Drug treatment for circadian rhythm sleep disorders

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Abstract

Medication with drugs that are active in the brain, and therein have an effect on the suprachiasmatic nuclei of the anterior hypothalamus or areas of the posterior thalamus involved in control of sleep and wakefulness, can have either therapeutic or adverse effects on individuals with circadian rhythm sleep disorder. Currently, with a high degree of clinical certainty, there is no generally accepted patient care strategy with any compound. Hypnotic or stimulant medication may be useful in shift work disorder, but their safety issues need attention. Melatonin is effective in the treatment of delayed sleep phase syndrome, jet lag, and free-running type of circadian rhythm sleep disorder. Melatonin receptor agonists and investigational pipeline drugs require more data to judge their clinical efficacy and suitability as treatment for circadian rhythm sleep disorders.

Introduction

Disruption of alignment of circadian rhythms with the sleep-wake cycle, or desynchronization between core body temperature and the remaining circadian rhythms, may result in circadian rhythm sleep disorder. Therefore, medication with drugs that are active in the central nervous system, and therein have an effect on the suprachiasmatic nuclei in particular or other brain areas involved in control of sleep and wakefulness in general, can have either therapeutic or adverse effects on individuals with circadian rhythm sleep disorder. Their therapeutic aim is to resynchronize the circadian rhythms and to correct the misalignment, or to alleviate sleep disturbance through enhancing sleep or sustaining wakefulness (Table 1). Please note that currently, with a high degree of clinical certainty, there is no generally accepted patient care strategy with any compound.

Table 1. Medication for circadian rhythm sleep disorders.

Disorder	Guideline	Option	Experimental
Shift work type	Hypnotics (triazolam, zopiclone). Stimulants (armodafinil, modafinil).		
Jet lag type	Melatonin.	Hypnotics (zopiclone, zolpidem). Stimulants (armodafinil). Ramelteon.	
Delayed sleep phase type	Melatonin.		NR1D1 agonists? CRY1 inhibitors?
Advanced sleep phase type		Lithium, if bipolar disorder. Agomelatine, if depressive disorder.	GSK3B inhibitors? CSNK1D inhibitors? NR1D1 antagonists? CRY2 inhibitors?
Irregular sleep-wake type			CSNK1D inhibitors?
Free-running type	Melatonin.	Tasimelteon.	CSNK1D inhibitors?

Definition:
Guideline = A patient care strategy that reflects a moderate degree of clinical certainty.
Option = A patient care strategy that reflects uncertain clinical use.
Experimental = Compounds identified in basic science that may have relevance and potential for human use.

Hypnotics

Most cells in the suprachiasmatic nuclei are gamma-aminobutyric acidergic neurons, and gamma-aminobutyric acid evokes excitatory responses in a subset of these neurons. Therefore, it is not surprising that hypnotics which act at the benzodiazepine recognition site of gamma-aminobutyric acid, type A, receptors can induce shifts in the phase of circadian rhythms. So-called non-benzodiazepines have a more selective receptor-binding profile as compared with the structurally classical benzodiazepines.

The benzodiazepine triazolam as well as the pharmacologically related non-benzodiazepines zopiclone and zolpidem are effective in reducing sleep onset latency, indicating their potential suitability as treatment for insomnia but not necessarily for circadian rhythm sleep disorders.

Shift work disorder

Concerning shift work disorder the American Academy of Sleep Medicine guides, with a moderate degree of clinical certainty, that triazolam and zopiclone, administered after the night shift, may be indicated to promote or improve daytime sleep among night shift workers.

Jet lag disorder

Concerning jet lag disorder the American Academy of Sleep Medicine guides, with a low degree of clinical certainty, that zopiclone and zolpidem, administered after the flight for 1 day to 4 days before the local bedtime, may be indicated for the treatment of jet lag induced insomnia.

Risks

These hypnotics may have risks that must be weighed prior to use, since their risk-benefit balance for shift workers is not clear. It is of note that triazolam, zopiclone and zolpidem can be abused, and that their usage can lead to dependence. In addition, emergence of residual effects such as carry-over of sedation to the night shift or daytime activities and complex sleep-related behaviours, with potential safety hazards, need to be considered. As with benzodiazepines, the non-benzodiazepine hypnotic compounds are advised to be used for a limited period only.

Stimulants

Armodafinil (Nuvigil; Cephalon, Inc., Frazer, PA, USA) is an enantiopure drug that consists of the active R-enantiomer of the racemic drug modafinil (Provigil). The precise mechanisms of action through which armodafinil or modafinil promote wakefulness are unknown. Armodafinil and modafinil are effective in improving wakefulness, indicating their potential suitability as treatment for excessive sleepiness but not necessarily for circadian rhythm sleep disorders. It is of note that, as compared with placebo, treatment of jet lag disorder with armodafinil at 150 mg per day has resulted in circadian rhythm sleep disorder as an adverse event in 5% of the patients.

Shift work disorder

According to the U.S. Food and Drug Administration, armodafinil and modafinil are indicated to improve wakefulness in adults who are very sleepy due to shift work disorder, obstructive sleep apnoea or narcolepsy. Further, the American Academy of Sleep Medicine guides, with a moderate degree of clinical certainty, that modafinil may be indicated to improve alertness during the night shift for patients with shift work disorder.

