Circadian Rhythm Sleep-Wake Disorders

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Circadian rhythms are endogenous, near-24-hour biological rhythms that exist in all living organisms. The internal near-24-hour circadian timekeeping system is entrained or synchronized to the 24-hour light-dark cycle. In humans, the endogenous period of the circadian oscillation is genetically determined and typically is slightly longer than 24 hours. To maintain entrainment, the endogenous clock must be recalibrated each day to the 24-hour clock time. For optimal sleep, the actual sleep episode should match the circadian rhythm of sleep propensity. Therefore, a recurrent or chronic pattern of sleep and wake disturbance may result from: 1) a disturbance of the internal circadian timing system itself or its entrainment mechanisms; or 2) a misalignment between the timing of the individual's circadian sleep-wake propensity and the 24-hour social and physical environments (e.g., sleep episodes scheduled entirely or in part during a phase of circadian alertness promotion). Insomnia and excessive sleepiness during wake time are the most frequent symptoms of a CRSWD. Given the increasingly recognized role of the circadian system in multiple physiological systems, circadian disorders have far-reaching implications for health.

Most CRSWDs arise when a substantial misalignment exists between the internal rhythm of sleep-wake propensity and the required timing of the patient's school, work, or social activities. Therefore, estimating endogenous circadian timing is essential for the accurate diagnosis of CRSWDs. In addition to the history, multiple tools are available to assess sleep-wake patterns. Sleep logs and actigraphy are important instruments in evaluating most CRSWDs and should be conducted for at least seven days, preferably for 14 days, to capture work/school nights and non-work/off-school nights. Circadian chronotype questionnaires and physiological measures of endogenous circadian timing (salivary or plasma dim light melatonin onset and urinary 6-sulfatoxymelatonin acrophase) may also provide helpful diagnostic information. Circadian chronotype is a reflection of an individual's optimal timing of sleep and wake propensity, as well as other physiological and mental functions. Several questionnaires are useful in assessing the chronotype of "eveningness" or "morningness" (e.g., Munich Chronotype Questionnaire or Morningness-Eveningness Questionnaire).

The consequences of CRSWDs and the associated symptoms include adverse health outcomes, impairments in social, occupational, and educational performance, and safety concerns. Significant advances have been made in the identification of clinical CRSWD subtypes. However, the challenge remains to develop more precise and clinically practical tools to improve diagnostic accuracy for CRSWDs.

General Criteria for Circadian Rhythm Sleep-Wake Disorder

Criteria A-C must be met

    A. A chronic or recurrent pattern of sleep-wake rhythm disruption, primarily due to alteration of the endogenous circadian timing system or its entrainment mechanisms, or to misalignment between the endogenous circadian rhythm and the sleep-wake schedule desired or required by an individual's physical environment or social/work schedules.

    B. The circadian rhythm disruption leads to insomnia symptoms, excessive sleepiness, or both.

    C. The sleep and wake disturbances cause clinically significant distress or impairment in mental, physical, social, occupational, educational, or other important areas of functioning.

All disorders described in the following section imply a sleep or wakefulness difficulty that meets all the above criteria. The individual diagnostic criteria include the specific features that characterize each type of CRSWD.

Delayed Sleep-Wake Phase Disorder

ICD-9-CM code: 327.31
ICD-10-CM code: G47.21

Alternate Names

Delayed sleep phase syndrome, delayed sleep phase disorder, delayed sleep phase pattern, motivated delayed sleep phase disorder.

Diagnostic Criteria

Criteria A-E must be met

    A. There is a significant delay in the phase of the major sleep episode in relation to the desired or required sleep onset time and wake-up time, as evidenced by:
        1. A chronic or recurrent complaint by the patient or a caregiver of inability to fall asleep at the desired or required time; and
        2. Difficulty awakening at a desired or required clock time.

    B. The symptoms have been present for at least three months.

    C. When patients are allowed to choose their ad libitum schedule, they will exhibit improved sleep quality and duration for age and maintain a delayed phase of the 24-hour sleep-wake pattern.[1]

    D. Sleep logs are required, accompanied by actigraphy monitoring, whenever possible, for at least seven days, preferably 14 days. These demonstrate a delay in the timing of the habitual sleep period. Both work/school days and free days should be included within this monitoring.

E. The sleep disturbance is not better explained by another current sleep disorder, medical disorder, mental disorder, or medication/substance use.

Notes

1. Chronic insomnia is a common complication of delayed sleep-wake phase disorder. Repeated attempts to initiate sleep in advance of the circadian sleep preference may result in frustration and conditioned arousal. Individuals with comorbid chronic insomnia disorder may not manifest improved sleep quality and duration at the preferred delayed phase. Still, the circadian preference should be apparent based upon the clinical history and continued observed delay in either sleep onset or offset, depending upon the nature of insomnia complaints.

2. Standardized chronotype questionnaires are useful tools to assess the chronotypes of eveningness and morningness. Individuals with this disorder typically score as evening types. This tool can also help determine whether an eveningness circadian preference contributes to sleep initiation difficulties among those who do not meet the full criteria for the disorder.

3. Demonstration of a delay in the timing of other circadian rhythms, such as melatonin (measured by dim light melatonin onset or urinary 6-sulfatoxymelatonin, sampled across a 24-hour period), may confirm the delayed circadian phase. However, more than 40% of individuals meeting the diagnostic criteria delineated above do not have a delayed dim light melatonin onset (see Clinical and Pathophysiological Subtypes).

Essential Features

Delayed sleep-wake phase disorder (DSWPD) is characterized by habitual sleep-wake timing that is delayed, usually more than two hours, relative to conventional or socially acceptable timing. Affected individuals complain of difficulty falling asleep at a socially acceptable time, as required to obtain sufficient sleep duration on a school or work night. Once sleep onset occurs, sleep duration is reportedly normal if allowed an ad-lib wake time. These individuals also experience difficulty waking at a socially acceptable time, as required to prepare for school or work. When allowed to follow their preferred schedule, the patients' timing of sleep onset and wake time is delayed.

Associated Features

Individuals with DSWPD may demonstrate excessive sleep inertia (extreme difficulty awakening and confusion) in the morning due to curtailed sleep duration and awakening during a circadian phase of high sleep propensity. Individuals with this disorder and normal sleepers with evening chronotypes may have increased rates of mental disturbances, such as Diagnostic and Statistical Manual of Mental Disorders (DSM) conditions or symptoms (e.g., mood disorders or depressive symptoms). Patients who exhibit delayed timing of melatonin secretion may be more prone to depression than those who do not demonstrate a physiologic phase delay (i.e., circadian vs. non-circadian DSWPD, respectively). The condition is also associated with adverse academic, occupational, financial, and social outcomes.

Frequent tardiness or absence from school or work may result in academic failure or loss of employment. In some individuals with DSWPD, there may be an overlap with non-24-hour sleep-wake disorder or an alternation between symptoms of the two disorders. Frustration and negative expectations due to the inability to fall asleep earlier may result in the development of an insomnia disorder. Individuals may use alcohol, sedatives, hypnotics, or stimulant substances to alleviate the insomnia symptoms and excessive sleepiness, thereby perpetuating their underlying sleep disorder.

Clinical and Pathophysiological Subtypes

Motivated delayed sleep-wake phase disorder is a subtype typically observed among children or adolescents who maintain a delayed schedule to avoid normal daytime activities such as regular school attendance and developmentally appropriate peer interactions. A history of mood or anxiety disorder (especially school phobia and separation or social anxiety) or other factors such as learning disabilities or attention-deficit/hyperactivity disorder is often present. These factors may - consciously or unconsciously - underlie the motivation to avoid a return to normal adolescent activities and especially regular school attendance. Ill-defined medical issues such as chronic fatigue, recurrent mononucleosis episodes, or pain syndromes may trigger the onset or complicate the course of the disorder. Important clues, in addition to the existence of premorbid mental disorders, include exaggerated presenting symptoms (e.g., "can't wake up even if I throw cold water on him") and failure to comply with basic, straightforward treatment recommendations (e.g., refusal or inability to stop napping during the day).

Social, psychological, and environmental factors, as described, may play a significant role in the development and maintenance of delayed sleep-wake phase disorder. However, the International Classification of Sleep Disorders, 3rd Edition, recognizing that most cases reflect variable chronobiologic and behavioral contribution, has chosen to list only a single delayed sleep-wake phase diagnosis. Salivary dim light melatonin onset time (DLMO) has been employed to distinguish so-called "circadian" DSWPD (when DLMO occurs 30 minutes before desired bedtime or any time after that) from "non-circadian" DSWPD (when DLMO occurs >30 minutes before the desired bedtime). The discrete diagnostic significance of these delineations remains to be determined.

