TABLE 3 Comparison between Groups A and B

Variable	Group A (n = 68) Mean	SD	N, B, Ab	Group B (n = 67) Mean	SD	N, B, Ab	*p* value for score	*p* value for the clinical distribution
I. Withdrawn	55.3	6.6	66, 1, 1	53.0	4.9	66, 0, 1	<0.05	NS
II. Somatic complaints	51.9	4.1	67, 0, 1	51.1	3.3	66, 1, 0	NS	NS
III. Anxious/ depressed	54.6	6.6	65, 1, 2	52.6	4.1	66, 0, 1	<0.05	NS
IV. Social problems	54.4	5.8	65, 1, 2	52.9	4.1	66, 1, 0	NS	NS
V. Thought problems	51.8	5.8	64, 1, 3	50.5	3.3	66, 0, 1	NS	NS
VI. Attention problems	53.9	5.8	66, 2, 0	52.8	4.1	67, 0, 0	NS	NS
VII. Delinquent behavior	55.9	6.6	62, 4, 2	54.5	4.9	65, 2, 0	NS	NS
VIII. Aggressive behavior	56.4	7.4	63, 2, 3	53.9	4.9	66, 1, 0	<0.05	NS
Internalizing	52.7	8.2	58, 3, 7	49.6	6.5	64, 0, 3	<0.05	NS
Externalizing	54.9	9.1	54, 4, 10	51.7	7.4	58, 2, 7	<0.05	NS
Total	54.0	9.1	54, 4, 10	49.8	8.2	62, 2, 3	<0.01	NS

Abbreviations: N = normal; B = borderline; Ab = abnormal; NS = not significant.

answers did not mark 0, and 21 of these 22 answers had free descriptions. Twelve listed complaints of "talking in their sleep," and the other 9 complained of "walking in their sleep."

Correlation between Sleeping Habits and T-Scores

High and statistically significant positive correlation coefficient values (>0.22) were obtained between the following:

- wake-up times and "withdrawn," "social problems," "attention problems," "aggressive behavior," internalizing, externalizing, and total scales;
- bedtimes and "withdrawn," "anxious/depressed," "social problems," "aggressive behavior," internalizing, and total scales;
- wake-up time range of variation and "social problems," "attention problems," "aggressive behavior," and total scales; and
- bedtime range of variation and total scales (see Table 4).

Although sleep duration did not exhibit a significant correlation with the total scale, the total scale showed highly positive significant correlations with wake-up times, bedtimes, and both wake-up time and bedtime range of variation. The total scale did not differ in a statistically significant manner between kindergarten and nursery school children.

TABLE 4 Correlation Coefficients between Sleep Habits and T-scores on Each Scale

Variable	Wake-up times	Bedtimes	Nocturnal sleep duration	Nap duration	Total sleep duration	Wake-up time range	Bedtime range
I. Withdrawn	0.24†	0.25†	−0.16	0.18*	−0.08	0.22*	0.15
II. Somatic complaints	0.09	0.11	−0.08	0.02	−0.08	0.09	0.13
III. Anxious/ depressed	0.19*	0.26†	−0.20*	0.21*	−0.10	0.16	0.17*
IV. Social problems	0.30†	0.23†	−0.09	0.01	−0.09	0.27†	0.14
V. Thought problems	0.17*	0.21	−0.16	0.19*	−0.08	0.19*	0.12
VI. Attention problems	0.31†	0.16	0.02	0.09	0.07	0.32†	0.14
VII. Delinquent behavior	0.20*	0.16	−0.07	0.00	−0.10	0.15	0.20*
VIII. Aggressive behavior	0.32†	0.23†	−0.06	0.08	−0.03	0.26†	0.22*
Internalizing	0.23†	0.26†	−0.18*	0.15	−0.12	0.19*	0.20*
Externalizing	0.27†	0.21*	−0.07	0.04	−0.07	0.20*	0.21*
Total	0.33†	0.26†	−0.10	0.09	−0.06	0.27†	0.24†

Statistical significance: *$p < 0.05$; †$p < 0.01$.

Comparison of Clinical Classification and Exceptional Sleeping Habits

The distribution of clinical classification and total scale score showed significant differences between early and late risers (Normal/Borderline/Abnormal = 29/0/2; early risers, 20/2/7; late risers, $p < 0.05$), and also between regular and irregular sleepers (37/1/1; regular sleepers, 22/0/9; irregular sleepers, $p < 0.01$). The number of children classified as normal, with reference to the total scale, was higher in early risers and regular sleepers than in late risers and irregular sleepers. Correspondingly, the number of children classified as abnormal, with reference to the total scale, was higher in late risers and irregular sleepers than in early risers and regular sleepers. In addition, the distribution of clinical classifications of regular sleepers also showed significant differences for delinquent behavior (39/0/0; regular sleeper, 25/6/0; irregular sleeper, $p < 0.01$), as well as for the internalizing scale (38/0/1; regular sleeper, 23/1/7; irregular sleeper, $p < 0.05$). No other significance differences for the clinical classifications between children exhibiting exceptional sleeping habits were obtained.

The distribution of the clinical classification in terms of the total scale showed no significant difference between kindergarten and nursery school children.

DISCUSSION

We examined the association between sleep habits and behaviors of healthy preschool children. We believe that problematic behaviors are associated with late and irregular wake-up times and bedtimes, but not with sleep duration. However, before discussing this issue, several other issues remain to be discussed.

Based on our common sense, for children aged 4–6 yrs, it might be hard to understand how and why the caretakers of children of group A allowed a bedtime after 23:00 h, to return home with their children after 21:00 h, and to leave home with their children after 21:00 h. In Japan, these conditions are not uncommon, not only in the urban areas but also in the rural areas, partly because many shopping centers are open 24 h and there is unrestricted access to media around the clock. Unfortunately, we were confident the three criteria we determined were not peculiar for most people in Japan, 2005. Nonetheless, this was not the case for those children of group B. It is of interest that no other differences were found between groups A and B (see Table 1).

CBCL, which has been translated into 58 languages, is currently the standard method used for evaluating behavioral problems in children. Its scaling system is widely accepted as being consistent, and it bypasses national and cultural differences. It was previously found that the higher the score, the greater the possibility of problematic behaviors in that scale (Achenbach, 1991); however, high CBCL scores do not mean "undesirable behaviors."

This preliminary study has several limitations. For example, no objective measures were applied to the data on sleep habits. Acebo et al. (2005) reported the overall similarities between actigraph sleep measures and mother-reported measures, although actigraph-based nocturnal wake minutes were higher than maternal diary reports. The present study neglected nocturnal waking because of a lack of measuring tools. Further investigations combined with objective measures are therefore warranted in the future. Another limitation of this study was the partial inability to control for the economic background among the caretakers of our young subjects. Socioeconomic (Clarisse et al., 2004), ethnic, and sociocultural environments (Giannotti et al., 2005) of the family are known to affect sleep habits of children. Although our subjects were all Japanese, data on the income of each family were not obtained. However, mother's employment status, which partially reflects socioeconomic status (Anderson et al., 2003), did not differ between groups A and B. In future studies, various other factors, including educational background and the income of each caretaker, should be taken into consideration. Question #92 of the CBCL asked about "talks or walks in sleep." There were no significant differences among the answer categories (not true, somewhat or sometimes true, and very true or often true) for this question between groups A and B. Although no direct questions were asked about sleep-related respiratory disturbances, no descriptions, such as snoring or sleep apnea, were found for question #100 of the CBCL that specifically addressed "trouble sleeping." According to these results, we concluded that no obvious sleep disturbances were likely to have affected the current results. Finally, we did not ask about media exposure, although the association between the duration of television viewing and the irregularity of sleep habits in young children has been described (Thompson & Christakis, 2005). This issue should be taken into consideration in future studies.