Risks

These stimulants may have risks that must be weighed prior to use. It is of note that both armodafinil and modafinil can be abused, and that their usage can lead to dependence. In addition, a range of psychiatric adverse experiences may emerge when patients, with or without a history of mental and behavioural disorders, are being treated with armodafinil or modafinil. Daytime sleep periods after the night shift must not be impaired due to treatment with armodafinil or modafinil in patients with shift work disorder.

Melatonin

Melatonin is a hormone that is excreted primarily from pinealocytes of the pineal gland behind the 3rd ventricle and between the two hemispheres of the brain. Passive excretion is most abundant during the night, however, only on condition that the night is black or dark enough, as light exposure shuts down the synthesis of melatonin.

There is one long-acting melatonin (Circadin; RAD Neurim Pharmaceuticals EEC Limited, Reading, UK) and many short-acting melatonin compounds available by prescription. In addition to these medicinal products, 1 mg short-acting melatonin tablets are sold as dietary supplements.

Delayed sleep phase syndrome

Delayed sleep phase syndrome involves undesirably late bedtimes and arising times, early night insomnia and poor morning alertness, but when there is no insomnia on vacations. Bedtime and arising time on average are 4:00 a.m. and 10:38 a.m. respectively.

Short-acting melatonin at 0.3-6 mg in the evening advances the sleep onset by 42 minutes on average (ranges from 21 to 62 minutes) in delayed sleep phase syndrome, and it is more effective than placebo.

Jet lag disorder

Short-acting melatonin at 0.5-5 mg in the evening alleviates symptoms of jet lag more effectively than placebo.

Free-running disorder

In circadian rhythm sleep disorder, free-running type, sleep and wake times progressively delay each day even in normal living environments. In other words, sleep is not entrained, or synchronized, to the 24-hour day. This circadian rhythm sleep disorder is frequent in blind people, but it may occur in sighted individuals as well.

Short-acting melatonin at 0.3-10 mg in the evening can entrain free-running circadian rhythms of blind individuals that would otherwise drift later each day, and alleviates insomnia and excessive daytime sleepiness.

Ramelteon

Most, if not all, high-affinity melatonin-binding sites represent the G-protein-coupled melatonin receptors, having a wide distribution covering the suprachiasmatic nuclei among others in the central nervous system. Therefore, compounds which bind to and act through these receptors can induce shifts in the phase of circadian rhythms, and if their administration is precisely scheduled, they may also resynchronize the circadian rhythms and regularize the sleep-wake cycle.

Ramelteon (Rozerem; Takeda Pharmaceutical Company Limited, Osaka, Japan) is an orally active, selective agonist for the melatonin MTNR1A and MTNR1B receptors. It is effective in reducing sleep onset latency, indicating its potential suitability as treatment for insomnia but not necessarily for circadian rhythm sleep disorders. Ramelteon is well tolerated, and it does not appear to induce residual drowsiness, rebound insomnia on drug withdrawal, involve abuse potential or dependence. However, it is of note that, as compared with placebo, treatment of jet lag with ramelteon,

independent of the dosage in use, has resulted in worse performance on the immediate memory recall test on day 4. In addition, the European Committee for Medicinal Products for Human Use has issued a negative opinion on the use of ramelteon, due to its unfavourable risk-benefit balance, in the treatment of insomnia.

According to the U.S. Food and Drug Administration, ramelteon is indicated for adults to treat insomnia where the problem is trouble falling asleep. Concerning jet lag disorder on the basis of recent data, ramelteon may be indicated for the treatment of jet lag induced insomnia, if it is administered after the flight for up to 3 days before the local bedtime.

Risks

The selective serotonin reuptake inhibitor fluvoxamine, which is also a strong CYP1A2 inhibitor, increases systemic exposures of ramelteon, and so ramelteon should not be used in combination with fluvoxamine. In addition, due to increased systemic exposures of ramelteon, patients should be closely monitored when ramelteon is co-administered with doxepin or with donepezil. The co-administration with doxepin is of special note here, because the low-dose doxepin administration is actively being studied as an option for treatment of insomnia, since it seems to have efficacy for sleep maintenance insomnia and early morning awakenings.

Tasimelteon

Tasimelteon (VEC-162; developed by Vanda Pharmaceuticals, Inc., Rockville, MD, USA, under license from Bristol-Myers Squibb, New York, NY, USA) is an orally active, selective agonist for the melatonin MTNR1A and MTNR1B receptors. It is effective in reducing sleep onset latency, in improving sleep maintenance, and in resetting the circadian melatonin rhythm. These outcomes indicate its potential suitability as treatment for circadian rhythm sleep disorders. Tasimelteon is well tolerated, and it does not appear to induce next-day residual effects, involve abuse potential or dependence. It seems to be safe in short-term treatment. However, toxicological data are required for assessing its long-term safety.

The U.S. Food and Drug Administration has granted the orphan drug designation status for tasimelteon in non-24-hour sleep-wake disorder, or free-running circadian rhythm sleep disorder, in blind individuals without light perception.