Demographics

The exact prevalence of DSWPD in the general population is unknown and difficult to estimate due to inconsistent diagnostic criteria and other variables, including geographical location and school start times. Prevalence estimates among adults utilizing large-scale population-based survey methods hover around 1%, with a Norwegian derivation of 0.17% and a New Zealand derivation of 1.51%. The condition is more common among adolescents and young adults. A separate Norwegian population-based study found an adolescent prevalence of 3.3%. Two smaller studies of adolescents, one from Norway and one from Australia, identified prevalence of 8.4% and 1.1%, respectively. A small Swedish study involving individuals aged 16-26 described a DSWPD prevalence of 4.6%. No rigorous studies have been

performed among North American populations. Estimates suggest that DSWPD is seen in approximately 10% of patients presenting in sleep clinics with recurrent insomnia complaints. Several international studies have reported a higher prevalence among male adolescents than females. There have been no studies assessing racial/ethnic differences in DSWPD.

Predisposing and Precipitating Factors

Most individuals with DSWPD are evening chronotypes. Many adolescents experience an endogenous biological shift towards later bedtimes beginning around puberty. Possible genetic factors such as polymorphisms in the circadian clock gene *hPer3* are associated with DSWPD; polymorphisms in arylalkylamine *N*-acetyltransferase, human leukocyte antigen, and *Clock* genes may also serve as predisposing factors. Environmental factors may exacerbate the delayed circadian phase. These include: 1) increased exposure to bright light during the phase delay portion of the phase response curve (PRC, i.e., late in the evening) or 2) decreased exposure to light during the phase advance region of the PRC (i.e., due to later wake times). Individuals may have increased sensitivity to light in the phase delay region or decreased sensitivity in the phase advance region of the phase response curve. Maladjustment to changes in academic, occupational, or social schedules, travel across time zones, and shift work can precipitate this disorder. In addition, individuals may consume excessive caffeine and other stimulants, which may further delay sleep onset and thus exacerbate the delayed sleep time.

Social and behavioral factors play an important role in developing and maintaining the delayed sleep patterns for many affected individuals. Personal, social, and occupational activities that continue into the late evening may perpetuate and exacerbate the sleep phase delay. In adolescents, school avoidance, social maladjustment, and family dysfunction should be considered as contributing factors. In addition, individuals with a psychiatric disorder, such as a mood disorder (major depression or bipolar disorder), severe obsessive-compulsive disorder, attention-deficit/hyperactivity disorder, or other neurodevelopmental disorders appear to be at greater risk for DSWPD.

Familial Patterns

A positive family history has been reported in approximately 40% of individuals with DSWPD. In one pedigree, DSWPD possibly segregated as an autosomal dominant trait. Polymorphisms in *hPer3*, arylalkylamine *N*-acetyltransferase, human leukocyte antigen, and Clock may be associated with DSWPD. In addition, a familial form of DSWPD associated with a mutation in the *CRY1* gene has been identified.

Onset, Course, and Complications

A delayed sleep pattern typically begins during adolescence. Onset in early childhood is also described, especially in familial cases. The onset may follow psychological, medical, or environmental stressors.

DSWPD is a chronic condition that may last into late life without treatment. However, with increasing age across adulthood, the circadian timing of the sleep-wake cycle may advance, thereby decreasing the propensity to delayed sleep phase. Despite treatment, there is usually a continual tendency and preference for delayed sleep hours, and recurrence is high. Use of alcohol, sedatives, hypnotics, or stimulants to treat symptoms of insomnia and sleepiness during regular waking hours may lead to substance abuse.

Developmental Issues

DSWPD may be encountered in any age group but is especially prevalent among adolescents and young adults. In addition to the clinical features described elsewhere, DSWPD may present in older children and adolescents with chief complaints of truancy, chronic tardiness or school failure, rather than sleep complaints per se. In severe cases, school attendance is completely curtailed, and the patient may have failed to attend school regularly for many months. Extreme difficulty in morning awakening, requiring intensive parental involvement, may also be the presenting concern. Delayed sleep onset and resultant insufficient sleep, in adolescents, are associated with an increased risk of motor vehicle accidents; thus, a car crash or "near-miss" incident should alert the clinician to probe for additional evidence of circadian pathology. Adolescents may also present primarily with mood complaints (depression, suicidal ideation). Chronic insomnia is commonly associated with and may be the chief presenting complaint in adolescents with DSWPD due to repeated attempts and failures to achieve sleep onset at their desired bedtime.

In younger children, the condition may be associated with delays in other markers of circadian phase, including the typical pre-sleep surge in alertness referred to as the "wake maintenance zone" or "second wind phenomenon." Thus, especially in younger children, DSWPD may present primarily as bedtime resistance, as caregivers attempt to establish bedtimes that directly conflict with the child's circadian rhythm of sleep propensity.

 Several pediatric populations appear to have an increased vulnerability to DSWPD and sleep disturbances, likely of multifactorial etiology. These include children with attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD). Several studies have examined melatonin onset in children with ADHD, compared to normally developing children. These investigations reported significant delays in onset that were responsive to treatment with melatonin. Children with ASD have a high prevalence (up to 80%) of sleep disturbances, including delayed sleep onset, night and early morning awakenings, and irregular sleep patterns, at least some of which appear to be associated with circadian abnormalities. Children with ASD and alterations in expression of clock genes and genes regulating melatonin pathways have shown delayed and irregular sleep phases. However, children with ASD do not consistently show differences in DLMO compared to typically developing children. In both the ASD and ADHD populations, higher media use may contribute to eveningness circadian preference and delayed sleep onset.

Little is known about the natural history of the clinical entity of DSWPD in the pediatric population, including the impact of various treatment modalities, the likelihood of spontaneous resolution of symptoms, or the long-term consequences.

There is increasing evidence to suggest that the evening chronotype in both children and adolescents is associated with numerous physical and mental health problems. These include decreased health-related quality of life, higher rates of behavioral/emotional problems including depression and suicidality, reduced sleep duration and increased daytime sleepiness, more sleep complaints, impairments in academic functioning, and increased likelihood of substance use.

Pathology and Pathophysiology

The exact mechanisms responsible for DSWPD are unknown. Possible etiologies include: (1) an alteration in the ability of the circadian clock to phase advance; (2) a dominant phase delay region of the light phase response curve to entraining agents; (3) altered strength of entraining agents, such as light exposure at the appropriate circadian time (voluntarily or involuntarily induced); (4) a longer endogenous circadian period of the pacemaker; 5) an abnormal interaction between the endogenous circadian rhythm and the sleep homeostatic process; and 6) the post-pubertal circadian shift toward later bedtime preference.

Early studies reported a consistent alteration in phase relationship between the desired or required sleep-wake cycle and circadian phase. In contrast, more recent studies indicate that many patients diagnosed with DSWPD maintain a normal phase relationship (i.e., "non-circadian" DSWPD).

In patients with true "circadian" DSWPD, sleep onset, sleep offset, and phase of circadian markers such as core body temperature and melatonin are delayed relative to clock time compared with controls. Although this condition may be predominantly due to a misalignment between circadian timing and the external environment, alterations in the length of the circadian period or an altered homeostatic process (indicated by decreased sleep propensity in response to sleep deprivation) may also be contributing factors. In children and adults, voluntary behaviors such as staying awake late at night and waking up late in the morning or afternoon may result in an abnormal relationship between the endogenous circadian rhythm and the sleep homeostatic process. Delayed bedtimes and wake times may increase exposure to bright light in the late evening (promoting further delay) and decrease exposure to light in the morning (thereby inhibiting phase advancement), promoting and perpetuating the delay in the circadian sleep phase. When a significant discrepancy exists between early and late wake times, the early wake times may precede the minimum core body temperature. As a result, bright light exposure at this time may occur during the maximal phase delay region, perpetuating the circadian phase delay and the disorder. In addition, individuals may have altered sensitivity to the phase-shifting effects of light. For example, partial sleep deprivation, which may occur as a result of delayed sleep onset, can attenuate the ability to phase-advance the circadian system. As a result, the delayed circadian phase may be further exacerbated. There is some evidence of individuals developing DSWPD after traumatic brain injury, possibly due to disruption of circadian regulatory systems.

Objective Findings

Recordings of sleep logs and actigraphy over an interval of at least seven (and preferably fourteen) consecutive days demonstrate delayed sleep onset and sleep offset (typically greater than two hours) relative to socially acceptable times. Though clock times may be culture-dependent, sleep onset is generally delayed for many affected individuals until 1:00 a.m. to 6:00 a.m. (though it may be earlier based on age and developmental status). Wake time typically occurs in the late morning or afternoon when not restricted. Daily demands and schedules may result in an earlier than desired wake-up time during work or school days, but bedtime and wake-up time are almost always delayed during free days and vacation. Polysomnography (though not routinely indicated nor required for the diagnosis), when performed at preferred (delayed) sleep times, is usually normal for age; however, development of comorbid chronic insomnia disorder may result in prolonged sleep latencies, even on the delayed s"0chedule. If a conventional bedtime and wake-up time are enforced, polysomnographic recording may show prolonged sleep latency and decreased total sleep time. Laboratory measures of circadian timing may show the expected phase delay in the nadir of the core body temperature rhythm and dim-light melatonin onset (DLMO).

