CNS SPECTRUMS

CME Review Article

Twisting the night away: a review of the neurobiology, genetics, diagnosis, and treatment of shift work disorder

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Statement of need

Despite the potential long-term consequences of shift work disorder, there is both significant under-recognition and under-treatment of this condition. This suggests that there is a need for improved assessment and management of shift work disorder.

There are competencies that clinicians need to demonstrate in order to have a successful role in improving outcomes for patients with shift work disorder:

- Provide early identification and diagnose of shift work disorder
- Educate patients about the dangers of altered sleep/wake cycles and practical sleep hygiene techniques for shift workers
- Apply evidence-based guidelines in the treatment of shift work disorder, including both pharmacological and nonpharmacological strategies

To help address these professional practice gaps and improve outcomes for patients with shift work disorder, quality improvement efforts need to provide education regarding (1) application of evidence-based practice guidelines to the accurate identification and diagnosis of shift work disorder, (2) encouraging clinicians to talk with their patients about the consequences of disturbed sleep/wake as well as practical sleep hygiene techniques for shift workers, and (3) implementing pharmacological and nonpharmacological treatment strategies for patients with shift work disorder.

Learning objectives

After completing this activity, participants should be better able to:

- Explain the neurobiology and genetics of shift work disorder
- Implement guideline-based assessment strategies for patients with suspected shift work disorder
- Educate patients on how to incorporate practical sleep hygiene techniques into their daily lives
- Implement guideline-based treatment strategies for patients with shift work disorder

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CME REVIEW ARTICLE

Twisting the night away: a review of the neurobiology, genetics, diagnosis, and treatment of shift work disorder

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Although not all individuals who work outside of standard daytime hours develop physical and psychiatric issues, there is a substantial portion of shift workers who develop shift work disorder. Shift work disorder is due to a misalignment between an individual's endogenous circadian rhythms and environmental stimuli, and can have potentially serious consequences to an individual's health and quality of life. This article reviews the neurobiological and genetic underpinnings of shift work disorder, and describes how desynchronization of the molecular clock may lead to both physical and psychiatric illnesses. Diagnostic tools and treatment guidelines to address the circadian misalignment, excessive sleepiness, and insomnia experienced by patients with shift work disorder are also discussed.

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Keywords: Armodafinil, circadian rhythm disorder, melatonin, molecular clock, modafinil.

Introduction

Shift work is defined as work occurring between 6 pm and 7 am, thus outside of the standard daytime working hours. Shift workers include those who work night shifts, evening shifts, or rotating shifts, and comprise approximately 15–25% of the workforce in the United States.[1,2] Shift workers' sleep/wake schedules are often out of phase with their endogenous circadian rhythms, and, as a result, many (but not all) individuals who work nonstandard or rotating schedules develop shift work disorder (SWD). In fact, it is estimated that as many as 10–32% of shift workers develop shift work disorder, and as many as 9.1% of shift workers develop a severe form of the disorder.[1,3] Younger age and "eveningness" (a.k.a. "night owls" rather than "morning larks") may provide some protection from the development of SWD; however, not all individuals who perform shift work have these seemingly protective characteristics.[4] Unfortunately, although SWD can have a severe impact the individual shift worker, his or her family, society, and the economy, it is under-recognized, under-diagnosed, and under-treated.[5,6]

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Circadian Rhythms and the Molecular Clock

Virtually all living creatures have an internal clock that synchronizes biological processes to a 24-hour circadian rhythm. These biological rhythms are endogenously regulated and will continue without external stimuli, but they are reset by environmental stimuli such as light. Circadian rhythms are evident in multiple biological functions, including body temperature, hormone levels, blood pressure, metabolism, cellular regeneration, sleep/wake cycles, and DNA transcription and translation.[7]

At the molecular level, the internal clock consists of various transcription factors working together in a series of negative feedback loops.[8] Transcription factors are proteins that bind to DNA regions called promoters; the binding of a transcription factor to a promoter may turn a gene on or off. The transcription factors involved in circadian rhythm generation, collectively referred to as the "molecular clock," control production of the many proteins that are expressed with a period of approximately 24 hours and include circadian locomotor output cycles kaput (CLOCK), brain and