The current preliminary study demonstrated three issues. First, sleep duration did not affect either total T-scores or the distribution of clinical classification. Second, children in group A showed significantly higher T-scores for some of the eleven scales (including the total scale) than those in group B. The later the wake-up time and bedtime, the higher the total CBCL scale and the greater the range of variation in the wake-up and bedtimes. Third, the distribution of the clinical classifications by the total scale showed significant differences between early and late risers, and also between regular and irregular sleepers. The number of children classified into normal by the total scale was higher in early risers and regular sleepers than in late risers and irregular sleepers. The first issue indicated little association between problematic behaviors and sleep duration. Both of the other two issues showed an association between problematic behaviors and group A, late risers, late sleepers, irregular risers, and irregular sleepers.

With regard to the first issue, we need to consider that in adults there are both long and short sleepers. Such habits are considered to develop at a young age (American Academy of Sleep Medicine, 2005). The required sleep duration of an individual person is very difficult to determine, because the need for sleep is variable and can depend on several factors (Carskadon & Dement, 2005). Such interindividual variability might, therefore, have produced the present results that sleep duration showed little association with CBCL T-scores as well as the distribution of clinical classification.

Two possibilities were raised from the obtained association between problematic behaviors and group A, late risers, late sleepers, irregular risers, and irregular sleepers. Children who had higher CBCL scores were likely to show similar sleeping habits to group A, and children who exhibited similar sleeping habits to Group A had a greater possibility of exhibiting problematic behaviors. With regard to the former possibility, children with autism, ADHD, or intellectual disability are known to have sleep problems (O'Brien et al., 2003; Richdale, 2001; Robinson & Richdale, 2004). In addition, CBCL is reported to be a useful instrument to identify autistic and ADHD children (Chen et al., 1994; Duarte et al., 2003). However, according to the current CBCL as well as the caretakers' self report, no participating children in our study were considered to be suffering from chronic disorders, such as autism, ADHD, or intellectual disability. Thus, it is unlikely that the present results were affected by such disordered children. Moreover, it could be assumed that behavioral problems that appeared around sleep-onset time resulted in difficulty in falling asleep. Although the distribution of answers to question #100 that addressed trouble sleeping showed a significant difference between the children of group A versus group B, no concrete child behavior that prevented them from falling asleep was described in the free description column. Further studies are needed to confirm the possibility that children who have higher CBCL scores are likely to show similar sleeping habits as children of group A.

Many reports have described that the evening type, which is often accompanied by delayed wake-up times, delayed bedtimes, and an irregular lifestyle, is associated with problematic behaviors (Caci et al., 2005; Carney et al., 2006; Gau et al., 2004, 2007; Gaina et al., 2006; Monk et al., 2004; Soehner et al., 2007; Susman et al., 2007). These reports are consistent with the current results that preschool children who showed similar sleep habits as group A showed a greater risk of showing problematic behaviors. Kerkhof and Van Dongen (1996) mentioned that the endogenous phasing of their circadian biological clock of individuals with morning types differs from that of evening types. According to Bailey and Heitkemper (2003), evening types have a later morning temperature rise and later wake-up time than do morning types. Moreover, individuals who are maximally alert in the morning have an earlier peak in their temperature circadian rhythm than individuals who are most alert in the evening (Duffy et al., 2001). These reports suggested that evening types suffer from circadian desynchronization (Katz et al., 2001; Rivkees, 2001). Taking these reports into consideration, we hypothesize that children with an evening preference (preschool children who belonged to group A as well as late risers, late sleepers, irregular risers, and irregular sleepers in the current study) suffer from circadian desynchronization.

Exposure to morning light and avoidance of nocturnal light are essentially important for human beings to synchronize their biological clock to the Earth's 24 h cycle (Minors et al., 1991). Without this synchronization, one could be suffering from circadian desynchronization, resulting in various physical and mental disturbances (Arendt et al., 2005). In addition, exposure to sunlight in the morning is known to activate the serotonergic system (Cagampang et al., 1993). The concept of low serotonin syndrome—as characterized by aggressiveness, impulsiveness, and suicidal attempts—has been previously proposed (Linnoila et al., 1992). Reduced serotonergic activity was reported to be a disadvantage and enhanced activity an advantage to adult male vervet monkeys in attaining high social dominance status (Raleigh et al., 1991). For adolescents, Gaina et al. (2006) and Gau et al. (2007) recommended a morning preference to reduce behavioral/emotional problems. The current, preliminary study suggests that this recommendation should extend to preschoolers.

REFERENCES

Acebo C, Sadeh A, Seifer R, Tzischinsky O, Hafer A, Carskadon MA. (2005). Sleep/wake patterns derived from activity monitoring and maternal report for healthy 1- to 5-year-old children. *Sleep* 28:1568–1577.

Achenbach TM. (1991). *Manual for the Child Behavior Checklist/4–18 and 1991 Profile*. Burlington, Vt.: University of Vermont Department of Psychiatry.

American Academy of Sleep Medicine. (2005). *The International Classification of Sleep Disorder*, 2nd edn. Westchester, III.

Anderson PM, Butcher KF, Levine PB. (2003). Maternal employment and overweight children. *J. Health Econ.* 22:477–504.

Arendt J, Stone B, Skene DJ. (2005). Sleep disruption in jet lag and other circadian rhythm-related disorders. In Kryger MH, Roth T, Dement WC (eds.) *Principles and Practice of Sleep Medicine*, 4th edn. Elsevier Saunders, pp. 659–672.

Bailey SL, Heitkemper MM. (2003). Circadian rhythmicity of cortisol and body temperature: Morningness-eveningness effects. *Chronobiol. Int.* 18:249–261.

Benesse Corporation. (2005). *The Third Infant's Life Questionnaire Report, 2005*. Tokyo: Benesse [in Japanese].

Caci H, Mattei V, Bayle FJ, Nadalet L, Dossios C, Robert P, Boyer P. (2005). Impulsivity but not venturesomeness is related to morningness. *Psychiatry Res.* 134:259–265.

Cagampang FR, Yamazaki S, Otori Y, Inouye SI. (1993). Serotonin in the raphe nuclei: Regulation by light and an endogenous pacemaker. *Neuroreport* 5:49–52.

Carney CE, Edinger JD, Meyer B, Lindman L, Istre T. (2006). Daily activities and sleep quality in college students. *Chronobiol. Int.* 23:623–637.

Carskadon MA, Dement WC. (2005). Normal human sleep: an overview. In Kryger MH, Roth T, Dement WC (eds.) *Principles and Practice of Sleep Medicine*, 4th edn. Elsevier Saunders, pp. 13–23.

Chen WJ, Faraone SV, Biederman J, Tsuang MT. (1994). Diagnostic accuracy of the Child Behavior Checklist scales for attention-deficit hyperactivity disorder: A receiver-operating characteristic analysis. *J. Consult. Clin. Psychol.* 62:1017–1025.

Clarisse R, Testu F, Maintier C, Alaphilippe D, Le Floc'h N, Janvier B. (2004). A comparative study of nocturnal sleep duration and timetable of children between five- and ten-years-old according to their age and socio-economic environment (in French). *Arch. Pediatr.* 11:85–92.

Cornwell AC, Feigenbaum P. (2006). Sleep biological rhythms in normal infants and those at high risk for SIDS. *Chronobiol. Int.* 23:935–961.

Duarte CS, Bordin IA, de Oliveira A, Bird H. (2003). The CBCL and the identification of children with autism and related conditions in Brazil: Pilot findings. *J. Autism Develop. Dis.* 33:703–707.

Duffy JF, Rimmer DW, Czeisler CA. (2001). Association of intrinsic circadian period with morningness-eveningness, usual wake time, and circadian phase. *Behav. Neurosci.* 115:895–899.

Gaina A, Sekine M, Kanayama H, Takashi Y, Hu L, Sengoku K, Kagamimori S. (2006). Morning-evening preference: Sleep pattern spectrum and lifestyle habits among Japanese junior high school pupils. *Chronobiol. Int.* 23:607–621.

Gau SS, Soong WT, Merikangas KR. (2004). Correlates of sleep-wake patterns among children and young adolescents in Taiwan. *Sleep* 27:512–519.

Gau SS, Shang CY, Merikangas KR, Chiu YN, Soong WT, Cheng AT. (2007). Association between morningness-eveningness and behavioral/emotional problems among adolescents. *J. Biol. Rhythms.* 22:268–274.