Several questionnaires are useful in assessing chronotype (e.g., "Morningness-Eveningness Questionnaire," "Munich Chronotype Questionnaire"). Individuals with DSWPD typically score as evening types, though normal sleepers can also score high on eveningness. When sleep duration is curtailed, measures of daytime sleepiness (e.g., the Epworth Sleepiness Scale) are generally elevated.

The results of polysomnography and other diagnostic tools in younger age groups are similar to those in adults. As with adults, actigraphy and sleep logs are helpful in the diagnosis of DSWPD in the pediatric population. Several validated instruments are available for assessing phase preference in the pediatric and adolescent populations. These include the Children's Chronotype Questionnaire (CCTQ) (parent-report), the Morningness-Eveningness Scale for Children (self-report), and the Morningness-Eveningness Questionnaire for Children and Adolescents.

Differential Diagnosis

Normal sleep. Delayed sleep-wake phase disorder must be distinguished from "normal" sleep patterns, particularly in adolescents and young adults who maintain delayed schedules regularly or intermittently, without distress or impaired functioning.

Chronic insomnia disorder. DSWPD must also be differentiated from other causes of difficulty initiating sleep, including *chronic insomnia disorder*. In DSWPD, sleep initiation and maintenance are improved when the patient is allowed to sleep on the preferred schedule (barring the presence of comorbid chronic insomnia disorder).

Hypersomnolence disorders. When individuals with DSWPD must arise before the desired wake time, excessive sleep inertia and excessive daytime sleepiness may be evident. This sleepiness must be distinguished from other forms of excessive daytime sleepiness, including *narcolepsy*, *idiopathic hypersomnia*, and *voluntary sleep restriction*, which do not generally exhibit the pronounced circadian pattern and do not abate with alterations in the sleep-wake schedule.

Unresolved Issues and Further Directions

There is limited knowledge of the underlying pathophysiology of DSWPD. Extant evidence suggests that alteration in the homeostatic regulation of sleep and alertness may play an important role. The intrinsic circadian period may be abnormally long. Recent advances in understanding the molecular basis for the generation and entrainment of circadian rhythms, together with the identification of a familial form of DSWPD, will lead to an improved understanding of the mechanisms responsible for this condition. Finally, the utility of physiologic circadian assessments for purposes of diagnosis warrants further research as their use may assist with further delineation of clinical and pathophysiological subtypes.

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Advanced Sleep-Wake Phase Disorder
ICD-9-CM code: 327.32
ICD-10-CM code: G47.22

Alternate Names

Advanced sleep phase syndrome, advanced sleep phase disorder.

Diagnostic Criteria

Criteria A-E must be met
  A. There is a significant advance (earlier timing) in the phase of the major sleep episode in relation to the desired or required sleep onset time and wake-up time, as evidenced by:

1. A chronic or recurrent complaint by the patient or caregiver of difficulty staying awake until the required or desired conventional bedtime; and
2. Difficulty remaining asleep until the required or desired time for awakening.

B. The symptoms have been present for at least three months.
C. When patients are allowed to choose their ad libitum schedule, they will exhibit improved sleep quality and duration and maintain an advanced phase of the 24-hour sleep-wake pattern.
D. Sleep logs are required, accompanied by actigraphy monitoring, whenever possible, for at least seven days, preferably 14 days. These demonstrate a stable advance in the timing of the habitual sleep period. Both work/school days and free days should be included within this monitoring.
E. The sleep disturbance is not better explained by another current sleep disorder, medical disorder, mental disorder, or medication/substance use.

Notes
1. Standardized chronotype questionnaires are useful tools to assess the chronotypes of eveningness and morningness. Individuals with advanced sleep phase typically score as morning types.
2. Demonstration of an advance (typically two or more hours) in the timing of circadian rhythms, as measured by DLMO or urinary 6-sulfatoxymelatonin, is desirable to confirm the advanced circadian phase.

Essential Features

Advanced sleep-wake phase disorder (ASWPD) is characterized by a stable advance (earlier timing) of the major sleep episode, such that habitual sleep onset and offset occur typically two or more hours before required or desired times. As a result, affected individuals complain of early morning awakenings and excessive afternoon or early evening sleepiness. When affected individuals are allowed to maintain an advanced schedule, sleep quality and quantity are improved.

Associated Features

Individuals with ASWPD may experience chronic partial sleep loss due to early morning awakening, particularly if sleep is resisted during the early evening. Several mutations associated with familial advanced sleep phase co-segregate with migraines, depression, and seasonal mood changes. On the other hand, morningness has also been associated with increased resilience, higher subjective well-being, and less depression.

Clinical and Pathophysiological Subtypes

Cohorts with familial advanced sleep phase disorder have been described, some of which have been correlated with genetic anomalies (see below).

Demographics

The prevalence of ASWPD in the general population is unknown and has been difficult to assess due to inconsistent criteria. In one large survey study involving middle-aged adults (40-64 years), the population prevalence was estimated at 1%. However, it is unclear what proportion of these participants would deem their schedule sufficiently troublesome to warrant clinical attention. A study of a general population of adults from New Zealand, assessed by questionnaires and detailed sleep logs, demonstrated a prevalence estimate of 0.3%. In another study of patients referred to a sleep clinic, the prevalence was estimated to be 0.04% based on detailed assessments with questionnaires, interviews with family members, and validation of diagnoses, when possible, with salivary measures of dim light melatonin onset (DLMO). There is no known sex difference.

Predisposing and Precipitating Factors

Advanced age appears to be a risk factor. Among a cohort aged 20 to 59 years, older age was associated with increased morningness which, in turn, was determined to be a significant mediator of numerous age-sleep relationships. A patient's ability to sleep at an abnormal circadian phase (phase tolerance) also impacts the degree to which they experience adverse symptoms; this adaptability varies among individuals. Studies report conflicting results concerning the relationship between age and phase tolerance, with some suggesting that age decreases phase tolerance and others suggesting that age may be protective. Genetic factors also can influence the condition, as has been definitively demonstrated among select familial cohorts (see Pathology and Pathophysiology section). Environmental influences may precipitate, maintain, or exacerbate the advanced circadian phase, but this has not been proven. ASWPD has been reported in children with neurodevelopmental disorders. In particular, studies in children with autism spectrum disorders and Smith-Magenis syndrome have shown profound alterations in melatonin secretion profiles, which may manifest as a phase advance with very early morning waking.

Increased morningness traits have been described in persons of African and Mayan descent, suggesting an ethnic vulnerability to developing ASWPD.

Familial Patterns

Various groups have described kindreds with familial ASWPD. These cases are characterized by an earlier age of onset. In addition, several genetic mutations and polymorphisms have been associated with familial ASWPD (see Pathology and Pathophysiology).

Onset, Course, and Complications

ASWPD onset is most often seen in later adulthood, although earlier onset in childhood can be observed in familial ASWPD. Repetitive attempts to resume sleep with awakenings may result in the development of a comorbid chronic insomnia disorder. In addition, individuals may use alcohol, other sedatives, or stimulants to alleviate symptoms, potentially exacerbating the underlying sleep/wake disorder. The impact on caregivers of children with neurodevelopmental disorders and ASWPD may be particularly profound.

Developmental Issues

ASWPD is most frequently encountered among older age groups. Consequently, the early age of onset of ASWPD should prompt further probing for a familial pattern. Caregivers may report that a child wakes "too early" in the morning, potentially disrupting the household routine and prematurely curtailing parental sleep. This problem is particularly true for younger children, who may require adult supervision once awake. Some presentations of ASWPD in children may reflect a strong chronobiological preference for morningness (see Pathology and Pathophysiology – familial advanced sleep-wake phase disorder). However, complaints regarding early awakening may also reflect unrealistic caregiver expectations regarding developmentally appropriate bedtime and wake time for a young child. Therefore, caregiver complaints of early awakening may, in fact, be a result of excessive time in bed rather than a true advance in sleep onset and offset.

Parental attention or the opportunity to engage electronic media upon waking may reinforce early rise times. The complaint that a child "falls asleep too early" in the evening, especially in adolescence, is rare and should also raise concerns regarding the possibility of chronic insufficient sleep or a sleep disorder resulting in increased sleep needs. The rarity of observations of advanced sleep onset and offset times among young children may also be due, in part, to societal expectations of earlier bed and wake times for this age group. Thus, a misalignment between social expectations or desired sleep patterns and circadian preference is less likely.

Pathology and Pathophysiology

Possible etiologies include: (1) an alteration in the ability of the circadian clock to phase delay; (2) a dominant phase advance region of the light phase response curve to entraining agents; (3) altered strength of entraining agents, such as light exposure, at the appropriate circadian time (voluntarily or involuntarily induced); or (4) a shortened endogenous circadian period of the pacemaker. However, only the latter has been definitively demonstrated among select familial ASWPD subjects.