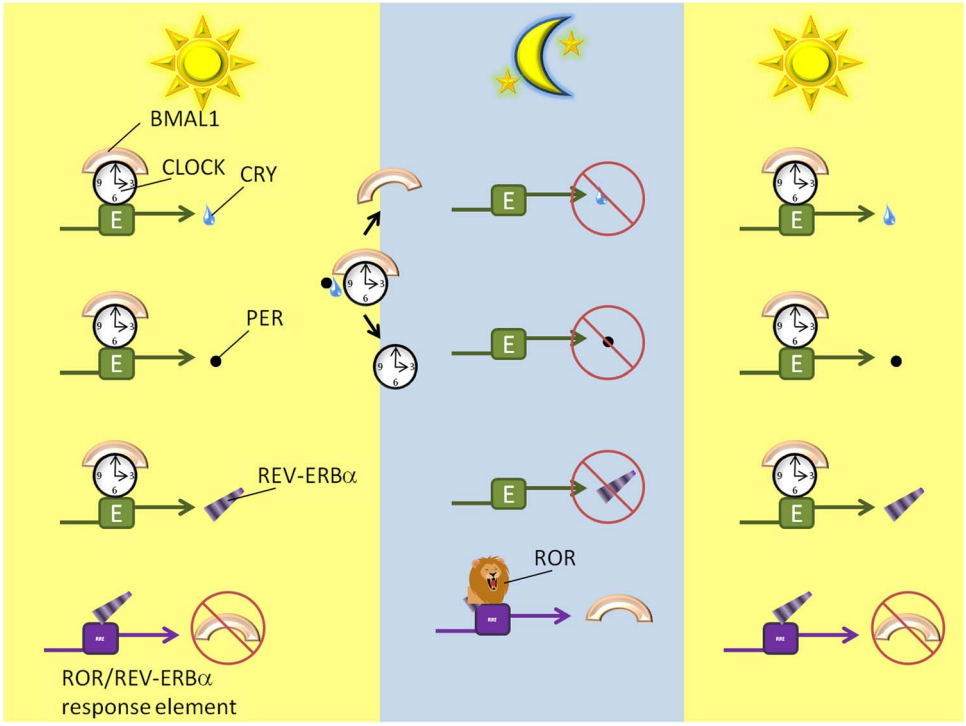

FIGURE 1. The molecular clock. Heterodimers of CLOCK and BMAL1 bind to the E box promoter regions that regulate transcription of various proteins, including PER and CRY. As PER and CRY accumulate, they heterodimerize to form a complex. Expression of the nuclear receptor, REV-ERBa, is also regulated by binding of the BMAL/CLOCK complex to an upstream E box promoter. REV-ERB alpha itself binds to the ROR/REV-ERB alpha response element (RRE) in the promoter region that controls expression of BMAL1. Binding of REV-ERB alpha to RRE prevents further expression of BMAL1. The PER/CRY heterodimer prevents interaction between the BMAL1/CLOCK complex and the E box promoter region. The concentration of BMAL1 is consequently lessened as BMAL1 is degraded. In the absence of the BMAL1/CLOCK heterodimer, expression of PER, CRY, and REV-ERB alpha is turned off. Therefore, feedback inhibition of BMAL1/CLOCK by the PER/CRY complex no longer occurs. Additionally, the nuclear receptor ROR is stimulated to translocate into the nucleus where it binds to the RRE promoter region controlling BMAL1 expression. Contrary to REV-ERB alpha, binding of ROR to the RRE region stimulates expression of BMAL1. Once present, BMAL1 can again heterodimerize with CLOCK to begin the cycle of expression and feedback inhibition again. This cycle oscillates approximately every 24 hours. Given that the transcription factors comprising the molecular clock also mediate expression of various other genes, it is thought that the molecular clock regulates biological processes that cycle with a circadian rhythm, including sleep/wake cycles. *Copyright 2013 Neuroscience Education Institute. Used with permission.*

muscle ARNT-like-1 (BMAL1), period (PER), cryptochrome (CRY), and REV-ERB alpha. The transcription factors comprising the molecular clock control expression of one another in an intricate cycle of production and degradation and also mediate expression of various other genes involved in biological functions such as metabolism, sleep, and mood (Figure 1).

Although this molecular clock is self-sustaining, it needs to be reset daily or it will drift and become out of synch with environmental cues. These environmental cues, termed "zeitgebers," include light/dark cycles generated by the movement of the Earth, social interactions, and food availability. The most powerful zeitgeber is light; light entering through the eye is translated via the retinohypothalamic tract to the suprachiasmatic nucleus (SCN) within the hypothalamus (Figure 2). In the SCN, light increases production of the clock gene PER, and in doing so can reset the molecular clock.[9] During periods of darkness, the SCN induces release of melatonin from the pineal gland. Interestingly, melatonin can then act on receptors in the SCN to help reset the molecular clock.[10]

The internal coordination ordered by the circadian rhythm is essential to optimal health, and problems may arise when there is dysynchrony between the internal clock and external cues. Thus, desynchronization of the molecular clock, often presenting as a circadian rhythm disorder, can have severe consequences on both mental and physical well-being.[11] Circadian rhythm disorders can occur as a result of social or lifestyle factors, including shift work, as well as from inherent polymorphisms in components of the molecular clock. In patients with circadian rhythm disorders, severe physical and psychiatric issues can result if discrepancies between the endogenous clock and environmental cues are not resolved.