Giannotti F, Cortesi F, Sebastiani T, Vagnoni C. (2005). Sleeping habits in Italian children and adolescents. *Sleep Biol. Rhythms* 3:15–21.

Itani T, Kanbayashi Y, Nakata Y, Kita M, Fujii H, Kuramoto H, Negishi A, Tuduka M, Okada A, Natori H. (2001). Study on validity of the Japanese version of CBCL/4–18. *Shyoni No Seishin To Shinkei* 4:243–252 [in Japanese].

Janvier B, Testu F. (2007). Age-related differences in daily attention patterns in preschool, kindergarten, first-grade, and fifth-grade pupils. *Chronobiol. Int.* 24:327–343.

Katz G, Durst R, Zislin Y, Barel Y, Knobler HY. (2001). Psychiatric aspects of jet lag: Review and hypothesis. *Med. Hypotheses* 56:20–23.

Kerkhof GA, Van Dongen HP. (1996). Morning-type and evening-type individuals differ in the phase position of their endogenous circadian oscillator. *Neurosci. Lett.* 218:153–156.

Kohyama J, Shiiki T, Ohinata-Sugimoto J, Hasegawa T. (2002). Potentially harmful sleep habits of three-year-old children in Japan. *J. Dev. Behav. Pediatri.* 23:67–70.

Kohyama J, Furushima W, Hasegawa T. (2003). Behavioral problems in children evaluated for sleep disordered breathing. *Sleep Hypnosis* 5:89–94.

Lehnkering H, Siegmund R. (2007). Influence of chronotype, season, and sex of subject on sleep behavior of young adults. *Chronobiol. Int.* 24:875–888.

Linnoila VM, Virkkunen M. (1992). Aggression, suicidality, and serotonin. *J. Clin. Psychiatry* 53 (Suppl.):46–51.

Mallis MM, DeRoshia CW. (2005). Circadian rhythms, sleep, and performance in space. *Aviat. Space Environ. Med.* 76(6 Suppl.):B94–B107.

Mieda M, Williams SC, Richardson JA, Tanaka K, Yanagisawa M. (2006). The dorsomedial hypothalamic nucleus as a putative food-entrainable circadian pacemaker. *Proc. Natl. Acad. Sci. USA.* 103: 12150–12155.

Minors DS, Waterhouse JM, Wirz-Justice A. (1991). A human phase-response curve to light. *Neurosci. Lett.* 133:36–40.

Mitchell RB, Kelly J. (2006). Behavior, neurocognition and quality-of-life in children with sleep-disordered breathing. *Int. J. Pediatr. Otorhinolaryngol.* 70:395–406.

Monk TH, Buysse DJ, Potts JM, DeGrazia JM, Kupfer DJ. (2004). Morningness-eveningness and lifestyle regularity. *Chronobiol. Int.* 21:435–443.

O'Brien LM, Ivanenko A, Crabtree VM, Holbrook CR, Bruner JL, Klaus CJ, Gozal D. (2003). Sleep disturbances in children with attention deficit hyperactivity disorder. *Pediatr. Res.* 54:237–243.

Ohayon MM, Vecchierini MF. (2005). Normative sleep data, cognitive function and daily living activities in older adults in the community. *Sleep* 28:981–989.

Raleigh MJ, McGuire MT, Brammer GL, Pollack DB, Yuwiler A. (1991). Serotonergic mechanisms promote dominance acquisition in adult male vervet monkeys. *Brain Res.* 559:181–190.

Randazzo AC, Muehlbach MJ, Schweitzer PK, Walsh JK. (1998). Cognitive function following acute sleep restriction in children ages 10–14. *Sleep* 21:861–868.

Richdale A. (2001). Sleep in children with autism and Asperger's syndrome. In Stores G, Wiggs L (eds.) *Sleep Disturbance in Children and Adolescents with Disorders of Development. Its Significance and Management.* Cambridge: Cambridge University Press, pp. 181–191.

Rivkees SA. (2001). Mechanisms and clinical significance of circadian rhythms in children. *Curr. Opin. Pediatri.* 13:352–357.

Robinson AM, Richdale AL. (2004). Sleep problems in children with an intellectual disability: Parental perceptions of sleep problems, and views of treatment effectiveness. *Child Care Health Dev.* 30: 139–150.

Soehner AM, Kennedy KS, Monk TH. (2007). Personality correlates with sleep-wake variables. *Chronobiol Int.* 24:889–903.

Spiegel K, Leproult R, Van Cauter E. (1999). Impact of sleep debt on metabolic and endocrine function. *Lancet* 354:1435–1439.

Spiegel K, Knutson K, Leproult R, Tasali E, Van Cauter E. (2005). Sleep loss: A novel risk factor for insulin resistance and type 2 diabetes. *J. Appl. Physiol.* 99:2008–2019.

Susman EJ, Dockray S, Schiefelbein VL, Herwehe S, Heaton JA, Dorn LD. (2007). Morningness/eveningness, morning-to-afternoon cortisol ratio, and antisocial behavior problems during puberty. *Dev. Psychol.* 43:811–822.

Suzuki M, Takahashi C, Nomura Y, Segawa M. (2002). What do care workers worry about in relationships between modern young children and their parents? *J. Child Health* 61:593–598 [in Japanese].

Suzuki M, Nomura Y, Segawa M. (2003). Influence of the nursing environment on sleep-wake rhythms. *Jap. J. Clin. Ecol.* 12:122–127 [in Japanese].

Suzuki M, Nakamura T, Kohyama J, Nomura Y, Segawa M. (2005). Children's ability to copy triangular figures is affected by their sleep-wakefulness rhythms. *Sleep Biol. Rhythms* 3:86–91.

Taheri S. (2006). The link between short sleep duration and obesity: We should recommend more sleep to prevent obesity. *Arch. Dis. Child.* 91:881–884.

Teixeira LR, Lowden A, Turte SL, Nagai R, Moreno CR, Latorre MDR, Fischer FM. (2007). Sleep and sleepiness among working and non-working high school evening students. *Chronobiol. Int.* 24: 99–113.

Terman M, Terman JS. (2005). Light therapy. In Kryger MH, Roth T, Dement WC (eds.) *Principles and Practice of Sleep Medicine*, 4th edn. Elsevier Saunders, pp. 1424–1442.

The Japanese Society of Child Health. (2000). Health infant degree investigation report in fiscal year 2000. Available at http://www.aiiku.or.jp/aiiku/jigyo/contents/kanren/kr0108/kr0108.htm [in Japanese]. Accessed October 13, 2006.

Thompson DA, Christakis DA. (2005). The association between television viewing and irregular sleep schedules among children less than three years of age. *Pediatrics* 116:851–856.

Touitou Y, Smolensky MH, Portaluppi F. (2006). Ethics, standards, and procedures of animal and human chronobiology research. *Chronobiol. Int.* 23:1083–1096.

Ukai H, Kobayashi TJ, Nagano M, Masumoto KH, Sujino M, Kondo T, Yagita K, Shigeyoshi Y, Ueda HR. (2007). Melanopsin-dependent photo-perturbation reveals desynchronization underlying the singularity of mammalian circadian clocks. *Nat. Cell Biol.* 9:1327–1334.

Waterhouse J, Reilly T, Atkinson G, Edwards B. (2007). Jet lag: Trends and coping strategies. *Lancet* 368:1117–1129.

Wever RA. (1979). *The Circadian System of Man: Results of Experiments Under Temporal Isolation*. New York: Springer-Verlag.

Wolfson AR, Carskadon MA. (1998). Sleep schedules and daytime functioning in adolescents. *Child Dev.* 69:875–887.