Genetic analyses have revealed a missense mutation in a casein kinase (*CK1ε*) binding region of a Period gene (*hPer2*), culminating in hypophosphorylation by *CK1ε* in vitro. Hypophosphorylation of the Period protein results in promotion of its transcription and, ultimately, a decrease in the period"0 length of the clock. However, genetic heterogeneity is apparent within familial ASWPD, as demonstrated by the fact that other cohorts from this same study and another study did not reveal mutations in *hPer2*. A separate report of a Japanese familial ASWPD cohort described a missense mutation in a different casein kinase gene (*CKIδ*), resulting in decreased enzymatic activity in vitro. Yet another group described associations between *hPer1* and *hPer2* polymorphisms and questionnaire-based extreme morning circadian preferences without discrete ASWPD.

Further data have identified mutations in Timeless (*hTim*), Period 3 (*hPer3*), and Cryptochrome 2 (*hCry2*) genes in association with familial advanced sleep phase.

Objective Findings

Recordings of sleep logs and actigraphy over an interval of at least seven (and preferably fourteen) consecutive days demonstrate advanced sleep onset and sleep offset (typically greater than two hours) relative to socially acceptable times. Sleep onset is typically advanced to 6:00 p.m. to 9:00 p.m., with wake time between 2:00 a.m. to 5:00 a.m.

When performed at preferred (advanced) sleep times, polysomnography (though not routinely indicated nor required for the diagnosis) is essentially normal for age. However, if a conventional bedtime and wake-up time is enforced, polysomnographic recording may show short sleep latency and early awakening, curtailing total sleep time. Among patients with familial ASWPD, compared with unaffected controls, laboratory measures to determine the phase of circadian rhythms reliably show the expected phase advance in the timing of the nadir of the core body temperature rhythm and the dim light melatonin onset. Among those with nonfamilial ASWPD, a wider range of timing of circadian markers is found, with some values approaching those of unaffected controls. The Morning Eveningness questionnaire (MEQ) or other chronotype questionnaires may assist in determining the contribution of a morningness circadian preference to the presenting sleep/wake complaint.

Differential Diagnosis

Normal sleep. The elderly or very young may maintain advanced schedules without distress or impaired functioning. This pattern does not merit a diagnosis of ASWPD.

Chronic insomnia disorder. ASWPD must be distinguished from other causes of early awakening, including *chronic insomnia disorder*. Clinical diagnosis may be challenging. In ASWPD, sleep initiation and maintenance are improved when the patient is allowed to sleep on the preferred schedule (barring the presence of comorbid chronic insomnia disorder). Patients with true ASWPD are more likely to respond

to improved sleep hygiene and afternoon or evening light therapy with subsequent delay in sleep initiation and improvement in sleep quality. As with any sleep disturbances that persist over time, insomnia can develop secondarily. The Morning Eveningness questionnaire (MEQ) or other chronotype questionnaire may assist in determining the contribution of a morningness circadian preference to the presenting sleep/wake complaint. The presence of more than one contributing variable seems to be the norm, and each entity needs to be treated accordingly. Poor sleep hygiene practices, particularly evening napping among the elderly, may also suggest ASWPD.

Other circadian rhythm sleep-wake disorders. Individuals with an *irregular sleep-wake schedule* may demonstrate early bedtimes or early awakenings. However, these occur in the context of briefer sleep and wake periods that are scattered throughout the 24-hour period, without a defined major sleep period. The possibility of a *"free-running"* (non-entrained) circadian rhythm also merits consideration. However, patients with this condition are most commonly blind and report periodic insomnia complaints, depending on the relative relationship between the internal clock and the sleep-wake cycle.

Major depressive disorder is a common cause of early awakening. However, these patients do not typically manifest the early evening sleepiness characteristic of ASWPD.

Unresolved Issues and Further Directions

The existing literature suggests that clinicians are unlikely to encounter patients with stringently defined ASWPD. Until the identification of familial cohorts, only four cases were described. Assessment of study subjects with subjective reports of advanced sleep phase has revealed objectively conventional sleep and wake times. Select studies of patients with sole complaints of maintenance insomnia/early-morning awakenings have demonstrated marked advances (earlier timing) of physiologically measured circadian rhythms. The absence of the early evening sleepiness complaint may be due to the fact that the timing of sleep onset can be more readily modified than wake time. An early bedtime is more likely to be actively resisted due to its propensity to conflict with social or family obligations. Alternatively, evening sleep that occurs before entering the bed/bedroom may not be reported. If it is definitively demonstrated that the evening sleepiness complaint is not present or prominent, the term *advance-related sleep complaints* may be used in lieu of ASWPD. In these instances, sleep preferences should be established using actigraphy or MEQ. If this broader term is used, the condition is observed more commonly (~7% of respondents in a study of individuals aged 40-64 years). There is limited knowledge of the pathophysiology of ASWPD (or advance-related sleep complaints) beyond those associated with select cases of familial ASWPD. Increased use of physiologic circadian assessments will require the development of normative values to guide practitioners. Knowledge gaps are even more prominent within pediatric and adolescent populations.

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Irregular Sleep-Wake Rhythm Disorder

ICD-9-CM code: 327.33
ICD-10-CM code: G47.23

Alternate Names

Irregular sleep-wake cycle disorder, irregular sleep-wake rhythm type, irregular sleep-wake pattern.

Diagnostic Criteria

Criteria A-D must be met

A. The patient or caregiver reports a chronic or recurrent pattern of irregular sleep and wake episodes throughout the 24-hour period, characterized by symptoms of insomnia during the scheduled sleep period (usually at night), excessive sleepiness (napping) during the day, or both.
B. Symptoms are present for at least three months.
C. Sleep logs are required, accompanied by actigraphy monitoring, whenever possible, for at least seven days, preferably 14 days. These demonstrate no major sleep period and multiple irregular sleep bouts (at least three) during a 24-hour period.
D. The sleep disturbance is not better explained by another current sleep disorder, medical disorder, mental disorder, or medication/substance use.

Essential Features

Irregular sleep-wake rhythm disorder (ISWRD) is characterized by the lack of a clearly defined circadian rhythm of sleep and wake. The chronic or recurring sleep-wake pattern is temporally disorganized, with significant variability of sleep and wake episodes throughout the 24-hour cycle. Sleep and wake episodes across the 24-hour cycle are fragmented, with the longest sleep episode being typically less than four hours. Individuals or caregivers report frequent naps throughout the daytime. If recorded objectively with wrist actigraphy, total sleep time across the 24 hours may be normal for age. Individuals report symptoms of insomnia and excessive sleepiness, depending on the time of day and their particular sleep-wake pattern.

Associated Features

ISWRD is more commonly observed in neurodegenerative disorders, such as dementia, and some children with developmental disorders.

Clinical and Pathophysiological Subtypes

Older adults with Alzheimer's disease who experience sundowning may represent a clinical subtype with more severe sleep fragmentation and lower circadian rhythm amplitude than those who do not experience sundowning.

Demographics

The prevalence of ISWRD increases with advancing age, but it is likely that an age-related increase in neurodegenerative disorders, rather than aging per se, explains this relationship. Demographic patterns generally parallel those of associated risk factors such as neurodevelopmental and neurodegenerative disorders. There is limited information on the prevalence, sex ratio, and racial/ethnic characteristics of ISWRD.

Predisposing and Precipitating Factors

Children with certain developmental disorders are at increased risk for ISWRD. For example, children with autism, Asperger syndrome, or other pervasive developmental disorders often have highly irregular sleep patterns. Both ISWRD and non-24-hour sleep-wake rhythm disorder are common in Angelman syndrome, a neurodevelopmental disorder associated with an abnormality of chromosome 15q11-q13. The disorders have also been reported in children with Williams syndrome, a neurodevelopmental genetic disorder characterized by physical abnormalities and a distinctive cognitive profile with intellectual disabilities and learning difficulties. Children with such developmental disorders often have more severe and chronic circadian rhythm abnormalities and a higher risk of recurrence. In addition, certain medical conditions may also predispose typically developing children and adolescents to ISWRD. These include traumatic brain injury and chronic fatigue syndrome (myalgic encephalomyelitis).

Neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, and Huntington's disease increase the risk for ISWRD. Brain tumor survivors, especially patients who have experienced disruption in the hypothalamic-pituitary axis, may have an increased prevalence of circadian rhythm disorders, including ISWRD. Poor sleep hygiene and lack of exposure to external synchronizing agents such as light, activity, and social schedules may be precipitating factors for ISWRD, particularly in the institutionalized elderly.

Familial Patterns

Familial patterns may reflect those of predisposing and precipitating disorders.