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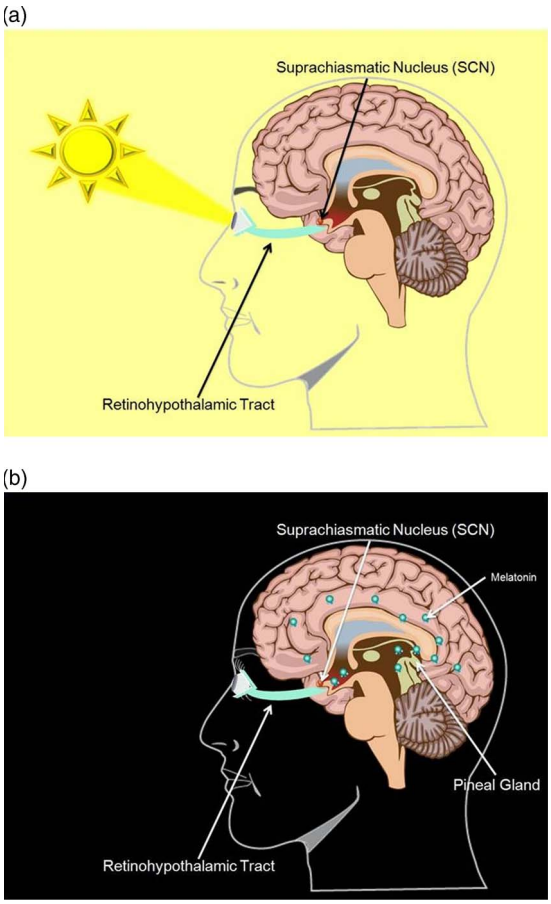

FIGURE 2. Resetting the molecular clock. (A) When light enters through the eye, it is translated via the retinohypothalamic tract to the suprachiasmatic nucleus (SCN) within the hypothalamus. (B) When light is not available, the SCN stimulates the pineal gland to release melatonin. *Copyright 2013 Neuroscience Education Institute. Used with permission.*

Shift work disorder is essentially a circadian rhythm disorder that is associated with the work schedule and persists for at least 1 month. A circadian rhythm disorder is one in which there is persistent sleep disturbance resulting in insomnia, excessive sleepiness, or both, and consequent impaired functioning.[7] Circadian rhythm disorders frequently present as either an advanced sleep phase rhythm or delayed sleep phase rhythm.[7] Individuals with advanced sleep phase syndrome fall asleep and awaken earlier than the desired time, whereas individuals with delayed sleep phase syndrome go to bed later and arise later than desired.[7] Interestingly, both advanced and delayed sleep phase rhythms have been associated with polymorphisms in various molecular clock genes.[12,13]

Consequences of Shift Work

Individuals with SWD often suffer with decreased alertness and impaired cognitive functioning as a result of sleep disturbance and/or circadian desynchronization.[11] A study by Rouch et al[14] indicated not only that shift workers have impaired immediate free recall, decreased processing speed, and selective attention, but that these cognitive impairments may worsen with longer duration (10–20 years) of shift work. It is not surprising then that shift workers have a much higher risk of vehicular accidents, job-related injuries, absenteeism, and quality control errors.[15] This may be particularly alarming given that many occupations that require shift work (eg, law enforcement, healthcare, transportation) represent situations where cognitive impairment and subsequent human error may have severe consequences to many individuals.

Cardiometabolic issues

Compared to day workers, shift workers have been shown to have a higher body mass index (BMI), elevated cholesterol and triglycerides, and a greater risk of hypertension.[11,16] In fact, the risk of developing cardiovascular disease may be as much as 40% higher in shift workers compared to day workers.[17] The increased risk for cardiometabolic issues in shift workers may stem from the fact that the expression of many of the hormones involved in metabolism, such as ghrelin and leptin, are regulated by molecular clock transcription factors.[16,18] Interestingly, polymorphisms in the CLOCK gene are associated with increased risk of obesity and metabolic syndrome, whereas polymorphisms in BMAL1 increase susceptibility to hypertension and type 2 diabetes.[18] Furthermore, chronic misalignment of endogenous circadian cycles and intake of food may result in cardiometabolic disorders, as well as DNA damage.[18]