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Review article

A newly proposed disease condition produced by light exposure during night: Asynchronization

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Abstract

The bedtime of preschoolers/pupils/students in Japan has become progressively later with the result sleep duration has become progressively shorter. With these changes, more than half of the preschoolers/pupils/students in Japan recently have complained of daytime sleepiness, while approximately one quarter of junior and senior high school students in Japan reportedly suffer from insomnia. These preschoolers/pupils/students may be suffering from behaviorally induced insufficient sleep syndrome due to inadequate sleep hygiene. If this diagnosis is correct, they should be free from these complaints after obtaining sufficient sleep by avoiding inadequate sleep hygiene. However, such a therapeutic approach often fails. Although social factors are often involved in these sleep disturbances, a novel clinical notion – asynchronization – can further a deeper understanding of the pathophysiology of these disturbances. The essence of asynchronization is a disturbance in various aspects (e.g., cycle, amplitude, phase and interrelationship) of the biological rhythms that normally exhibit circadian oscillation, presumably involving decreased activity of the serotonergic system. The major trigger of asynchronization is hypothesized to be a combination of light exposure during the night and a lack of light exposure in the morning. In addition to basic principles of morning light and an avoidance of nocturnal light exposure, presumable potential therapeutic approaches for asynchronization involve both conventional ones (light therapy, medications (hypnotics, antidepressants, melatonin, vitamin B12), physical activation, chronotherapy) and alternative ones (kampo, pulse therapy, direct contact, control of the autonomic nervous system, respiration (qigong, tanden breathing), chewing, crawling). A morning-type behavioral preference is described in several of the traditional textbooks for good health. The author recommends a morning-type behavioral lifestyle as a way to reduce behavioral/emotional problems, and to lessen the likelihood of falling into asynchronization.

Keywords: Desynchronization; Serotonin; Morningness; Eveningness; Sleep; Circadian rhythm

1. Introduction

The suprachismatic nucleus (SCN) is the site where circadian rhythms are generated. The SCN develops throughout the course of gestation, but is still immature for some time after birth. The SCN is suggested to be vulnerable to maternal influences [1]. Since disturbances of circadian rhythms in the young can impact the function of the SCN in the subsequent lifespan, techniques to deal with them are much needed. However, we have little knowledge about the pathophysiology of the disruption of circadian rhythms in the clinical setting, making it difficult to find an appropriate clinical approach to treating these patients. It is very difficult at present to take adequate measures against circadian disruptions in patients.

This review article introduces the recent phenomenon of a nocturnal lifestyle among preschoolers/pupils/students in Japan, and the association between this nocturnal lifestyle and behavior. Then, the presumed involvement of the biological clock and the serotonergic

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system in those who prefer a nocturnal lifestyle are reviewed. Finally, a new clinical entity – asynchronization – is proposed, in an attempt to elucidate the pathophysiology of circadian disruptions from which many preschoolers/pupils/students in Japan are evidently suffering, and to provide new clinical therapeutic approaches.

2. The recent phenomenon of a nocturnal lifestyle among preschoolers/pupils/students in Japan

2.1. Recent figures on bedtime and sleep duration of preschoolers/pupils/students in Japan

The percentage of 1-year-old children who went to bed later than 22:00 in Japan was 25.7%, 35.4%, 40.2%, and 54.4% in 1980, 1990, 1995, and 2000, respectively [2]. For 3-year-old children, these respective figures were 21.7%, 35.5%, 37.2%, and 52.0%. Kohyama et al. found that the latter figures were 43.8% in 1999 [3], and 49.8% in 1999–2000 [4]. In addition, in 2004, 51.1% of the 1-year-old children in Fukuoka went to bed later than 22:00 [5].

In 1979, no fourth grade pupils of the elementary school in Tokyo, Japan, reportedly went to bed later than 0:00, while in 2002, 2% of them went to bed later than 0:00 [6]. In the same study, approximately 40% of pupils in the fourth grade went to bed earlier than 21:00 in 1979, whereas this figure dropped to 6% in 2002. The Ministry of Education, Culture, Sports, Science and Technology reported that the mean bedtime in 2004 for elementary school pupils in the fifth and sixth grade was 22:03, that for junior high school students was 23:18, and that for the senior high school students was 0:06 [7]. According to a study performed by "Zenkokuyougokyouinkai" (a nationwide association of nurse–teachers in Japan) [8], the mean bedtime for pupils in the fifth grade of elementary school in 2005 was 22:10, that for pupils in the second grade of junior high school was 23:26, and that for students in the second grade of senior high school was 23:50. Tagaya et al. reported the average bedtime of senior high school students in Japan to be 0:03 [9].

In 3-year-old children, bedtime delay is reported to reduce total daily sleep duration [4]. Indeed, in accordance with the recent development of bedtime delay, the sleep duration of children in Japan was also reduced. Shimada et al. examined the published papers on sleep duration of infants and concluded that sleep duration in the early 1990s was reduced by 1–2 h of that in earlier Q13 reports [19]. For example, the mean total daily sleep duration of 1-year-old children was 12.9 h in 1985 [11], and was 10.9 h in 1-year-old children born between 1992 and 1994 [10]. According to consecutive studies conducted by the Bennesse Corporation, the nocturnal sleep duration of children aged 3–6 years in 2000 (10.10 h for children attending kindergarten, 9.35 h for children attending nursery, and 9.95 h for children attending neither kindergarten nor nursery) was reduced by 9–15 min in comparison with that in 1995 [12].

According to data obtained from the Japan Broadcasting Corporation and Japanese Society of School Health, between 1965 and 2000 the sleep duration of elementary school pupils, junior, and senior high school students in Japan had been reduced on average by 1.1–1.6 min per year [13]. The mean nocturnal sleep duration in 2004 for elementary school pupils in fifth and sixth grade was 8.77 h, that for junior high school students was 7.42 h, and that for senior high school students was 6.55 h [7]. Similarly, in 2005, the mean nocturnal sleep duration of fifth grade elementary school pupils was 8.40 h, that for second grade junior high school students was 7.23 h, and that for second grade senior high school students was 6.51 h [8]. Tagaya et al. reported the average sleep duration of senior high school students in Japan to be 6.30 h [9].

2.2. Complaints of preschoolers/pupils/students in Japan in recent years

In 1979, 8.1% of children attending day nurseries in Japan were reported as yawning frequently in the morning, and 10.5% as becoming easily tired, while these numbers increased remarkably in 2000 to 53.2% and 76.6%, respectively [14]. Accordingly, approximately 80% of kindergarten and nursery school teachers reported that many children are sleep deprived [15].

"Yougokyouyukennkyuukai" (an association of nurse–teachers in Tokyo) [16] reported that the rates of pupils and students who complained of sleepiness during the third and fourth lesson periods in the school (approximately from 10:00 to 12:00) were 50% for fifth and sixth grade elementary school boys, 60% for fifth and sixth grade elementary school girls, 70% for junior high school student boys, and 80% for junior high school student girls. In contrast to the early morning (around 4:00) and afternoon (around 14:00) periods, the late morning is the period when humans generally tend to be most alert and active [17].

In addition, according to "Zenkokuyougokyouinkai" [8], sleep insufficiency was reportedly felt by 47.3%, 60.8%, and 68.3% of fifth grade elementary school pupils, second grade junior high school students, and second grade senior high school students, respectively. The reasons given for the state of sleep insufficiency indicated by these pupils and students are shown in Table 1. Among these reasons, "hard to fall asleep" was listed among the top three reasons in all three age groups.

Kaneita et al. [18] conducted a nationwide study to ascertain the prevalence of insomnia, its symptoms, and associated factors among students in junior and

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Table 1
Reasons for sleep insufficiency

	Elementary school students (%)	Junior high school students (%)	Senior high school students (%)
1	Difficulties falling asleep (43.8)	TV and video (44.5)	Cellular phone (42.4)
2	TV and video (39.3)	Homework (32.2)	TV and video (38.8)
3	Homework (26.3)	Hard to fall asleep (31.1)	Difficulties falling asleep (27.1)

The number in parentheses indicates the percentage of pupils/students who listed the issue among the pupils/students who felt they suffered from sleep insufficiency.

senior high schools in Japan. A total of 103,650 adolescents responded, and 102,451 questionnaires were analyzed. The prevalence of a difficulty in initiating sleep, difficulty maintaining sleep, and early morning awakening was 14.8%, 11.3%, and 5.5%, respectively. Insomnia was defined as the presence of one or more of these three symptoms. The prevalence of insomnia was found to be 23.5%.