Onset, Course, and Complications

The onset of the condition may occur at any age, though it is important to note that irregular sleep-wake patterns are an expected feature of infant development. The natural history of ISWRD in the pediatric population, including the likelihood of spontaneous resolution of symptoms and the long-term consequences, has not been well-described. The impact on caregivers of children with neurodevelopmental disorders and ISWRD may be particularly profound.

Likewise, there is limited information regarding the course and complications of ISWRD in adults. Due to the multiple awakenings and nocturnal wandering, falls in the elderly can be an indirect complication. In addition to the patient's sleep-wake dysfunction, the caregiver's sleep is often disrupted. The sleep and wake disruption associated with ISWRD is a common cause of institutionalization.

Developmental Issues

Caregivers may report that a child with ISWRD has difficulty falling asleep at the desired bedtime or "falls asleep too early" in the evening, wakes "too early" or has difficulty waking in the morning, or exhibits developmentally inappropriate napping behavior during the day. Parents may complain that their child sleeps too much or too little or at inappropriate times. Attempts to keep the child awake during the day, especially during sedentary activities, are often unsuccessful.

There may be phenotypes of ISWRD in children, with differences regarding symptom presentation and severity and chronicity related to the underlying condition. For example, children with chronic neurologic disorders (e.g., autism or chromosomal syndromes characterized by developmental delays) may have a more intractable and treatment-resistant pattern than children with more self-limited conditions (e.g., post-concussion).

Although ISWRD appears to be rare in typically developing children, it may be environmentally or behaviorally induced. Such precipitants may be present in children with irregular or fragmented sleep/wake schedules as a result of living in a chaotic household.

Pathology and Pathophysiology

The etiology of ISWRD is likely multifactorial. Anatomic or functional abnormalities of the circadian system, ranging from impaired light input due to cataracts or macular degeneration to degeneration of the retinohypothalamic tract or the suprachiasmatic nucleus, can result in an arrhythmic pattern of rest and activity. Decreased exposure to environmental entraining agents, such as light and structured physical

and social activities (common in institutionalized elderly and children with developmental disorders), can also contribute to an irregular sleep-wake cycle.

Studies in children and adults with autism spectrum disorders and children with Smith-Magenis syndrome have shown profound alterations in melatonin secretion profiles which demonstrate decreased amplitude or abnormal timing. These findings may be due to polymorphisms affecting melatonin synthesis or variants in genes coding for melatonin receptors. Other postulated mechanisms for circadian rhythm disturbances, particularly ISWRD, in these populations include clock gene polymorphisms and decreased levels of entrainment by social/environmental cues.

Objective Findings

Sleep logs and actigraphy are indicated for the identification of irregular sleep-wake rhythm. In addition to a careful sleep history, sleep logs and actigraphy monitoring show the expected lack of a clearly defined circadian rhythm of the sleep-wake cycle. Instead, it is characterized by multiple irregular sleep and wake periods throughout the 24-hour period. The irregular sleep-wake pattern is characterized by multiple sleep episodes (typically 2–4 hours) during a 24-hour period. The pattern may vary from day to day. Thus, monitoring for at least seven days and preferably 14 days is necessary to differentiate the irregular pattern from other circadian rhythm sleep-wake disorders.

Polysomnography is not required to establish the diagnosis. However, polysomnography may help identify other comorbid sleep disorders. In addition, monitoring of other circadian rhythms markers, such as core body temperature and melatonin for at least 24 hours, may also show a loss of clear circadian rhythmicity or a low amplitude rhythm.

Differential Diagnosis

Poor sleep hygiene and voluntary maintenance of irregular sleep schedules must be distinguished from an irregular sleep-wake pattern. Individuals with irregular sleep-wake rhythms may present with complaints of insomnia. Careful analysis of sleep logs or actigraphy will demonstrate multiple irregular periods of sleep throughout the 24-hour cycle in patients with ISWRD.

Other CRSWDs it is also important to distinguish ISWSRD from DSWPD or N24SWD, which may exhibit irregularities in day-to-day timing and are occasionally accompanied by a long nap and a more extended primary sleep episode.

Comorbid medical and psychiatric disorders, other sleep disorders, or medication in both adults and children may cause sleep fragmentation and daytime napping but do not typically demonstrate the absence of a major sleep period as seen in IRSWD

Unresolved Issues and Further Directions

There is limited knowledge of the pathophysiology, natural history, and complications of IRSWD in adults and children. Further research is necessary to identify the relative contribution of alterations in environmental synchronizing agents, such as light and activity, versus a dysfunction of the endogenous circadian clock.

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Non-24-Hour Sleep-Wake Rhythm Disorder

ICD-9-CM code: 327.34
ICD-10-CM code: G47.24

Alternate Names

Free-running disorder, non-entrained disorder, hypernychthemeral syndrome.

Diagnostic Criteria

Criteria A-D must be met
   A. There is a history of insomnia, excessive daytime sleepiness, or both, alternating with asymptomatic episodes, due to a misalignment between the 24-hour light-dark cycle and the non-entrained endogenous circadian rhythm of sleep-wake propensity.
   B. Symptoms are present for at least three months.

C. Sleep logs are required, accompanied by actigraphy monitoring, whenever possible, for at least 14 days, preferably longer for blind individuals. These demonstrate a pattern of sleep and wake times that typically delay each day.

D. The sleep disturbance is not better explained by another current sleep disorder, medical disorder, mental disorder, or medication/substance use.

Notes
1. Patients may present with a progressively delaying sleep-wake pattern, intermittent insomnia, and excessive sleepiness. Individual symptoms depend on the timing of attempts to sleep in relation to the circadian rhythm of sleep-wake propensity. The magnitude of the daily delay shift will depend on the endogenous circadian period and may range from less than 30 minutes (when the period is close to 24 hours) to more than an hour (when the period is longer than 25 hours).

2. The symptomatic episode will typically begin with a gradual increase in sleep latency and delayed sleep onset. As the sleep propensity rhythm shifts into the daytime, patients will have difficulty falling asleep at night and staying awake during the day. As the sleep-wake propensity rhythm drifts further, patients will eventually complain of late afternoon and evening sleepiness and naps, an early sleep onset time, and short sleep latency.

3. Measurement of other circadian rhythms, such as the DLMO or urinary 6-sulfatoxymelatonin rhythm obtained at two time points, 2-4 weeks apart (which allows sufficient time for the drift to be apparent), is desirable to confirm the non-entrained rhythm.

Essential Features

Non-24-hour sleep-wake disorder (N24SWD) is characterized by symptoms of insomnia or excessive sleepiness because the intrinsic circadian pacemaker is not entrained to a 24-hour light/dark cycle. The non-24-hour period can be shorter or, more typically, longer than 24 hours. Because the endogenous circadian rhythm is not aligned to the external 24-hour environment, symptoms will depend on when an individual tries to sleep in relation to the circadian rhythm of sleep and wake propensity. Individuals typically present with episodes of difficulty falling asleep or staying asleep, excessive sleepiness, or both, alternating with short asymptomatic periods. The severity of individual sleep-wake symptoms can be variable. Starting with the asymptomatic period when the individual's endogenous rhythm is aligned to the external environment and required sleep-wake times, sleep latency will gradually increase, and the individual will complain of sleep-onset insomnia. As the sleep phase continues to drift so that maximal endogenous sleep propensity is now in the daytime, individuals will have trouble staying awake during the day (exhibiting multiple daytime naps) and complain of sleepiness.

Associated Features

Most individuals with non-entrained circadian rhythms are totally blind, and the failure to entrain circadian rhythms is related to the lack of photic input to the circadian pacemaker. However, a proportion of totally blind people may retain functional circadian photoreception and entrained rhythms. In these individuals, blindness is due exclusively to an outer retina disorder (rod and cone layer) with retention of functional, intrinsically photosensitive retinal ganglion cells and the retinohypothalamic pathway. Some blind people may also be able to entrain to nonphotic cues (e.g., the timing of physical activity), producing entrainment at an abnormal phase in some cases. In sighted people with N24SWD, there is an increased incidence of psychiatric disorders; as a result, behavioral factors associated with those disorders may play a role in the development and maintenance of the N24SWD. Occasionally, the disorder is seen in those with developmental intellectual disability or dementia. In sighted individuals, there is often a history of delayed sleep phase and decreased exposure to light and structured social and physical activity. Some sighted individuals with N24SWD also demonstrate increased sleep duration.

Clinical and Pathophysiologic Subtypes

Totally blind patients with N24SWD are clinically different than sighted patients with N24SWD. In sighted patients, the circadian period is often 25 hours or longer. In contrast, in totally blind patients with the disorder, the circadian period follows an average length that is often closer to 24 hours and rarely shorter than 24 hours.

Demographics

Estimates suggest that over half of totally blind individuals have non-24-hour circadian rhythms; 50% to 80% of blind individuals complain of sleep disturbances. The prevalence, sex, and racial/ethnic differences of N24SWD in adults and children are unknown.