Cancer

Accumulating evidence suggests that shift workers are at a significantly higher risk for the development of several different cancers, including breast cancer, prostate cancer, and colon cancer.[19] In fact, the World Health Organization International Agency for Research on Cancer recently stated: "Shift work that involves circadian disruption is probably carcinogenic to humans" (p. 1066).[20] One proposed mechanism for this increase in cancer risk is the "melatonin hypothesis," whereby exposure to light at night suppresses the release of melatonin.[21] Although incompletely understood, melatonin has been shown to have a pro-apoptotic effect on cancer cells.[22] Thus, the suppression of melatonin release from exposure to light during evening hours may increase cancer risk by allowing cancerous cells to survive and proliferate. Recent evidence also implicates molecular clock genes in the development of cancer;

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PER expression is aberrant in breast cancer cells, and several cell cycle genes are regulated by the CLOCK/BMAL complex.[23] The synchronization between circadian rhythms and the cell cycle likely prevents DNA replication from occurring during periods of high UV exposure or abundant metabolism (which generates byproducts that can damage cells).[23] When the cell cycle becomes out of synch with the circadian rhythm, DNA and cells are forced to operate under less-than-optimal conditions, damage may occur and accumulate, and cancer may be the result.

Gastrointestinal issues

Shift work may also increase the risk of gastrointestinal issues. For example, the prevalence of ulcers is more than double in shift workers compared to day workers (6% in day workers vs 15.4% in shift workers), and the prevalence of bowel disorders is also significantly increased (20% in day workers vs 38% in shift workers).[7] Another study found that shift work increases the prevalence of functional bowel disorder; interestingly, this association was independent of self-reported sleep quality.[24] There is also evidence that circadian rhythm dysfunction increases the risk of gastroesophageal reflux disease (GERD), gastric dyspepsia, inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), and gastrointestinal cancers.[25,26] Circadian rhythms regulate several important functions in gastrointestinal tract including motility, maintenance of the gut lining, and production of digestive enzymes.[25] According to a recently proposed model, molecular clock components regulate expression of both nitric oxide and acetylcholine, both of which modulate colonic motility.[27] Interestingly, one study demonstrated that administration of melatonin, a therapeutic agent often used in the treatment circadian rhythm disorders, may be effective in the treatment of IBS.[28]

Mood disorders

The prevalence of mood disorders is also increased in shift workers, and shift work is hypothesized to exacerbate existing mood disorders.[7] In line with this hypothesis, data have shown that monoamine oxidase A (MAO-A) expression is regulated by molecular clock proteins including CLOCK, PER, and BMAL1. MAO-A is involved in the degradation of dopamine, serotonin, and norepinephrine; thus impaired regulation of MAO-A from a desynchronized molecular clock might lead to imbalanced neurotransmission and subsequent psychiatric illness.[29] In fact, the prevalence of depression is significantly higher in shift workers (25% in day workers vs 32.6% in shift workers).[30]

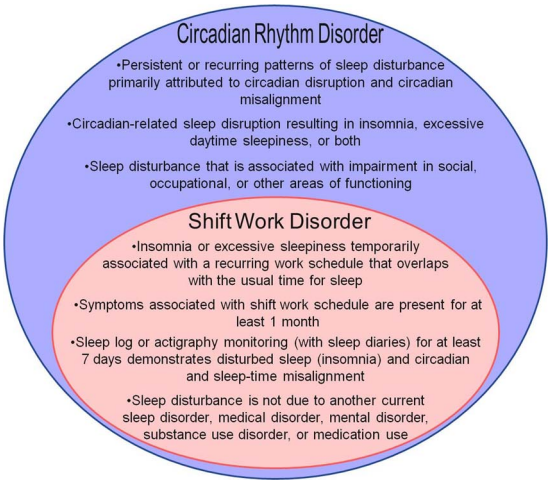

FIGURE 3. International Classification of Sleep Disorders (ICSD-2) diagnostic criteria. In addition to meeting all of the diagnostic criteria for a circadian rhythm disorder (blue circle), patients with shift work disorder also meet additional criteria (pink circle). *Copyright 2013 Neuroscience Education Institute. Used with permission.*

