is convenient and has been widely used to assess circadian status (196). First it should be noted that a large change in amplitude can look like a change in DLMO, depending on how the calculations are performed. The DLMOFF (dim light melatonin offset) in the morning is also useful as a circadian marker as is the “Synoff”—the time when production ceases (197). Urinary aMT6s provides less resolution, but even with 4 h day time/waketime samples and 8 h/oversleep the calculated acrophase is within 30 min of that derived from hourly sampling (193).

Each of the 3 matrices—plasma, saliva and urine, has advantages and disadvantages. Plasma is ideal and can be done overnight during sleep but requires catheterization and volume of blood loss is important. Saliva is practical but unless the subject is woken frequently for overnight sampling, the onset can easily be missed. Sequential urine samples have lower resolution but can readily be collected and measured by subjects in field studies, include the whole profile (much preferable to an early morning urine) and carried out long term.

For example workers on North Sea oil rigs collected, measured, aliquoted and froze urine continuously for 2–3 weeks whilst on the platform (198, 199). These samples provided a continuous record of circadian adaptation to night shift, or not depending on schedule. Similarly many blind subjects (135) and the crew of an Antarctic ship (200) have collected urine for 48 h at weekly intervals for 6 weeks or more. This approach provides an evolving picture of circadian status. It was particularly important in our work to judge the timing of melatonin treatment to entrain free running rhythms in blind subjects (76) and to find out to what extent particular shift schedules onshore, offshore and in Antarctica lead to desynchrony with associated sleep and metabolic problems (63). Melatonin profiling has been extensively used in research to provide a way of normalizing experimental subjects with diverse angles of entrainment relative to the sleep wake cycle, for comparative purposes.

WHY MEASURE MELATONIN?

In what clinical circumstances is there a need to know circadian status through melatonin measurement? Principally this is to identify desynchrony, delayed, advanced or free-running circadian status. Importantly it enables correct timing of treatment with melatonin and/or light or alternative zeitgebers as chronotherapies for disrupted rhythms, according to the appropriate PRC. Numerous drugs have large diurnal changes in pharmacokinetics which may or may not be circadian in nature...
The important question of timing of drug treatment has become more high profile in the clinic with the individualization of treatment regimes especially for cancer and the melatonin rhythm might well provide an individual circadian marker for timing specification (201).

THE UMBRELLA REVIEW

There are now so many reviews (systematic and narrative) and meta-analyses of the effects of melatonin on human and animal pathology that Posadzki et al. (33) have conducted what they refer to as “An umbrella review” or a “review of reviews” to pinpoint areas where a consensus may exist (Box 1). They identified 195 eligible articles according to their quality criteria, providing a valuable resource for evaluation of the evidence. Listed below and highly simplified are those effects and associations of melatonin in humans for which these authors found significant random effects in quantitative synthesis of eligible meta-analyses. The authors note that there is some overlap between the published meta-analyses which they identify. Furthermore, some of the analysis includes data from prolonged release melatonin circadin (two reviews) and melatonin agonists ramelteon (four reviews), agomelatine (two reviews), and tasimelteon (one review).

The conclusion from this tour de force is that the data supports the notion that endogenous and exogenous melatonin has benefits for health - a conclusion with which most people would agree. However, given the vast number of potential therapeutic uses for this hormone (as opposed to the accepted clinical therapeutic effects of melatonin). Firstly its association with risk of breast cancer and therapeutic intervention therein, is strongly related to disordered rhythms.

CONCLUDING REMARKS

It seems that there are two major schools of research into the clinical therapeutic effects of melatonin. Firstly its association with biological rhythms from cells to organisms, and particularly with the timing and quality of sleep. It acts via well-characterized membrane receptors, which will be considered in depth by others in this volume.

Secondly in the last 25 years the expanding field of protective effects, often considered not to require receptor signaling, has come into being. From a philosophical point of view it would be very satisfying to reconcile these two approaches. It is probably true to say that “everything is rhythmic unless proved otherwise.” If so, melatonin as a rhythm optimizer (synchronization, re-synchronization, entrainment, re-entrainment, coupling, phase and amplitude adjustment, phase and amplitude maintenance, periodicity), could well be invoked to explain many, even most therapeutic protective effects. Or at least a part of these effects.

It has been referred to as “circadian glue” but its influence on rhythms extends to other periodicities. Moreover, its “beneficial” effects on sleep may lead to a multitude of downstream events of therapeutic value. For example reducing the risk of insulin resistance, metabolic syndrome, obesity, diabetes, all of which have been associated with poor and/or insufficient sleep (see text). The association of melatonin with risk of cancer and therapeutic intervention therein, is strongly related to disordered rhythms.

Melatonin is good for human health, particularly via its ability to optimize sleep timing and often duration and quality with a multitude of downstream benefits. It can counter the debilitating effects of modern lifestyles: insufficient circadian time cues especially natural bright light, and exposure to artificial light at unsuitable times—the 24 h society. It is questionable whether or not long term use has deleterious effects and this is particularly important in pediatrics.

Circadian and other rhythm status, and reproductive function, during treatment with very large doses of melatonin needs investigation.

Finally, from personal anecdotal evidence, having taken melatonin in 2–5 mg oral fast release formulation on and off, mostly on, since 1981 after a mastectomy, I know that it does not prevent some of the pathologies associated with old age—osteoarthritis, Type II diabetes, spinal stenosis, uterine cancer. But I am still here!

DATA AVAILABILITY

All relevant data analyzed are included in this manuscript.
AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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Conflict of Interest Statement: JA is director of two companies Stockgrand Ltd and Surrey Assays Ltd which are concerned with measuring melatonin, 6-sulphatoxymelatonin, and other hormones. These companies had no influence on the writing of this text.

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