Predisposing and Precipitating Factors

Total blindness is the most common predisposing condition. Certain environmental conditions, such as decreased or inappropriately timed exposure to circadian entraining agents, particularly light, may induce the disorder in sighted people. In addition, delayed sleep-wake phase disorder may predispose to N24SWD in sighted persons. The condition has developed after chronotherapy for DSWPD. This disorder has also been reported in adults following traumatic brain injury.

Familial Patterns

Familial patterns may reflect those of any precipitating factors, especially genetic blindness disorders.

Onset, Course, and Complications

Onset may occur at any age in blind individuals, coincident with loss of light perception. In congenitally blind children, onset can occur from birth or during infancy. Onset in sighted individuals is more variable but is often first seen in adolescents or young adults, who initially present with delayed sleep-wake phase disorder and subsequently develop N24SWD. If untreated, the course is chronic. Attempts to regulate sleep and wake times may involve the use of alcohol, sedatives-hypnotics, and stimulants, which can exacerbate the underlying sleep disorder. Depressive symptoms and mood disorders can be comorbid, particularly in sighted patients. The adverse effects on school or work performance and other psychosocial complications, due to a lack of predictable sleep and wake times and excessive daytime sleepiness, are key motivations for seeking treatment.

Developmental Issues

Symptom presentation in children is dependent on the phase relationship between the desired sleep time and the circadian sleep propensity. Therefore, caregivers may report that a child has difficulty falling asleep at the desired bedtime, falls asleep too early in the evening, wakes too early, or has difficulty waking in the morning and staying awake during the day. Likewise, parents may complain that their child sleeps too much, too little, or at inappropriate times. The key characteristics that distinguish N24SWD from other sleep complaints or circadian sleep-wake disorders are twofold: (1) the predictable pattern of misalignment between the child's sleep patterns and the light-dark 24-hour cycle (i.e., a progressive delay in sleep onset and offset across days to weeks); and (2) periods of apparent "symptom remission" during those brief intervals when the child's circadian sleep-wake propensity coincides with the desired bed and wake times. The impact on caregivers' sleep and daytime functioning is often profound.

Although N24SWD is extremely rare in typically developing and sighted children, it has been reported with some frequency in children with intellectual disabilities and blindness. For example, children with optic nerve hypoplasia due to a variety of underlying causes (especially children with hypoplastic corpus callosum and comorbid severe intellectual and visual impairments) may demonstrate features of N24SWD. The disorder has also been described in pediatric patients with Rett syndrome, autism spectrum disorders, and Angelman syndrome. The common mechanism in all of these disorders is believed to be lack of entrainment to the 24-hour day resulting from the failure to perceive or attend to social/environmental zeitgebers (time cues). There have also been several case reports which describe the emergence of N24SWD in intellectually normal sighted children or adolescents who have limited or inappropriate exposure to environmental and other entraining cues (e.g., decreased light during the day or excessive light exposure in the evening). These individuals are likely to have significant psychiatric impairments that predispose them to avoidance of social interactions (e.g., anxiety) or medical conditions that involve enforced prolonged periods of inactivity (e.g., traumatic brain injury, chronic fatigue).

Little is known about the natural history of N24SWD in the pediatric population, including the impact of various treatment modalities, the likelihood of spontaneous resolution of symptoms, or long-term consequences.

There may be varying phenotypes of N24SWD in children, with differences in symptom presentation, severity, and chronicity related to the underlying condition. For example, children with chronic neurologic conditions such as blindness or neurodevelopmental disabilities may have a more intractable and treatment-resistant pattern than children with more self-limited conditions (e.g., traumatic brain injury).

Pathology and Pathophysiology

The intrinsic period of the human circadian pacemaker is usually longer than 24 hours and requires daily input from the environment to maintain synchrony to the 24-hour day. The light-dark cycle is the most critical environmental time cue (zeitgeber) in humans (as in other species), although nonphotic time cues also play a role in normal entrainment. A lack of photic input to the circadian pacemaker is clearly the cause of non-entrained rhythms in totally blind people. It has been suggested that in sighted individuals, a systematic delay due to inadequate exposure to light may contribute to the development of N24SWD. In addition, the disorder may be caused by an extremely prolonged or shortened endogenous circadian period that is outside of the range for entrainment to the 24-hour cycle or by an alteration in the response of the circadian clock to the entraining effects of light.

Objective Findings

Sleep studies yield different results depending on the degree of synchrony between sleep times and the circadian pacemaker when the sleep study is performed. Recording of sleep logs and actigraphy over prolonged periods (at least 14 days, but ideally longer in blind individuals) demonstrate the lack of a stable phase relationship between the timing of the sleep-wake cycle and the circadian phase. However, as external factors influence sleep-wake patterns, these individuals may not always demonstrate a consistent non-24-hour pattern. When sleep schedules follow the endogenous circadian propensity for sleep and wake, sleep onset and wake times are typically delayed each day. Serial measurements of circadian rhythms, such as melatonin, usually show a progressive daily delay of the phase of the rhythm consistent with a period longer than 24 hours.

Differential Diagnosis

Other CRSWDs Some individuals with severe *DSWPD* may demonstrate progressive delay of their sleep period by 30 minutes or more for several days, and their symptoms may be confused with N24SWD. However, individuals with DSWPD will typically reach a limit in how late sleep-wake timing occurs, rather than progressively moving around the clock. Similarly, ISWRD may be confused with N24SWD based on

clinical history; however, it can be distinguished through actigraphy and sleep logs demonstrating a pattern of daily progressive change in the primary sleep episode.

Unresolved Issues and Further Directions

There is only limited knowledge of the underlying pathophysiology of sighted persons with N24SWD. The primary risk factors in sighted persons appear to be twofold: a long circadian period beyond the range of entrainment to a 24-hour cycle or a progressive delay due to inappropriate exposure to light. This risk may explain the overlap between DSWPD and N24SWD. Future studies are needed to understand the role of genetic predisposition, environmental or social cues, and traumatic brain injury in the development of N24SWD, and to delineate other health consequences of the condition. Substantial knowledge gaps exist regarding the prevalence, pathophysiology, clinical presentation, natural history, effective treatment strategies, and prognosis of N24SWD in children and adolescents compared with adults.

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Shift Work Disorder
ICD-9-CM code: 327.36

ICD-10-CM code: G47.26

Alternate Names

Shift work sleep disorder.

Diagnostic Criteria

Criteria A-D must be met
   A. There is a report of insomnia or excessive sleepiness, accompanied by a reduction of total sleep time, which is associated with a recurring work schedule that overlaps the usual time for sleep.
   B. The symptoms have been present and associated with the shift work schedule for at least three months.
   C. Sleep logs are required, accompanied by actigraphy monitoring, whenever possible (preferably with concurrent light exposure measurement), for at least 14 days (work and free days). These demonstrate a disturbed sleep-wake pattern.
   D. The sleep disturbance is not better explained by another current sleep disorder, medical disorder, mental disorder, inadequate sleep hygiene, or medication/substance use.

Essential Features

Shift work disorder is characterized by complaints of insomnia or excessive sleepiness experienced in association with work hours that occur, at least in part, during the usual sleep episode. There are several types of shift-work schedules, including evening shifts, night shifts, early morning shifts, rotating shifts, split shifts, on-call overnight duty, and long duration work shifts that include work hours at night. The sleep disturbance is most commonly reported in association with night shifts, early morning shifts, and rotating shifts. Total sleep time in the major sleep episode is often curtailed by one to four hours. Sleep quality is unsatisfactory for night, early morning, and rotating shift workers and those who work long-duration shifts. Early morning work shifts can be associated with complaints of difficulty in sleep initiation as well as difficulty awakening. Permanent evening shifts may be primarily associated with sleep maintenance difficulty.

Excessive sleepiness usually occurs during work shifts (primarily night, early morning, and rotating shifts). An increased need to nap and a reduction in mental acuity may be evident. In addition to impaired performance at work, reduced alertness may compromise safety at work and on the commute to and from work.

The sleep disorder occurs despite attempts to optimize environmental conditions for sleep. The condition usually persists only for the duration of the shift work schedule. However, in some individuals, the sleep disturbance may persist beyond the duration of shift work.

Associated Features

Significant portions of free time may be required for recovery sleep, resulting in adverse social consequences. Compared with shift workers without shift work disorder, patients with shift work disorder report greater mood problems, such as impatience, avoidance of interaction with co-workers, a higher risk of depression, impaired social functioning, and lower coping skills. Patients with shift work disorder

also have a higher risk of subjective health complaints, ulcers, and substance abuse. The risk for sleepiness-related errors and accidents is highest at night, especially in the early morning hours for subjects with shift work disorder. Drowsy driving accident risk is highest in the morning when night shift workers commute home and early morning workers commute to work.