Diagnosing Shift Work Disorder

The diagnostic criteria for SWD according to the International Classification of Sleep Disorders (ICSD-2) are shown in Figure 3. In addition to these criteria, some supportive criteria have been proposed.[1,7] These supportive criteria include early morning shifts associated with difficulty initiating sleep and awakening; permanent evening shifts associated with difficulty initiating sleep; excessive sleepiness, impaired mental stability, and need to nap during the work shift; reduced alertness both on and off the work shift; reduced performance capacity; the necessity of using large segments of free time for recovery sleep; increased irritability; an irregular sleep/wake schedule that shifts by more than 2–4 hours between work days and days off; and insomnia or hypersomnia on either side of the scheduled sleep period.[1,7] The most common symptoms of SWD are insufficient sleep (with the average sleep duration being only 5.5 hours for shift workers), a tendency to dose off at work, unsatisfactory quality of sleep, and reduced physical and mental well-being.[1,7] Approximately 53% of patients with SWD report symptoms of insomnia including waking up earlier than desired and difficulties staying asleep; over 35% report excessive sleepiness, and 23.4% report both insomnia and excessive sleepiness.[2] Alarmingly, multiple sleep latency (the time it takes to fall asleep when in a quiet, dark room) in SWD is 2 min (vs 10–20 min in controls), which is well below the ICSD-2 criteria of <5 min that indicates pathological sleepiness.[1]

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The diagnosis of shift work sleep disorder generally begins with a detailed patient history including questions such as the following:

- Do you feel irritable or sleepy during your shift?
- Do you fall asleep sometimes while driving?
- Do you have difficulty paying attention, concentrating, and/or working to your full potential?
- Do you get told by others that you look tired?
- Do you have emotional outbursts?
- Do you feel like taking a nap while working?
- Do you require caffeinated beverages throughout the night to keep yourself going?[10]

There are also several diagnostic tools available to aid in the identification of SWD, including the Multiple Sleep Latency Test (MSLT); the Morningness-Eveningness Questionnaire (MEQ), which can help determine an individual's natural circadian rhythm (an online version of the MEQ can be found at http://www.cet.org/eng/Tools_ENG.html); and the Epworth Sleepiness Scale (ESS), which consists of 9 questions regarding an individual's propensity to fall asleep during various waking activities.

A sleep/wake diary is also a critical tool in the diagnosis of SWD.[1] In a sleep/wake diary, the patient records his or her sleep/wake habits including bedtime, amount of sleep, naps during the waking hours, and mood, and is usually kept for 1–2 weeks. An actigraphy, which measures motor activity to detect rest and activity, can be used in conjunction with the sleep/wake diary to substantiate some of the subjective items in the sleep/wake diary such as estimated number of awakenings.[1] Polysomnography, a multifaceted measure of sleep duration and quality is not typically used in the diagnosis of SWD per se, but may be helpful in ruling out other sleep/wake disorders such as sleep apnea and narcolepsy in the differential diagnosis.[7]

Treating Shift Work Disorder: Adapting Circadian Rhythms

Optimizing sleep hygiene

One of the first steps in treating a patient with circadian rhythm misalignment, including SWD, is to educate the patient on proper sleep hygiene. Patients with SWD should minimize exposure to bright light before and during scheduled sleep periods. In addition to maintaining a dark sleeping space, minimizing exposure to bright light during critical periods may necessitate wearing sunglasses following the work shift and during the commute home. Body temperature is maintained on a circadian rhythm, and it is important to retrain core body temperature to the shifted sleep/wake schedule; therefore, the sleeping quarters should be kept cool. Shift workers should avoid stimulants, including caffeine, during the second half of their work shift, although strategic use of caffeine during the first half of the shift may be useful.[10] If possible, decreasing extended work shifts, scheduling a clockwise progression of rotating shifts, and taking planned naps may also reduce circadian rhythm misalignment.[1]

Bright light therapy

Exposure to light acts as a powerful zeitgeber, as it alters circadian rhythms and suppresses melatonin release. Exposure to bright light at key times may therefore aid in the re-synchronization of the molecular clock in patients with SWD. One recent study investigated the effects of bright light therapy in night shift nurses.[31] The authors found that a treatment regimen consisting of full spectrum bright light during night shifts coupled with dark goggles during the morning commute home significantly increased the duration of sleep by nearly 1 hour compared to controls.[31] This same research team also found that treatment with intermittent full spectrum bright light throughout the night coupled with orange-tinted goggles in the morning increased the reaction time of police officers working a rotating shift over a period of 1 week.[32] Bright light therapy has also been shown to alleviate depression, which is a common psychiatric comorbidity seen in patients with SWD.[33] For antidepressant efficacy, 10,000 lux (bright light) for 30 min/day administered 7.5–9.5 hours after evening melatonin secretion seems to work best.[33] Melatonin secretion can be measured directly in biological samples or can be determined indirectly by using the Morningness-Eveningness Questionnaire.[33] Another form of light therapy, dawn simulation therapy, employs a slow incremental light signal at the end of the sleep cycle and has been shown to shift circadian rhythm phase.[34] Side effects of bright light therapy, including headaches, eyestrain, nausea, and agitation, are rare but should be discussed with the patient.