Taking these facts together, preschoolers/pupils/students in Japan are likely to be suffering from both daytime sleepiness and nocturnal insomnia. In a study of 9261 junior high school students (mean age of 12.8 years) in Toyama prefecture, Japan, Gaina et al. [19] found that (1) a total of 2328 students (25.2%) reported sleepiness almost always and 4401 (47.6%) reported sleepiness often, (2) reduced sleep time was significantly associated with sleepiness, and (3) a dose–response relation was found between sleepiness and sleep disturbances, physical activity, and media contact time. They concluded that sleep insufficiency is the main cause of daytime sleepiness in junior high school students in Japan, and that proper sleep habits, a high physical activity level, and limited TV viewing time should be promoted among junior high school students.

Exercise is one of the issues cited as important for good sleep hygiene [20], and an association between the duration of television viewing and the irregularity of sleep habits in young children has been described [21]. Television viewing in childhood and adolescence is reported to be associated with being overweight, poor fitness, smoking, and raised cholesterol in adulthood [22]. According to Gaina et al. [23], watching television along with playing videogames for a long period of time were significantly associated with prolonged sleep onset latency, which is associated with poor sleep hygiene and insufficient sleep time. Lack of sleep increases body weight [24]; being overweight tends to reduce physical activity, and a low physical activity level in turn tends to exacerbate being overweight. Low physical activity and excessive media exposure are likely to be factors that increase inadequate sleep hygiene, which can result in insomnia. In addition, lack of discipline in the home and in the public education system, and the prevalence of shopping centers that are open 24 h per day may stimulate the increase in insomnia. The insomnia induced by inadequate sleep hygiene can then lead to the reported sleep insufficiency and daytime sleepiness of pupils/students in Japan. This might be the reason why pupils/students in Japan are suffering from both daytime sleepiness and nocturnal insomnia.

According to research in March 2001 in Tokyo [6], three major complaints of elementary school pupils were "persistent need to yawn" (62%), "desire to sleep" (58%), and "desire to lie down" (47%). Complaints of junior high school students were "desire to sleep" (boys/girls; 73.8%/80.8%), "persistent need to yawn" (43.6%/69.1%), and "desire to lie down" (43.2%/47.2%). The other complaints raised by more than 20% of junior high school students were "hard to remember" (35.2%/33.6%), "hard to be active" (21.3%/28.0%), "hard to concentrate" (21.0%/23.8%), "irritated" (20.5%/24.2%), "hypersensitive" (20.0%/27.0%), "neck stiffness" (29.3%/35.1%), and "lumbago" (26.5%/23.2%). Irritability, concentration and attention deficits, reduced vigilance, distractibility, reduced motivation, anergia, dysphoria, fatigue, restlessness, incoordination, and malaise were issues that the International Classification of Sleep Disorders-2 (ICSD-2) [25] has described as associated features of behaviorally induced insufficient sleep syndrome. It should be noted that a not insignificant number of pupils/students in Japan complain about precisely these issues. Are these complaints explained only by sleep insufficiency? As mentioned previously, bedtime delay in youngsters reduces total daily sleep duration [4], and approximately 80% of kindergarten and nursery school teachers reported that many children are sleep deprived [15]. In fact, sleep deprivation has been demonstrated to exert a negative effect on daytime functioning [26–28], general well-being [29], metabolic and endocrine function [30,31], and body weight [24].

However, the required sleep duration of an individual person is very difficult to determine, because the need for sleep is variable and depends on several factors [32]. In adults there are people who normally sleep for both long and short periods, and such habits are considered to develop at a young age [25]. However, such individual differences should not be taken to say that people do not need to take care of their sleep duration. In general, the late morning is the period when humans tend to be most alert and active [17]. If people are alert and active during the late morning, their sleep duration, sleep quality, and life rhythms are likely healthy.

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3. Nocturnal lifestyles and behaviors

A shortage of sleep, and delayed bedtimes and wake-up times are known to produce physical, mental, and/or emotional problems.

3.1. Adults and older children

The later bedtimes and wake-up times have been found to be significantly associated with subclinical manic type symptoms among working adults [33], and evening schedule medical school students are reported to result in lower sleep efficiency than morning-type students [34]. To determine if someone is a morning-type or evening-type person, a self-assessment questionnaire has been used. According to the original report [35], morning-type people retired and arose significantly earlier than evening-type people. An association of being an evening-type with mood and anxiety symptoms was reported in young adolescents in Taiwan [36]. Among 6631 adolescents, aged 14.1–18.6 years, evening types were found to be of more attention problems, poor school achievement, more injuries and more emotionally upset than the other chronotypes [37]. Gaina et al. [38] reported that Japanese junior high school pupils with an evening preference were more likely to have poorer sleep–wake parameters and lifestyle habits than those who had a morning preference. Caci et al. [39] reported an association between being an evening-type person and impulsivity in students, and Gau et al. [40] reported that evening-type 12- to 13-year-old students were more likely to have behavioral/emotional problems, problems with suicidal behavior and ideation, and habitual substance use than morning-type students. Susman et al. [41] concluded that being an evening-type person is related to antisocial behavior, rule-breaking, attention problems, and conduct disorder symptoms in boys, and relational aggression in girls, among children aged 8–13 years.

An irregular lifestyle has also been known to be associated with delayed bed times and wake-up times. In college students, there was less regularity of social rhythms in poor sleepers relative to good sleepers, and later rising times and bed times were reported to be associated with worse sleep [42]. In adults, evening-type people have been reported to have a more irregular daily lifestyle than morning-type people [43].

Taking these reports together, the association of delayed wake-up times, delayed bedtimes, and an irregular lifestyle with problematic behaviors of older children, adolescents, and adults is evidently suggested.

3.2. Studies on preschoolers

In preschoolers, few studies described the association between sleep habits and behavior. Here, three of the papers in which this author was involved are briefly introduced. These papers examined sleep habits in association with the behavior of youngsters between the ages of one and six.

3.2.1. Child behavior checklist (CBCL) and sleep habits

Yokomaku et al. [44] examined the association between sleep habits and the behavior of healthy preschool children. They used an international standardized method, a child behavior checklist (CBCL), to evaluate behavioral problems in children [45]. Recently, it was reported that Japanese children in daycare nurseries had later bedtimes, earlier wake-up times, and a shorter total night sleep time than children in kindergarten [46]. Thus, Yokomaku et al. [44] allotted an equal number of kindergarten and nursery school children to each of their study groups, since the purpose of their study was to examine the association between sleep habits and behavior of presumably healthy preschool children. Yokomaku et al. [44] recruited a total of 135 Japanese children of both genders, aged 4–6 years, from the Tokyo metropolitan area and its suburbs who met the conditions outlined below. The children in Group A ($n = 68$) were required to meet one or more of the following three conditions: (1) they went out with adults after 21:00 two or more times a week, (2) they went to bed after 23:00 four or more times a week, and (3) they returned home after 21:00 three or more times a week. Those in Group B ($n = 67$) were required to meet none of these conditions. Questionnaires for self-completion, 2-week sleep diaries, and the Japanese version of the CBCL for 4–18 year olds were distributed to the caretakers with instructions to return them by mail.

The CBCL is made up of questions relating to a total of 113 items categorized into the following eight subscale items; (I) Withdrawn; (II) Somatic complaints; (III) Anxious/depressed; (IV) Social problems; (V) Thought problems; (VI) Attention problems; (VII) Delinquent behavior; and (VIII) Aggressive behavior. Internalizing (I + II + III), externalizing (VII + VIII), and total scales were also derived. Caretakers answered each question by selecting one of three choices of answers, 0 = not true, 1 = somewhat or sometimes true, and 2 = very true or often true. The eight subscale items and raw scores for the internalizing, externalizing, and total scales were calculated from these scores of the answers. The raw scores were then converted into T-scores according to the profile sheet [45,47]. It has been previously reported that the higher the score, the greater the likelihood of problematic behavior in that scale [45].

