CNS Spectrums (2014), **19**, 475–478. © Cambridge University Press 2014
doi:10.1017/S1092852914000637

BRAINSTORMS—Clinical Neuroscience Update

Mechanism of action of tasimelteon in non-24 sleep-wake syndrome: treatment for a circadian rhythm disorder in blind patients

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ISSUE:

Many individuals with total blindness can develop a circadian rhythm disorder—called non-24 sleep wake syndrome—because they cannot detect light to resynchronize their sleep–wake cycles. A new melatonin 1 and melatonin 2 agonist tasimelteon improves sleep in these patients, resetting their circadian sleep–wake clocks.

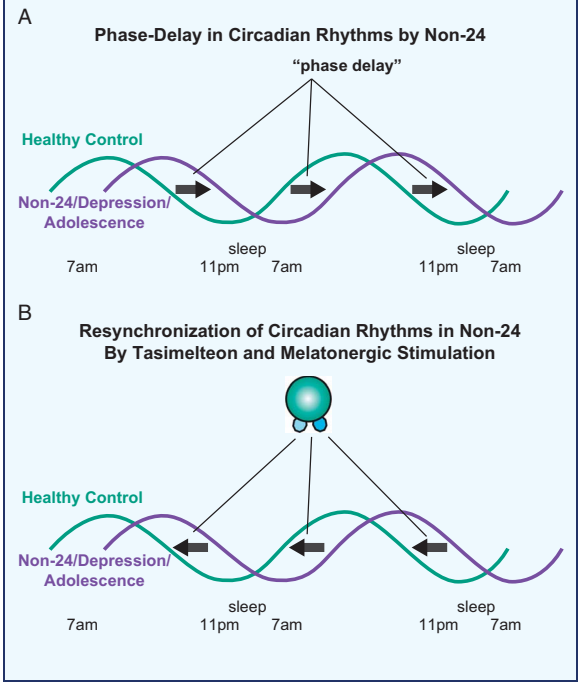
Take-Home Points

- Individuals with blindness lose their ability to synchronize their sleep–wake cycle to light, and many have a "free-running" circadian rhythm greater than 24 hours.
- This leads to a sleep/wake rhythm often delayed to longer than 24 hours in the absence of light synchronization, causing successive delays in sleep–wake times day after day.
- Sleep disturbances similar to "jet lag" may eventually occur, with difficulty in initiating sleep, in awakening, in progressively delayed sleep onset and offset times, and the inability to maintain a stable entrainment to a 24-hour sleep–wake pattern. For those who live in a 24-hour world, this can lead to serious problems in functioning in social environments, especially at work.
- Stimulation of melatonin 1 and 2 receptors with tasimelteon is now proven to improve sleep in such individuals.
- In blind individuals with non-24 sleep wake disorder and who also have depression or anxiety disorders and are not responding well to usual treatments, experience with the antidepressant agent agomelatine, which acts on monoamine as well as melatonin receptors, suggests that it may be necessary to add melatonin agonist actions to monoamine actions for robust antidepressant/anxiolytic effects to occur in such patients.

Non-24 Sleep Wake Disorder and Blindness

The suprachiasmatic nucleus is the brain's pacemaker; it synchronizes circadian rhythms to light during the day and to melatonin during the dark hours (Figure 1A).[1] Many individuals, whether sighted or blind, have an underlying circadian rhythm longer than 24 hours; this includes many normal adolescents and many with major depressive disorder.[1,2] For those who have sight, however, light generally resynchronizes their sleep–wake rhythms every day (Figure 1B).[2] However, for those who have total blindness, light can no longer play the role of daily synchronizer of the sleep–wake cycle, and many people with total blindness have a "free-running" circadian rhythm that is greater than 24 hours (Figure 1A).[3–6] The absence of light synchronization in patients with total blindness