Agomelatine

Agomelatine (Valdoxan/Thymanax; Servier, Suresnes, France) is an orally active, selective agonist for the melatonin MTNR1A and MTNR1B receptors and selective antagonist for the serotonin HTR2C receptor. Its receptor-binding profile may have a unique effect on receptor-coupled signalling processes and downstream signalling pathways indicated not only in mood disorders, but also in circadian rhythm sleep disorders. Agomelatine is suggested to contribute to resynchronization by inducing the sensitization of adenylate cyclase to sustain long enough to support the action of PER1 protein to repress PER2 protein, and subsequently to inhibit monoamine oxidase A activity, thus increasing dopamine release to the prefrontal cortex and the striatum. Agomelatine can restore NREM-REM sleep cycles and increase delta power ratio, and it can advance the phase of circadian rhythms and the sleep-wake cycle. These outcomes indicate its potential suitability as treatment for circadian rhythm sleep disorders.

In clinical practice, however, prescription of agomelatine is not indicated unless the patient's circadian rhythm sleep disorder is co-morbid with depressive disorder.

Lithium

Lithium lengthens in a concentration-dependent manner the free-running period of individual neurons in the suprachiasmatic nucleus, thereby slowing down firing rate rhythms of the principal circadian pacemaker that governs the sleep-wake cycle. Lithium is a direct inhibitor of glycogen synthase kinase-3-beta (GSK3B), and lithium treatment of cells leads to rapid proteasomal degradation of NR1D1 (REV-ERB-alpha) protein and activation of the ARNTL (BMAL1) gene, a key to the molecular circadian clock (see below, Non-clinical compounds).

In clinical practice, however, prescription of lithium is not indicated unless the patient's circadian rhythm sleep disorder is co-morbid with bipolar disorder.

Non-clinical compounds

Please note that the following compounds, or their sophisticated drug delivery formulations, are not in clinical use nor tested in humans so far. They are briefly presented here due to their potential for clinical drug development.

GSK3B inhibitors

GSK3B takes part in regulation of the circadian rhythms, as it phosphorylates and stabilizes NR1D1, a negative component of the circadian clock. In a screen of 1280 pharmacologically active compounds having an effect on the circadian period length, however, small molecule inhibitors of GSK3 consistently caused a short-period phenotype, as did silencing of the GSK3B gene, in contrast to the period lengthening by lithium (see above, Lithium). So, the mechanisms of action by which lithium produces a phase delay in the circadian rhythms are still controversial. It is of note that lithium has a number of targets to act on in addition to GSK3B, and that its therapeutic mechanism may be based on these actions which may or may not involve the circadian pacemaker or the sleep-wake cycle. To sum up, it is currently not clear whether GSK3 or selective GSK3B inhibitors will have a clinically meaningful role in the treatment of circadian rhythm sleep disorders.

CSNK1D inhibitors

Casein kinase 1 epsilon (CSNK1E) and delta (CSNK1D) influence the circadian period. Therefore, their pharmacological inhibitors PF-4800567 and PF-670462, respectively, may serve as a starting point for further optimization to develop compounds having an effect on the circadian period length. In particular, CSNK1D inhibitors that lengthen the circadian period in a phase-specific manner appear to be effective in synchronization of disrupted circadian rhythms. They might be of clinical use in the treatment of circadian rhythm sleep disorders.

NR1D1 agonists/antagonists

Two steps further in understanding the regulation of the circadian rhythms have been taken recently. First, the first non-porphyrin synthetic ligand for NR1D1, GSK4112, has been designed, and it mimics the action of haem acting as agonist. Second, the first NR1D1 antagonist, SR8278, has been designed. GSK4112 is competitive with haem

and profiles as a NR1D1 agonist in cells to inhibit expression of the target gene ARNTL. SR8278 is structurally similar to GSK4112, but it blocks the ability of GSK4112 to enhance the NR1D1-dependent repression of transcription of target genes. Thus, GSK4112 and SR8278 together are unique chemical tools for probing NR1D1 function, and they may serve as a point for initiation of design of NR1D1-based chemical probes with in vivo pharmacological activity as NR1D1 agonists or antagonists. This development may produce spin-offs that are relevant and of subsequent benefit to the treatment of circadian rhythm sleep disorders.

Cryptochrome inhibitors

The development of small-molecule modulators that directly target the core of the circadian clock has been initiated only recently. To identify novel small-molecule modulators by applying a two-step cell-based screening strategy based on E-box-mediated transcriptional activity, i.e. gene regulation by the binding site of transcription factors, more than 1000 drug-like compounds have been tested. Among these, a derivative of 2-ethoxypropanoic acid designated as compound 15 was the most promising candidate in terms of both efficacy and potency, and unbiased pull-down assays verified both cryptochromes 1 and 2 (CRY1 and CRY2), which are the actual repressors of the feedback loops in the core of circadian clocks, as its molecular targets. However, because of these two proteins, CRY2 has the power of balance and opposes the actions of CRY1, selective cryptochrome inhibitors need to be developed.

Further reading

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