Clinical and Pathophysiological Subtypes

There are substantial individual differences in the ability to adjust to shift work. However, mechanisms underlying these individual differences are not known. Three phenotypes are proposed: 1) an insomnia phenotype, with insomnia when the sleep episode occurs at an adverse circadian phase, but normal wakefulness during the desired wake episode (e.g., during the work shift), 2) a sleepy phenotype, with sleepiness during the desired wake episode (e.g., work shift), but no insomnia during the sleep episode, despite its occurrence at an adverse circadian phase, and 3) a mixed phenotype. The latter phenotype is associated with the most impairment.

The requirement of extended work hours, such as on-call overnight duty and long-duration work shifts that include work hours at night, represents a specific clinical subtype. In addition to the circadian misalignment (having to work during the night), sleep loss and fatigue associated with prolonged continuous work increase the severity of excessive sleepiness and performance impairments.

Demographics

The prevalence of shift work disorder depends on the prevalence of shift work in the population. It is estimated that approximately 20-30% of the workforce in industrialized countries are employed in a job that requires shift work. Although the actual prevalence of clinically significant sleep disturbance and excessive daytime sleepiness due to work schedules is unknown, the total number of night-shift workers suggests that an estimated prevalence of 2% to 5% of the general population is reasonable. The prevalence of shift work disorder among rotating- and night-shift workers is estimated to be between ~10% and 38%. These figures do not include individuals with early morning or split shift work who may represent other at-risk groups. Conflicting data exist regarding gender vulnerability to developing shift work disorder and associated complications.

Predisposing and Precipitating Factors

Depending on the type of shift, circadian preference may influence the ability to adjust to or tolerate shift work. There are conflicting data on chronotype and vulnerability to developing shift work disorder. The data suggest both morning and evening chronotypes may have a higher tolerance to shift work. Persons with a high sleep reactivity (the degree to which a stressor disturbs sleep) are more vulnerable to developing shift work disorder. Persons with comorbid medical, psychiatric (e.g., depression), or other

sleep disorders such as sleep apnea and individuals with a strong need for stable sleep duration may be at particular risk. Older age constitutes a higher risk of developing shift work disorder. Increased longevity of shift work is not protective against shift work disorder. Social pressures before and after a work shift also contribute to short sleep durations in shift workers (e.g., social interactions with family and friends, domestic obligations, a second job, and leisure activities). Social pressures also diminish the desire or willingness to maintain a consistent daytime sleep schedule on days off, thereby reducing the likelihood of circadian adjustment.

Familial Patterns

Not applicable or known.

Onset, Course, and Complications

The condition is closely linked to work schedules and typically remits when the major sleep episode is scheduled at a conventional time. The course is quite variable because there are so many different work schedules, ranging from an occasional overnight shift to regular night work. Because shift work is often combined with extended hours of duty, sleepiness due to sleep deprivation can complicate the disorder. Exposure to light at the wrong time of the day often counteracts circadian adaptation. The tendency of most workers to resume full daytime activities and nighttime sleep during weekends and vacations is further complicating. For some individuals, the condition may lead to chronic sleep disturbances. Health consequences associated with shift work are partially attributable to circadian misalignment at multiple levels: between the light-dark cycle and the endogenous circadian clock, between behavioral (sleep-wake, food) cycles and the endogenous circadian clock, and among endogenous circadian processes. Circadian misalignment is accompanied by acute and chronic sleep loss, further contributing to adverse health consequences.

Adverse effects may include cognitive impairment and exacerbation of gastrointestinal, metabolic, reproductive, immune, neoplastic, headache (including migraine), psychiatric (including mood and anxiety disorders), substance use, and cardiovascular disorders. Hunger, food preferences, and metabolism are distinctly affected by shift work. Subsequent mistimed eating and circadian misalignment are associated with weight gain, metabolic changes, reduced glucose tolerance, and a higher risk of developing diabetes. Night shift work is associated with obesity; women are affected more than men. Additional risks for obesity and related complications include a higher frequency of shifts (e.g., more than eight shifts per month), longer shift hour durations, and chronicity of shift work (especially of more than 20 years duration). Disruptions of social and family life are frequent. Drug and alcohol dependency may result from attempts to improve the sleep and wakefulness disturbances produced by shift work. Fatigue and excessive sleepiness due to sleep loss and circadian misalignment pose important safety concerns. The level of alertness required of the worker and the intensity of symptoms need to be taken into account when evaluating the disorder. For example, the threshold for intervention may be lower for workers

whose performance is critical for personal or public safety (e.g., health care workers or nuclear power plant/public transport operators).

Developmental Issues

Not applicable or known.

Pathology and Pathophysiology

The condition is thought to be directly related to circadian misalignment and subsequent sleep loss. The sleep disturbance occurs due to high circadian wake propensity when the worker needs to sleep. The excessive sleepiness during the night and early morning appears to be partly related to cumulative sleep loss and partly due to a decreased circadian alerting signal that corresponds with the work time and the commute to and from work. Tolerance to night work varies considerably and may involve differences in the ability to sleep at an abnormal circadian phase ("phase tolerance"), the degree of circadian adaptation ("clock resetting") to the shift work schedule, and the pattern/timing of light-dark exposure relative to the individual's circadian phase. Alternatively, tolerance may be related to individual differences in response to circadian and homeostatic influences on sleep and wakefulness regulation. Environmental and social factors may also exacerbate sleep loss associated with shift work schedules.

The variable number tandem repeat (VNTR) of the circadian clock gene, period 3 (*PER3*), has been implicated in the development of disturbances in sleep associated with shift work disorder. This gene has a coding sequence repeated four (4-repeat allele) or five (5-repeat allele) times. Specifically, patients who are homozygous for a 4-repeat allele of the PER3 gene appear to be more vulnerable to sleep disturbances of shift work related to stress. In contrast, patients homozygous for a 5-repeat allele of the PER3 gene appear to be more vulnerable to sleep disturbances related to circadian misalignment.

Objective Findings

The condition is usually diagnosed by history. Sleep logs or actigraphy are necessary to demonstrate a disrupted sleep-wake pattern consistent with shift work disorder. While not required for the diagnosis, polysomnography is recommended if the etiology of the sleep disturbance is in question (e.g., to rule out sleep apnea or narcolepsy). Polysomnography during a typical daytime sleep episode after a work shift can also be helpful to determine the severity of the sleep disruption. However, this is undertaken primarily for research purposes. Polysomnography may demonstrate poor sleep quality, with prolonged sleep latency, sleep maintenance difficulty, or shortened total sleep time, depending on the timing of the sleep episode in relation to the underlying phase of the circadian timing system. The sleep episode may be fragmented, with frequent arousals and awakenings. If available, measures of the unmasked melatonin rhythm can indicate the degree of circadian misalignment.

The use of validated questionnaires such as the Shift work Disorder Screening Questionnaire or the Munich Chronotype Questionnaire adjusted for shift work may be helpful to clarify a diagnosis of shift work disorder.

Differential Diagnosis

Chronic insomnia disorder. Sleep disturbance is common to both shift work disorder and chronic insomnia disorder. The historical relationship between disturbed sleep and work-hour distribution should provide sufficient information to indicate the correct diagnosis. However, increasing frustration, negative expectations, and poor sleep hygiene may predispose the shift worker to a coexisting *chronic insomnia disorder* that could persist beyond the shift work schedule (i.e., shift work may represent a precipitating event that leads to chronic insomnia).

Obstructive sleep apnea and hypersomnolence disorders. The excessive sleepiness seen in shift workers should be differentiated from that caused by other primary sleep disorders such as *obstructive sleep apnea* or *narcolepsy*. Data suggest a higher rate of obesity among shift workers, placing them at greater risk for obstructive sleep apnea. Therefore, the two disorders may coexist.

Insufficient sleep due to conflicting daytime activities (e.g., childcare) or environmental interference with sleep (e.g., daytime noise) often contributes to sleepiness.

Unresolved Issues and Further Directions

Although there is substantial information regarding the prevalence of shift work in industrialized populations, less information is available regarding the prevalence of shift work *disorder* and its impact on health and safety. Further research is needed to improve the definition of shift work disorder, to develop diagnostic tools for shift work disorder, and to determine the prevalence of shift work disorder using diagnostic criteria. Efforts to elucidate the burden of shift work disorder over and above that which may be due to shift work in general are needed. In addition, investigation of mechanisms underlying the health and safety consequences of shift work disorder and identification of shift workers at greatest risk of shift work disorder are essential to improve understanding and management of the disorder.

Identifying the short- and long-term effects of shift work on mental and physical health, including endocrine and immune functions, telomerase activity/homeostasis, and gut microbiota changes, will improve our understanding of the consequences of the disorder. In addition, disentangling the effects of light at night, circadian misalignment, and stress at work on complications related to shift work will be essential for devising future interventions for shift work disorder. Finally, there is limited and conflicting information on the role of age, sex, and circadian chronotype on the vulnerability to shift work disorder.