Figure 1. Circadian rhythms occur on a 24-hour cycle, and regulate sleep–wake cycles and many other biological processes. (A) Individuals who are phase-delayed (such as those with depression, or during normal adolescence, or many individuals with total blindness), experience wakefulness that is promoted later in the day. Such individuals tend to sleep later in the morning and go to bed later at night. Individuals with non-24 have a "free running" circadian rhythm delay that fails to resynchronize to light in the morning, and causes the sleep–wake cycle to slip progressively further into the day over time. (B) Light and melatonergic stimulation of MT1/MT2 receptors by tasimelteon (or melatonin) can both resynchronize circadian rhythms. Melatonergic stimulation is now proven effective by tasimelteon, even in totally blind individuals with non-24 sleep wake syndrome.



who have a free-running circadian rhythm greater than 24 hours can lead to successive delays in the sleep–wake cycle that accumulate day after day.[3–6] This can eventually lead to sleep disturbances similar to "jet lag," with difficulty in initiating sleep, in awakening, in progressively delayed sleep onset and offset times, and the inability to maintain a stable entrainment to a 24-hour sleep–wake pattern. This condition is called "non-24 sleep-wake syndrome" (non-24) or "free-running disorder (FRD)."[3–6] Most individuals live in a 24-hour world, so non-24 can lead to serious problems in functioning in social environments, and especially at work.

Some sighted patients have non-24, but it is rare.[5] About 50,000–100,000 patients with total blindness in the U.S. are estimated to have non-24.[7] Thus, many mental health professionals may have patients with total blindness in their practices; they need to become aware of this condition, and screen for non-24 in patients who are totally blind, since there is treatment now available. Furthermore, non-24 sleep wake syndrome that is comorbid with psychiatric disorders may require treatment not only to improve the circadian rhythm disorder, but also to optimize the outcomes of comorbid conditions such as depression and anxiety.

Melatonin Stimulation Can Resynchronize the Sleep–Wake Cycle

Melatonin normally causes resynchronization of circadian rhythms when secreted daily at night and in the dark (Figure 1B).[1,2] In blind patients with non-24, melatonin stimulation can resynchronize their sleep–wake cycle, even in the absence of light detection (Figure 1B).[3–6] This can be done either with melatonin itself[3–6] or with the potent and selective melatonin receptor type 1 and type 2 (MT1/MT2) agonist tasimelteon.[8] Both melatonin and tasimelteon thus induce "non-photic" circadian synchronization (Figure 1B). No studies of the MT1/MT2 agonist ramelteon have been conducted, but this agent could be theoretically effective in non-24; however, ramelteon has relatively low and erratic oral bioavailability that may prevent consistent efficacy.[2] Melatonin itself is not reliably available over the counter in the U.S. in formulations of pharmaceutical grade, but pharmaceutical-grade melatonin is effective in non-24 disorder.[3–6]

Tasimelteon has robust actions in improving sleep efficiency (percentage of total sleep time divided by the total sleep episode) in totally blind patients with non-24.[7] This is not surprising, since previous trials of tasimelteon have also been effective in the treatment of transient insomnia after sleep-time shift, an experimental model of both shift work disorder and of jet lag in sighted individuals.[8] The U.S. Food and Drug Administration (FDA) has now approved tasimelteon (Hetlioz) for the treatment of non-24, and tasimelteon

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is the only approved treatment for this condition, but it is expensive.

A related drug, agomelatine has MT1 and MT2 agonist actions, but also 5HT2C and 5HT2B antagonist actions that appear to be critical for its antidepressant effects.[2,10] Agomelatine is approved for the treatment of depression in many countries, but not in the U.S. There are no published studies of agomelatine, however, in non-24.