Melatonin

Melatonin is released from the pineal gland during periods of darkness; consistent with this, melatonin receptor levels are normally high during the evening and low during the night.[10] Melatonin administered in the evening advances the circadian rhythm, allowing a person to sleep earlier, whereas melatonin given early in the morning can cause a phase delay, so that a person will not feel sleepy until later.[35] Shift workers often display reduced melatonin levels, likely due to the limited exposure to darkness that is a consequence of being awake during the night and asleep during the day.

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Melatonin treatment in shift workers has been shown to increase the quality and duration of sleep, as well as increasing alertness during the work shift.[36,37] In patients with SWD, it may be best to administer melatonin (3–6 mg) during the night, at around the normal circadian low of 03:00, and approximately 3 hours before dim-light melatonin onset.[1]

The melatonin agonist, ramelteon, is not FDA approved for the treatment of SWD, but is indicated for insomnia characterized by difficulty of sleep onset. Ramelteon has a longer half-life and binds to melatonin receptors with a higher affinity than melatonin, and there is evidence for the effectiveness of ramelteon in improving daytime sleep.[38,39] The most common side effects associated with ramelteon include somnolence, dizziness, fatigue, and nausea.[1]

Treating Shift Work Disorder: Sleeping When You Need To

Benzodiazepine and non-benzodiazepine hypnotics

Benzodiazepines are gamma-aminobutyric acid (GABA) receptor agonists that bind to the alpha subunit of the GABA receptor leading to sedation. Benzodiazepines bind with equal affinity to the different alpha subunits (alpha-1, alpha-2, alpha-3, and alpha-5); however, the selectivity of a benzodiazepine for different alpha subunits is thought to be responsible for a benzodiazepine's non-sedative effects, such as anxiolytic, anti-pain, and tolerance.[10] Among the benzodiazepines, estazolam, flurazepam, quazepam, temazepam, and triazolam are FDA-approved for the treatment of insomnia and may be useful in patients with SWD. Like benzodiazepines, the non-benzodiazepine hypnotics (eszopiclone, zaleplon, and zolpidem) also bind to the alpha subunit of GABA-A receptors; however, the non-benzodiazepine hypnotics bind selectively to only 1 or 2 of the alpha subunits.[10] Eszopiclone is selective for alpha-2 and alpha-3 subunits and is the only hypnotic approved for use over 35 days, whereas zaleplon is selective for alpha-1 subunits and can be used for awakening during the night without residual daytime effects. Zolpidem is also selective for alpha-1 subunits and has a sublingual formulation approved for middle of the night awakening. However, although hypnotics may improve daytime sleep, they do not appear to improve the sleep maintenance and nighttime alertness that are often issues for patients with SWD.[1] Hypnotics may also cause residual sedation during work hours, which could potentially make SWD symptoms worse.[1] Common side effects of the hypnotics as a class may also include risk of tolerance and withdrawal effects, headache, dizziness, gastrointestinal effects, and risk of falls, and should be used only for short-term treatment of insomnia.[10]

Antidepressants

The antidepressant agents doxepin and trazodone both have binding affinity for receptors that can be exploited for the treatment of insomnia. Doxepin is a tricyclic antidepressant (TCA) that at antidepressant doses (150–300 mg/day) inhibits serotonin and norepinephrine reuptake and is an antagonist at histamine 1, muscarinic 1, and alpha 1 adrenergic receptors. However, at low doses (1–6 mg/day), doxepin is highly selective for histamine 1 receptors and acts more as a hypnotic agent rather than an antidepressant. Doxepin is FDA approved for the treatment of insomnia and has been shown to improve sleep without residual daytime impairment. At antidepressant doses (150–600 mg/day), trazodone is a serotonin reuptake inhibitor and also has serotonin 2A and 2C antagonism. Trazodone is also a histamine 1 and alpha 1 adrenergic receptor antagonist, which can make it very sedating, particularly when given at antidepressant doses during the day. At low doses (25–150 mg/day), trazodone does not adequately block serotonin reuptake but can still block serotonergic, histaminic, and adrenergic receptors, leading to sedation. Trazodone has a relatively short half-life (6–8 hours); thus it may improve sleep without having daytime effects if dosed only once daily at night.[10]