There was no significant difference in any of the background factors (age, gender, number of children attending kindergarten or nursery school, number of siblings, ratio of older brothers or sisters, mothers' age and employment status, and type of housing) between groups. The children in Group A showed a significantly

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shorter average duration of nocturnal sleep, napping, and total sleep, significantly later average bedtimes and wake-up times, and a significantly wider average range of variation in bedtimes and wake-up times than the children in Group B (Table 2). A significant difference in the T-scores of the CBCL between Groups A and B was detected in three subscale items (withdrawn, anxious/depressed, and aggressive behavior items), and in the internalizing, externalizing, and total scales (Table 3). High and statistically significant positive correlation coefficient values ($p > 0.22$) were obtained between: (i) wake-up times and "withdrawn", "social problems", "attention problems", "aggressive behavior", internalizing, externalizing, and total scales; (ii) between bedtimes and "withdrawn", "anxious/depressed", "social problems", "aggressive behavior", internalizing, and total scales; (iii) between wake-up time range of variation and "social problems", "attention problems", "aggressive behavior", and total scales; and (iv) between bedtime range of variation and total scales (Table 4). Although sleep duration did not exhibit a significant correlation with the total scale, the total scale did display high positive significant correlations with wake-up times, bedtimes, and both wake-up time and bed time range of variation.

In summary, problematic behaviors in preschoolers were found to be associated with late and irregular wake-up times and bedtimes, but not with sleep duration.

3.2.2. The ability to copy a triangle and sleep habits

Suzuki et al. [47] examined the relationship of a 2-week sleep diary and the ability to copy a triangular figure for the first time in 222 children aged 5 and 6 years. Thirty four of the 222 children had a standard deviation exceeding 1.5 h in either those with a nocturnal sleep onset time ($n = 11$) or morning wake-up time ($n = 23$). These 34 children were designated as children with irregular sleep–wakefulness rhythms. The remaining 188 children were defined as children with regular sleep–wakefulness rhythms.

The triangular figure was successfully copied by 184 children but not the remaining 38 children. Children who successfully copied a triangle showed a significantly earlier mean morning wake-up time, and a significantly longer mean total sleep duration than children who failed to copy the triangle. The rate of children with irregular sleep–wakefulness rhythms among children who failed to copy the triangle (23/38) was significantly higher than that among children who succeeded (11/184). Compared with children with regular sleep–wakefulness rhythms, children with irregular sleep–wakefulness rhythms had a 5.9 times greater risk of not being able to copy the triangle. A semi-structured interview with 16 teachers identified 48 troublesome episodes in 42 children. The rate of children with irregular sleep–wakefulness rhythms among the children with the troublesome episodes (19/42) was significantly higher than that among children without such troublesome episodes (15/180).

It is evident that children with irregular sleep–wakefulness rhythms have behavioral problems as well as problems with the integration of cognition and motor activity.

3.2.3. Physical activity and sleep habits

In 204 children aged from 12 to 40 months (mean 22.6 months), the daily average physical activity counts per minute (PA) was assessed [48]. An actigraphic device was placed on the ankle of each child for 7 consecutive days, and attendants recorded sleep logs for the children during this period. PA, nap duration on the day the PA was determined, morning wake-up time on the day the PA was determined, nocturnal sleep duration of the previous night, and bedtime of the previous night were examined. Among the correlation coefficients calculated (Table 5), significant positive correlations were obtained between older age and PA, and between bedtime and wake-up time. Significant negative correlations were obtained between wake-up time and PA, and between age and nap duration. Male gender was found to increase PA significantly. Based on multiple linear regression analysis, a significantly predictable regression

Table 2
Difference in sleeping habits between Group A and Group B

	Group A	Group B	Significance
Wake-up time	7:51 ± 40 min	7:08 ± 24 min	$p < 0.01$
Bedtime	22:51 ± 39 min	20:46 ± 28 min	$p < 0.01$
Nocturnal sleep duration	9.03 ± 0.73 h	10.37 ± 0.53 h	$p < 0.01$
Nap duration	0.75 ± 0.65 h	0.35 ± 0.45 h	$p < 0.01$
Total sleep duration	9.77 ± 0.77 h	10.72 ± 0.58 h	$p < 0.01$
Wake-up time band	1.97 ± 0.88 h	1.32 ± 0.65 h	$p < 0.01$
Bedtime band	2.67 ± 1.28 h	1.52 ± 1.02 h	$p < 0.01$

Results represent the means ± SD.

Table 3
Comparison between Groups A and B

	Group A $N = 68$		Group B $N = 67$		p-Value for score
	Mean	SD	Mean	SD	
I. Withdrawn	55.3	6.6	53.0	4.9	<0.05
II. Somatic complaints	51.9	4.1	51.1	3.3	NS
III. Anxious/depressed	54.6	6.6	52.6	4.1	<0.05
IV. Social problems	54.4	5.8	52.9	4.1	NS
V. Thought problems	51.8	5.8	50.5	3.3	NS
VI. Attention problems	53.9	5.8	52.8	4.1	NS
VII. Delinquent behavior	55.9	6.6	54.5	4.9	NS
VIII. Aggressive behavior	56.4	7.4	53.9	4.9	<0.05
Internalizing	52.7	8.2	49.6	6.5	<0.05
Externalizing	54.9	9.1	51.7	7.4	<0.05
Total	54.0	9.1	49.8	8.2	<0.01

N, normal; B, borderline; Ab, abnormal; NS, not significant.

Table 4
Correlation coefficients between sleeping habits and T-scores on each scale

	Wake-up times	Bedtimes	Nocturnal sleep duration	Nap duration	Total sleep duration	Wake-up time bands	Bedtime bands
I. Withdrawn	0.24**	0.25**	−0.16	0.18*	−0.08	0.22*	0.15
II. Somatic complaints	0.09	0.11	−0.08	0.02	−0.08	0.09	0.13
III. Anxious/depressed	0.19*	0.26**	−0.20*	0.21*	−0.10	0.16	0.17*
IV. Social problems	0.30**	0.23**	−0.09	0.01	−0.09	0.27**	0.14
V. Thought problems	0.17*	0.21	−0.16	0.19*	−0.08	0.19*	0.12
VI. Attention problems	0.31**	0.16	0.02	0.09	0.07	0.32**	0.14
VII. Delinquent behavior	0.20*	0.16	−0.07	0.00	−0.10	0.15	0.20*
VIII. Aggressive behavior	0.32**	0.23**	−0.06	0.08	−0.03	0.26**	0.22*
Internalizing	0.23**	0.26**	−0.18*	0.15	−0.12	0.19*	0.20*
Externalizing	0.27**	0.21*	−0.07	0.04	−0.07	0.20*	0.21*
Total	0.33**	0.26**	−0.10	0.09	−0.06	0.27**	0.24**

* $p < 0.05$.
** $p < 0.01$.

formula was obtained for PA. Significant regression coefficients with respect to PA were obtained for gender ($p = 0.006$), wake-up time ($p = 0.008$), and age in months ($p = 0.010$).

It was found that an older age, male gender, and early wake-up time displayed significant positive correlations with PA.

4. Presumed involvement of the biological clock and serotonergic system on unhealthy conditions seen in late risers and sleepers

Taking these reports on preschoolers together with previously cited papers on older children, adolescents, and adults, problematic behaviors are likely to be associated with delayed wake-up times, delayed bedtimes, and an irregular lifestyle. Although delayed bedtimes also produced sleep loss [4], problematic behaviors are found to be likely to be associated with delayed wake-up times, delayed bedtimes, and an irregular lifestyle, regardless of sleep duration [44]. In the following section, the presumed background neuronal mechanisms associated with this result are discussed.