Mechanism of Action of Tasimelteon

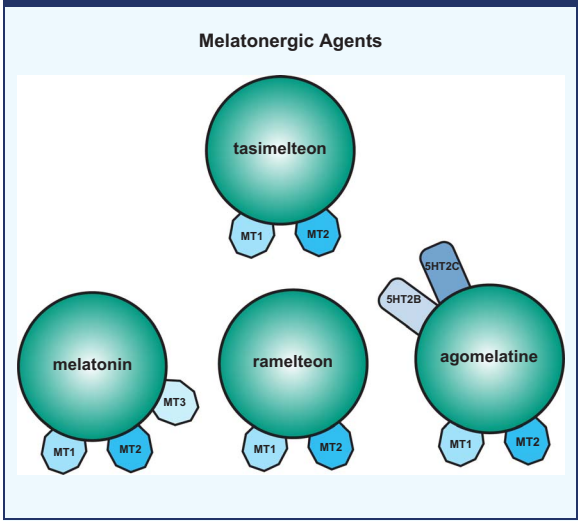
Tasimelteon is an MT2-preferring and MT1 agonist (Figure 2). Theoretically, the phase-shifting and circadian rhythm effects of tasimelteon on the sleep–wake cycle are primarily mediated by MT2 receptors, which entrain phase-shifting and circadian signals in the suprachiasmatic nucleus.[2] Tasimelteon also acts on MT1 receptors. MT1-mediated inhibition of neurons in the suprachiasmatic nucleus could help to promote sleep by decreasing the wake-promoting actions of the circadian clock (or pacemaker) that functions there, perhaps by attenuating the suprachiasmatic nucleus' alerting signals, allowing sleep signals to predominate and thus inducing sleep. Tasimelteon does not act at a third melatonin site, although melatonin itself does (Figure 2).[2] This site, sometimes called the MT3 site, is the enzyme NRH:quinine oxidoreductase 2, which is probably not involved in sleep physiology.[2]

Ramelteon (Figure 2) is an MT1/MT2 agonist marketed for insomnia, and improves sleep onset but not necessarily sleep maintenance. It has the problems of poor oral bioavailability and inconsistent absorption. A sublingual formulation of ramelteon is currently in clinical trials to attempt to avoid these problems. There is no published study of ramelteon in non-24.

Non-24 and Comorbid Psychiatric Disorders

Since non-24 in totally blind individuals is relatively rare, there are no known studies of psychiatric disorders specifically in these individuals. However, since circadian rhythm disorders are commonly associated with depression and anxiety,[2] it would not be surprising if some patients with non-24 developed these comorbid psychiatric conditions as well. It is interesting to note that prior studies of melatonin have generally failed to improve depression, and augmentation studies of melatonin or tasimelteon added to antidepressants in depressed sighted patients without a circadian rhythm disorder but with an inadequate response to their antidepressant have been inconsistently effective in improving depression. Currently, the sublingual formulation of ramelteon is being tested as an augmenting agent for depressed patients with inadequate responses to their antidepressant.

Figure 2. Melatonergic agents. Tasimelteon, which was recently approved for the treatment of non-24, is a potent, selective MT1/MT2 agonist. Melatonin itself acts on MT1 and MT2 receptors, as well as a third site, MT3. Ramelteon is a MT1/MT2 agonist that is approved as a hypnotic. Agomelatine is a MT1/MT2 agonist and a 5HT2C and 5HT2B antagonist approved for major depressive disorder.



For blind patients with non-24 who may have depression or anxiety, and who are not responding adequately to their antidepressant alone, the lessons from the pharmacologic synergy demonstrated for agomelatine[11,12] suggest that adding tasimelteon to such individuals may not only help improve their non-24, but may also help to improve their depression or anxiety disorder. That is, there are numerous examples of the pharmacologic synergy of the 5HT2C antagonist properties of agomelatine with its MT1/MT2 properties.[11,12] This may account for agomelatine's unique therapeutic actions in depression.[10–12] Since some antidepressants have 5HT2C antagonist properties (eg, fluoxetine, mirtazpine, atypical antipsychotics with antidepressant properties, such as quetiapine and olanzapine),[2] it may be useful, in blind patients with depression, to consider augmenting their antidepressant regimen with tasimelteon with the hope that this would help both their non-24

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and their depression. Formal studies of this possibility are certainly warranted.

Conclusion

It is time for mental health professionals to become vigilant to the possibility of non-24 sleep wake syndrome in their patients with total blindness and to become familiar with prescribing the newly approved MT1/MT2 agonist tasimelteon. In addition, it is possible that blind patients with depression who are not responding to their treatment may have their comorbid psychiatric condition improved by the addition of melatonergic stimulation, but this remains to be proven.

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