Treating Shift Work Disorder: Staying Awake When You Need To

Modafinil and armodafinil

Modafinil and armodafinil are both FDA approved for the treatment of excessive sleepiness in patients with SWD, narcolepsy, and sleep apnea. Modafinil activates brain areas involved in controlling wakefulness, such as the hypothalamus; however, its mechanism of action is complex and not completely understood (Figure 4).[40–44] Modafinil consists of both R (long-acting) and S (short-acting) isomers, whereas armodafinil is composed of only the R isomer. Because of this difference, armodafinil has less plasma drug variability and is more effective in promoting wakefulness toward the end of an 8-hour shift in patients with SWD.[45–47] Both modafinil and armodafinil have been shown to immediately reduce daytime sleepiness and improve cognitive performance; however, optimization can take several days.[48] Side effects of modafinil and armodafinil include headache, nausea, dizziness, and insomnia; however, these agents have less risk of causing anxiety, jitteriness, and rebound effects compared to traditional stimulants.[49] Unfortunately, modafinil and armodafinil carry risk of other serious side effects, including rare activation of (hypo)mania, anxiety, hallucinations, or suicidal ideation; rare severe dermatologic reactions

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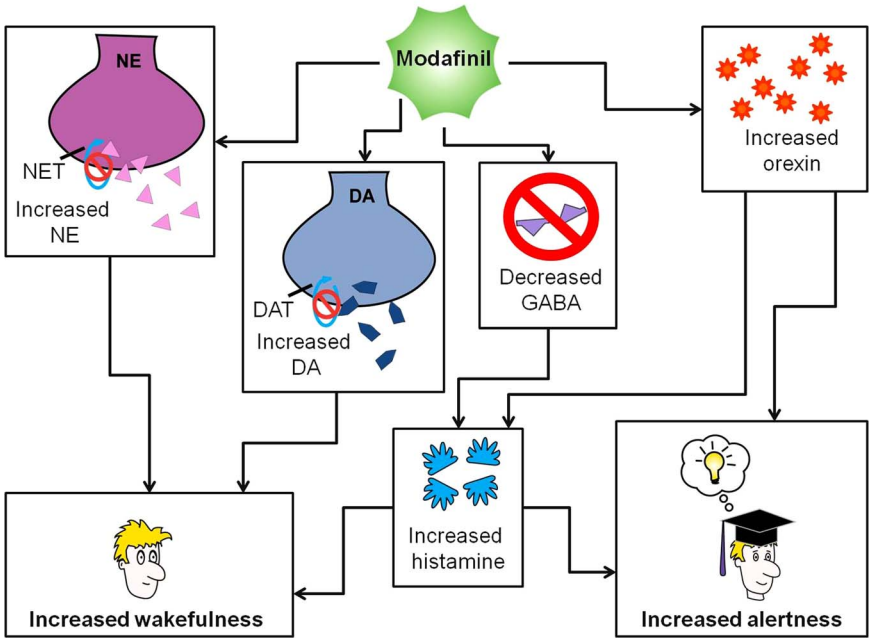

FIGURE 4. Possible mechanisms of action of modafinil. Modafinil increases both norepinephrine (NE) and dopamine (DA), possibly via its blockade of both the NE and DA reuptake transporters (NET and DAT, respectively). The actions of NE at alpha-adrenergic receptors and of DA at dopamine D2 receptors is thought to contribute to the wake-promoting properties of modafinil. Orexin is a key component of the arousal system; thus the hypothesized action of modafinil on the orexinergic system may help to increase alertness. Additionally, modafinil may indirectly increase histamine either by reducing GABAergic inhibition of histaminergic neurons or via actions at orexinergic neurons. The increase in histamine may contribute to both modafinil's wake-promoting effects as well as its potential to increase alertness. *Copyright 2013 Neuroscience Education Institute. Used with permission.*