4.1. Biological clock and desynchronization

Circadian signals from the SCN come to the dorsomedial nucleus of the hypothalamus via the subparaventricular zone. The dorsomedial nucleus of the hypothalamus combines inputs from the SCN with those from other areas, allowing for flexible control, and sends signals to structures that regulate various circadian rhythms such as feeding, locomotion, sleep–wake alternation, corticosterone secretion [49], and the autonomic nervous system [50]. The endogenous period of the circadian clock of most people is longer than 24 h, and it is through exposure to sunlight in the morning people are entrained to the Earth 24 h cycle [51]. Conversely, light exposure at night delays the phase of the circadian clock [51] or disrupts its function [52]. In addition, bright light during night decreases the secretion of melatonin [53], which shifts circadian phase, acts as a hypnotic, is an effective free radical scavenger and antioxidant, and induces the expression of gonadotropin-inhibitory hormone. Non-photic cues, e.g., the timing of feeding [54], activity [55], etc. also serve to synchronize the circadian system to the 24 h day. In the absence of such time cues, our daily rhythms are apt to become altered, and show their own rhythm. After spending life under such conditions for a considerable period of time, the staging of various biological rhythms, such as sleep–wakefulness and temperature, has been shown to change [56]. Under such conditions, reciprocal phase interactions within the circadian rhythms are disturbed. In general, most people spontaneously wake-up in the morning when body temperature begins to rise from its lowest

Table 5
Correlation coefficients for the obtained data

($n = 204$)	Gender (male: 1, female: 2)	Age in months	Wake-up times	Bedtimes	Nocturnal sleep duration	Nap duration	Wake-up time bands	Bedtime bands
PA	−0.21**	0.14*	−0.17*	−0.07	−0.11	−0.07	−0.09	−0.01
Age in months	nc	nc	0.21**	0.17*	0.05	−0.29**	−0.03	0.10

nc, not calculated.
* $p < 0.05$.
** $p < 0.01$.

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level, and fall asleep in the evening when body temperature begins to decline from its highest level. However, once the reciprocal interaction is impaired, the phase relationship between body temperature and sleep–wake circadian rhythms is disrupted [56]. This condition, which is known as circadian desynchronization [57–60], may produce various physical and mood disturbances (disturbed nighttime sleep, impaired daytime alertness and performance, disorientation, gastrointestinal problems, loss of appetite, inappropriate timing of defecation, excessive need to urinate during the night). Similar complaints and mood alterations are observed in patients with jet lag [59], seasonal affective disorder [60] and in astronauts [61].

Kerkhof and Van Dongen [62] have reported that the endogenous phasing of the circadian biological clock of morning-type individuals differs from that of evening-type individuals. According to Bailey and Heitkemper [63], evening-type individuals have a later morning temperature rise, and later wake-up time than morning types. Moreover, individuals who are at their most alert in the morning have an earlier peak in their temperature circadian rhythm than individuals who are most alert in the evening [64]. These reports suggested that evening-type individuals suffer from circadian desynchronization [57,58]. Taking these reports into consideration, those with delayed wake-up times, delayed bedtimes, and an irregular lifestyle (an evening preference) are hypothesized to suffer from circadian desynchronization.

Arendt et al. [59] showed that the rate of recovery from jet lag, whose symptoms may be ascribed in large part to temporary circadian desynchronization, varies with individuals, as well as with the direction of time zone change. The susceptibility for manifesting symptoms, presumably due to desynchronization, is likely to be different in different individuals. In this regard, the following reports suggest that susceptibility to desynchronization is affected by biological background.

Nilssen et al. [65] compared the prevalence of sleep problems in two ethnically different populations living under the same extreme arctic climate. A total of 453 Norwegians (319 males and 134 females) were compared with 450 Russians (317 males and 133 females), all aged 18 years or older, living in Svalbard, the northernmost regular settlement in the world. In Russians, 81% of the male subjects and 77% of the female subjects reported sleeping problems lasting for at least 2 weeks. The corresponding figures for the Norwegians were 22% (for males) and 25% (for females). Whereas sleeping problems among Norwegians were approximately equally frequent throughout the year, Russians reported more problems during the polar night. The 1 year prevalence of self-reported depression in the same two ethnically different populations was also compared [66]. Among Russians, the 1 year prevalence of self-reported depression lasting for at least 2 weeks was 26.8% for men and 44.7% for women. The corresponding figures for Norwegians were 10.7% and 15.6%. For the period with the polar night the figures were 5.5% and 6.7% for Norwegian men and women, respectively, and 21.7% and 37.1% for Russian men and women, respectively. More than 50% of the Norwegian population in these studies [65,66] came from the northern part of Norway, whereas the Russian subjects were mostly recruited from the southern part of Russia and from the Ukraine. Nilssen et al. [65,66] postulated that insufficient acclimatization after migration to the north is essential for understanding these results. The susceptibility to manifesting symptoms that are presumably due to desynchronization is likely to be affected in part by unknown biological background factors, including acclimatization that cannot be altered at least within one generation.

4.2. Serotonergic system

The hypothesis that depression is related to a decreased availability of either norepinephrine, or serotonin, or both, is called the biogenic amine hypothesis, and was derived from studies of the effects of various drugs on the serotonergic and noradrenergic systems of the brain [67]. Indeed, an agent that is considered to increase the availability of serotonin at the synaptic cleft, termed a selective serotonin reuptake inhibitor, has been widely used in the treatment of patients with depression. Recently, reports showed the serotonergic system is activated through rhythmic movements, such as gait, chewing, and respiration [68]. Adequate physical activity could thus be important in activating the serotonergic system. Interestingly, one of the major diagnostic criteria for a major depressive episode is “markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation by others)” [69]. Depressed infants were described as withdrawn and apathetic, exhibiting hypotonia and lethargy, and having an obviously sad facial expression [70]. Patients with depression tend to show sedentary behaviors. Physical activity is also known to enhance brain health [71]. Exercise-derived benefits to brain function have been elucidated at the molecular level [72], and physical activity has been reported to decrease the risk of Alzheimer’s disease [73–75]. Physical activity, which is involved in activating serotonergic activity, is one of the key behaviors in promoting brain function in animals, including humans. Exposure to sunlight in the morning is also known to activate the serotonergic system [76].

The concept of low serotonin syndrome – aggressiveness, impulsivity, and suicidal behavior associated with low levels of serotonin – has been proposed [77]. Reduced serotonergic activity is reported to be a disadvantage and enhanced activity an advantage to adult

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male vervet monkeys in attaining a high social dominance status [78]. The disturbance of the lateral orbito-prefrontal circuit has been implicated in the induction of aggressive behavior and in the loss of sociability [79]. The serotonergic system is known to activate this circuit [80]. Serotonin is also known to be one of the key factors involved in enhancing learning ability through exercise [81]. Activity of the serotonergic system is profoundly affected by the sleep–wakefulness cycle [82]. Taking these facts together, it is postulated that an irregular sleep–wakefulness rhythm disturbs emotional control and sociability through a decrease in the serotonergic activation of the lateral orbito-prefrontal circuit.

4.3. *Serotonergic system and desynchronization*

It is likely that circadian desynchronization results in unsatisfactory physical, mental and/or emotional conditions, presumably leading to decreased physical activity. Decreased physical activity is insufficient to activate the serotonergic system, which is hard to activate without morning light. The following negative cycles (solid filled lines in Fig. 1) can therefore be postulated in those with delayed wake-up times, delayed bedtimes, and an irregular lifestyle.

5. Asynchronization

More than half of the preschoolers/pupils/students in Japan complain about daytime sleepiness, while about one quarter of junior high school students in Japan suffer from insomnia. Indeed, more than 20% of the pupils/students in Japan complained of "a need to yawn", "desire to lie down", "irritation", "hypersensitivity", "neck stiffness", and "lumbago". Since these complaints were compatible with the associated features of behaviorally induced insufficient sleep syndrome [25], these preschoolers/pupils/students could be diagnosed as having behaviorally induced insufficient sleep syndrome due to inadequate sleep hygiene. If many preschoolers/pupils/students in Japan are simply suffering from behaviorally induced insufficient sleep syndrome, they should be free from their symptoms after obtaining sufficient sleep (by exclusion of the dotted lines in Fig. 1). However, such a therapeutic approach evidently often fails. The students could not fall asleep in spite of sleep loss, partly due to inadequate sleep hygiene such as excessive media exposure and a low level of physical activity. Even if adequate sleep hygiene is provided, they find it hard to fall asleep. Of course, delayed wake-up times and delayed bedtimes could be the symptoms of a delayed sleep phase type of circadian rhythm sleep disorder. Although this article does not discuss this disorder in detail, it should be noted that there is often confusion between this disorder and the biological- and lifestyle-related sleep phase delays that are especially common during adolescence [83].