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Jet Lag Disorder

ICD-9-CM code: 327.35

ICD-10-CM code: G47.25

Alternate Names

Jet lag, time zone change syndrome, jet lag syndrome, jet lag type, flight dysrhythmia

Diagnostic Criteria

Criteria A-C must be met

  A. There is a complaint of insomnia or excessive daytime sleepiness, accompanied by a reduction of total sleep time, associated with transmeridian jet travel across at least two time zones.
  B. There is associated impairment of daytime function, general malaise, or somatic symptoms (e.g., gastrointestinal disturbance) within one to two days after travel.
  C. The sleep disturbance is not better explained by another current sleep disorder, medical disorder, mental disorder, or medication/substance use.

Essential Features

Jet lag disorder is characterized by a temporary mismatch between the timing of the sleep and wake cycle generated by the endogenous circadian clock and that of the sleep and wake pattern required by a change

in time zone. As a result, individuals complain of disturbed sleep, sleepiness, and impaired daytime function. In addition to sleep disturbance and decreased daytime alertness, associated features may include general malaise and gastrointestinal symptoms. The severity and duration of symptoms are dependent on the number of time zones traveled, the ability to sleep while traveling, exposure to appropriate circadian times cues in the new environment, tolerance to circadian misalignment during the biological night, and the direction of the travel. Eastward travel (requiring advancement of circadian rhythms and the sleep-wake cycle) is usually more difficult to adjust to than westward travel.

Associated Features

Numerous other variables related to travel, such as sleep loss, decreased mobility, and alcohol or caffeine intake, contribute to the overall fatigue. Daytime sleepiness can lead to memory impairments, problems concentrating, driving and flying, and impaired decision-making. Emerging evidence suggests that jet lag can precipitate mood episodes, with increased incidence of depressive episodes following westward travel and hypomanic/manic episodes following eastward travel. Concerns have also been raised about the possible exacerbation of pre-existing psychotic disorders. Sleepiness, sleep disturbance, and circadian misalignment associated with jet lag may also impair athletic performance. Jet lag affects not only travelers but can also have significant consequences for airline pilots and flight attendants.

Clinical and Pathophysiological Subtypes

There are individual differences in the ability to adjust to rapid shifts in time zones; however, specific clinical subtypes have not been identified.

Demographics

Jet lag affects all age, sex, and racial groups. There are no large-scale studies on the prevalence of jet lag disorder. Data from a global surveillance network indicates that among a sample of international student travelers from the US, 7% were diagnosed with jet lag after returning home.

Predisposing and Precipitating Factors

Disturbed sleep, prolonged wakefulness, or shortened sleep duration before and during travel contribute to jet lag symptoms. Prolonged uncomfortable sitting positions, air quality and pressure, stress, and excessive caffeine and alcohol consumption may increase the severity of insomnia and impaired alertness and function associated with transmeridian travel.

Eastward travel often leads to difficulties with sleep onset as attempts to sleep are made at an earlier internal circadian time when the traveler's biological clock is promoting alertness (i.e., 'biological day'). Difficulty awakening and daytime sleepiness occur because the environmental wake time also occurs at an earlier biological time when the circadian clock is still promoting sleep (i.e., during the traveler's 'biological night').

Westward jet travel often leads to sleepiness in the evening hours of the new time zone as the traveler's internal circadian clock promotes sleep (i.e., biological night). Sleep disturbance in the new time zone typically manifests as a sleep maintenance issue. The traveler's circadian clock is promoting wakefulness (i.e., biological day) during the latter portion of the sleep episode, resulting in early morning awakenings and difficulty returning to sleep.

Basic circadian science principles suggest that inappropriately timed exposure to light and darkness during and immediately after jet travel can shift the circadian clock in the wrong direction, thereby increasing the duration of jet lag symptoms. The time at the destination upon arrival may also influence jet lag symptoms, with fewer symptoms reported following midday arrivals after eastward travel.

An individual's innate circadian preference may also confer a greater or lesser ability to adjust to a particular time shift, but this finding has not been systematically assessed. As noted, jet lag is typically worse after eastward than westward travel for most travelers. Westward travel is generally less problematic because the genetically determined period of the circadian clock in humans is, on average, longer than 24 hours. A circadian period longer than 24 hours is associated with a physiological tendency for sleep and wake times to shift later, thus making it easier to shift the circadian clock to more delayed sleep and wake times following westward travel. However, 20% to 25% of humans have circadian periods closer to or shorter than 24 hours, and these individuals may find it easier to adapt to eastward travel.

Familial Patterns

Not applicable or known.

Onset, Course, and Complications

Jet lag is usually a temporary condition. Symptoms begin approximately one to two days after air travel across at least two time zones and are self-limited. The severity and duration of symptoms are usually in proportion to the number of time zones traveled and the direction of travel. It is estimated that it takes one day per time zone for circadian rhythms to adjust to the local time. However, if traveling more than six time zones, circadian rhythms may shift in the opposite direction ("antidromic re-entrainment"), resulting in a prolonged period of adjustment (up to several weeks) and increased severity of jet-lag symptoms. In addition, exposure to light at inappropriate times may prolong the adjustment time by shifting the circadian rhythms in the opposite direction.

Menstrual and reproductive problems have been associated with frequent transmeridian travel in female airline personnel. Poor sleep hygiene practices may perpetuate sleep/wake complaints, and repetitive failed attempts to initiate or maintain sleep at desired times may predispose to the development of an insomnia disorder.

Developmental Issues

The effect of age on the development or severity of jet lag disorder symptoms is unknown. Limited available data suggest that older individuals may experience fewer jet lag symptoms than younger individuals. However, older individuals may be more sensitive to the adverse effects of jet lag on sleep due to a lower ability to sleep in conditions of circadian misalignment. However, the data have limitations, and further research is needed to better define the relationship between age and the development of jet lag disorder.

Pathology and Pathophysiology

The symptoms of jet lag disorder are due to both desynchronization of endogenous circadian rhythms with local time and the associated sleep disturbance. The local environment and behaviors of the traveler may influence the severity of symptoms. Factors inherent to jet travel, including prolonged time spent sitting in a confined space, decreased physical activity, and a low atmospheric pressure and humidity environment, may influence severity, as may the traveler's ability to sleep in-flight.

Objective Findings

Objective laboratory testing is usually not indicated. However, polysomnography or actigraphy, if performed, shows disturbed sleep and a loss of a normal sleep-wake pattern, or a mismatch between the timing of sleep and wakefulness and the desired sleep-wake pattern of the local time. Applied primarily for research purposes, circadian phase assessment (e.g., through measurement of the urinary 6-sulfatoxymelatonin rhythm) may help determine the extent of circadian adaptation to the new time zone.

Differential Diagnosis

The direct temporal relationship between disturbed sleep, daytime symptoms, and the transmeridian should provide sufficient information to indicate the correct diagnosis. If symptoms persist, a thorough history and physical examination should be considered to exclude other mental, physical, or sleep disorders. For example, sustained somatic complaints of gastrointestinal symptoms may indicate an underlying medical condition.

When jet lag symptoms persist, increasing frustration, negative expectations, and poor sleep hygiene may predispose the individual to the development of *chronic insomnia disorder*.

Unresolved Issues and Further Directions

The translatability of knowledge gained from animal models of jet lag to simulated jet lag in human laboratory studies and, ultimately, to actual transmeridian travel is not entirely clear. There is a need for more human field studies. Understanding mechanisms of individual differences in vulnerability and tolerance to disturbed sleep and wakefulness during jet lag is necessary. The potential impacts of jet lag on mental and physical health in travelers should also be further investigated. For example, early findings suggest that jet lag may alter diurnal microbiota variations and intestinal dysbiosis. Furthermore, emerging evidence suggesting associations between jet lag symptoms and alterations in brain functional connectivity open new promising avenues to better understand the pathophysiology and cognitive alterations associated with jet lag disorder. Finally, development and real-world testing of effective and practical strategies to combat jet-lag symptoms and improve sleep, performance, and safety are needed.

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Circadian Rhythm Sleep-Wake Disorder, Not Otherwise Specified (NOS)

ICD-9-CM code: 327.30
ICD-10-CM code: G47.20

Patients who meet all of the general diagnostic criteria for a CRSWD but do not meet criteria for one of the specific circadian rhythm sleep-wake disorders are classified here. In some cases, circadian rhythm sleep-wake disorder, NOS is a temporary diagnosis before establishing a more specific CRSWD diagnosis. CRSWDs due to an underlying medical, neurologic, or psychiatric disorder that meet all criteria for a specific CRSWD should be diagnosed with the specific circadian disorder and the comorbid condition noted. The sleep-wake pattern of patients with a CRSWD due to a comorbid condition may range from alterations in the phase of the sleep-wake cycle to irregular sleep-wake patterns. Recordings of sleep logs and actigraphy over a period of at least seven days, preferably for 14 days or longer, demonstrate sleep onsets and sleep offsets that may be delayed or advanced relative to conventional times, irregular or non-24-hour.