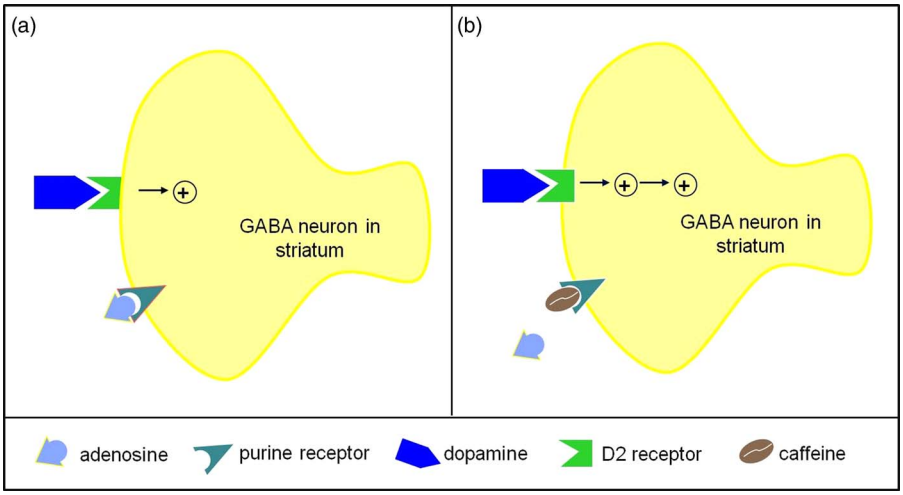

FIGURE 5. Modulation of dopaminergic neurotransmission by caffeine. (A) Both adenosine 2A receptors and dopamine 2 receptors are localized on GABAergic neurons in the striatum, forming a heteromeric complex. When adenosine stimulates adenosine 2A receptors, this reduces the affinity of nearby dopamine 2 receptors for dopamine. (B) By blocking adenosine from binding to adenosine 2A receptors, caffeine prevents the lowered affinity of dopamine 2 receptors for dopamine. The increased GABAergic neurotransmission disinhibits downstream excitatory glutamatergic neurotransmission. *Copyright 2013 Neuroscience Education Institute. Used with permission.*

(Stevens-Johnson syndrome and others); angioedema; anaphylactoid reactions; and multi-organ hypersensitivity reactions.[50] There is also concern for females of child-bearing age, as modafinil (and arfmodafinil) may affect the efficacy of oral contraceptives.[51]

Stimulants

A low (5–10 mg) dose of methamphetamine has been shown to increase alertness during a simulated night shift. However, higher (10–20 mg) doses have a high risk of

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causing a myriad of adverse effects, including anxiety, depression, difficulty concentrating, confusion, insomnia, and gastrointestinal effects.[52] Also, stimulants such as methamphetamine generally work by increasing dopaminergic neurotransmission, and therefore have a high potential for abuse, so long-term administration may be contraindicated in patients with a history of substance use.

Caffeine intake is often a strategy employed by those who perform shift work, and has been shown to increase performance and alertness in a simulated night shift study.[53] A recent Cochrane review found insufficient evidence to support a recommendation against the use of caffeine in shift workers, although it also found no evidence showing a beneficial effect of caffeine use on injuries in shift workers.[54] The primary mechanism of action of caffeine is as an adenosine receptor antagonist (Figure 5).[55] By blocking the actions of adenosine, caffeine modulates dopaminergic, noradrenergic, cholinergic, serotoninergic, glutamatergic, and GABAergic neurotransmission in various areas of the brain involved in sleep/wake processes as well as attention.[56]

Conclusions

It seems that the development of a circadian rhythm disorder, such as SWD, as well as the propensity for chronic physical and mental illness as a result of circadian misalignment, is dependent upon a combination of both lifestyle factors and genetic predisposition. Thus, not all shift workers develop SWD, nor do they succumb to depression, gastrointestinal issues, or cancer. It may be that those who do develop these illnesses have particular polymorphisms in components of the molecular clock that leave them vulnerable to the stressor of an altered circadian rhythm. For those who do develop SWD, it is critical that they are diagnosed early and are educated about the importance of the sleep/wake cycle and of the potential consequences when endogenous circadian rhythms are desynchronized with external cues. There are lifestyle changes that can mitigate some of the symptoms of SWD, including changing to a day shift if possible and practicing good sleep hygiene. However, many patients with SWD will require pharmacological interventions, including agents that increase wakefulness and those that promote sleep, and it is likely that a combination of pharmacological and non-pharmacological treatment measures will be more effective than the sum of individual treatments.

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1. Janet is a 53-year-old night shift nurse who presents with excessive sleepiness that is interfering with her ability to perform her job. While reviewing her sleep/wake dairy, you notice that the patient's sleep environment includes a pitch dark bedroom maintained at a cozy temperature of 80–83°F. You explain to her that she can improve her sleep hygiene by:

   A. Maintaining a dimly lit atmosphere while sleeping
   B. Adjusting the room temperature so that it is cooler while sleeping
   C. Both of the above
   D. None of the above

2. Danny is a 30-year-old patient with shift work disorder who works the night shift at a brightly lit power plant. You explain to this patient that his internal clock is out of synch with stimuli in his environment. Part of the reason for this desynchronization is that light transmitted to the suprachiasmatic nucleus:

   A. Increases production of melatonin
   B. Decreases production of the molecular clock gene CRY
   C. Increases production of the molecular clock gene PER
   D. All of the above
   E. None of the above

3. Anthony is a 27-year-old police officer with shift work disorder. Until recently, he was taking modafinil (200 mg/day) but was experiencing sleepiness toward the end of the 8-hour work shift. The patient was recently switched to armodafinil (150 mg/day) and is now experiencing minimal sleepiness for the entire work shift. Armodafinil differs from modafinil because:

   A. Armodafinil consists of the R enantiomer only
   B. Armodafinil consists of the S enantiomer only
   C. Armodafinil consists of both the R and S enantiomers

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