It is possible certain factors other than simple sleep loss and inadequate sleep hygiene are involved in many preschoolers/pupils/students in Japan who exhibit delayed wake-up times, delayed bedtimes, and an irregular lifestyle. According to the previous section, it is assumed that decreased serotonergic system activity and desynchronization are candidates to explain (their) the pathophysiology. In the following section, the pathophysiology of other disease conditions which are thought to involve circadian and/or serotonergic systems is discussed.

5.1. *Disease conditions presumably involving the circadian and/or serotonergic systems*

Jet lag has three major components; external desynchronization, internal desynchronization, and sleep deprivation [84]. External desynchronization refers to the conflict between the internal clock with external time cues. As the individual is exposed to these new external time cues, the internal clock adjusts to the new time zone. This process may take several days. Internal desynchronization, a loss of coupling of phases between phenomena revealing circadian oscillation, occurs during the process of the readjustment of internal clocks, because each system adjusts itself differently. Internal desynchronization can also be induced by acute manipulation resulting in phase alteration [85], which is the case in jet lag. As a result of the internal and external desynchronization, sleep loss occurs. Sleep loss decreases the quality and quantity of various activities [24,26–31], presumably resulting in decreased serotonergic activity. For the transmeridian traveler, both physical (daylight-darkness) and social (mealtime, noise, etc.) cues for circadian rhythms encourage the realignment of the circadian system. In contrast, for the shift worker, physical cues are resolutely opposed to a nocturnal alignment, as are most of the social cues stemming from a day-oriented society. Thus, circadian realignment of shift workers takes longer than that associated with jet lag [86]. In addition, it should be noted that desynchronization can also be induced by a forced extraordinary schedule [87].

A British cohort study of more than 30 years duration [88] has shown that sedentary behavior during childhood also increases the risk of chronic fatigue syndrome/myalgic encephalomyelitis, in which depressive symptoms are one of the major symptoms. The efficacy of selective serotonin reuptake inhibitors on patients with chronic fatigue syndrome has been reported [89]. It was assumed that decreased serotonergic activity was involved in the occurrence of this syndrome. Miike et al. [90] described the presence of deranged circadian rhythms in childhood chronic fatigue syndrome, and

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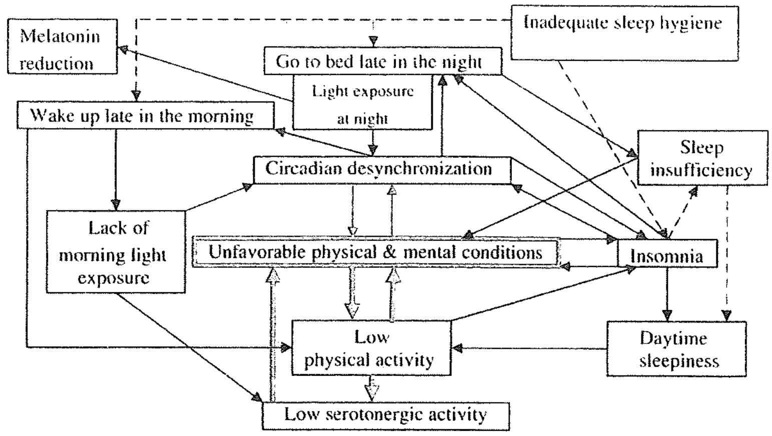

Fig. 1. Schematic drawing of the development of asynchronization.

showed that patients with childhood chronic fatigue syndrome suffer from an atypical but continuous jet lag condition. In addition, Tanaka [91] reported that one third of children with chronic fatigue syndrome showed abnormal cardiovascular adjustment during postural change (orthostatic dysregulation) which is characterized by instantaneous orthostatic hypotension, postural tachycardia or neurally mediated syncope. Orthostatic dysregulation is a well-established clinical concept among pediatricians in Japan.

The characteristic clinical symptoms of burnout, first described in 1974 [92], are excessive and persistent fatigue, emotional distress, and cognitive dysfunction. The symptomatology is shared to some extent with disorders such as depression, chronic fatigue syndrome and vital exhaustion [93]. Burnout is positively associated with poor quality of sleep, a sensation of not feeling refreshed on awakening, and sleepiness and/or fatigue during the day [94]. Burned-out subjects are reported to show a higher frequency of arousal during sleep compared with others [93]. A study on nurses who worked in a University Hospital found that exposure to daylight for at least 3 h a day resulted in less stress and higher job satisfaction, both of which were favorable factors for reducing burnout [95]. The involvement of the serotonergic system in the pathophysiology of burnout has been hypothesized by Tops et al. [96].

Vital exhaustion, a construct conceptually akin to burnout, has been introduced by Appels and his colleagues [97]. Vital exhaustion refers to a state characterized by excessive fatigue, lack of energy, increased irritability, sleep disturbances, and feelings of demoralization. In a prospective study of a large sample of healthy men, Appels and Mulder [98] found that vital exhaustion was composed of three factors – fatigue, depressive affect, and irritability – and that the risk of subsequent myocardial infarction was attributable to the fatigue dimension of vital exhaustion. Vital exhaustion was also found to be associated with sleep disturbances. Polysomnographic recordings indicated that the deep sleep stage was significantly diminished in exhausted subjects compared with control subjects, suggesting that the normal restoration processes that take place during sleep are impaired in exhausted subjects [99]. In addition, exhausted subjects reported more sleep complaints, shorter sleep duration and frequent napping, and poorer sleep quality, than did vital subjects [97,100–102].

According to ICSD-2 [25], fibromyalgia is characterized by widespread pain of at least 3 months duration and muscle tenderness, as determined by palpation. Patients with fibromyalgia commonly complain of light and unrefreshing sleep, fatigue, cognitive difficulties, and psychological distress, including symptoms of depression and anxiety. Interestingly, Rooks [103] reported a serotonin and norepinephrine-reuptake inhibitor to be a promising agent for treating patients with fibromyalgia.

Souetre et al. [104] studied circadian rhythms of body temperature, plasma cortisol, norepinephrine, thyroid stimulating hormone, and melatonin in patients with depression. They found that depressed patients had a reduced circadian rhythm amplitude. Decreased amplitude in circadian core body temperature changes was also reported in school delinquent patients who are supposed to be in a desynchronized condition [105].

As described here, jet lag, shift work, chronic fatigue syndrome, orthostatic dysregulation, burnout, vital exhaustion, fibromyalgia, and depression are likely to be caused to some extent by desynchronization and decreased serotonergic activity, although each of these disease conditions has its own specific origin, major symptoms, and course. There is a similarity of the pathophysiology of these disease conditions and the condition which many Japanese preschoolers/pupils/students are suffering.

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5.2. Asynchronization

Aschoff and Wever described in 1976 [106] that the activity rhythm (wakefulness and sleep) and other rhythmic variables (e.g., temperature) often have the same circadian period of approximately 25 h, but on occasions the activity period may become substantially longer (e.g., 33 h), while the other rhythms continue with a period of about 25 h. Such a state is termed internal desynchronization. Thus, circadian desynchronization is the term used to indicate a loss of the coupling of phases between phenomena leading to circadian oscillation. It should be noted that this term came from basic studies and was not originally a clinical-oriented term.

Many preschoolers/pupils/students in Japan who exhibit delayed wake-up times, delayed bedtimes, and an irregular lifestyle may have a loss of the coupling of phases between phenomena that lead to circadian oscillation, and a decrease in amplitudes of certain other phenomena, although no concrete evidence has been as yet obtained. Desynchronization by itself is not an adequate term to describe the conditions from which many preschoolers/pupils/students in Japan are suffering. In addition, reduced serotonergic activity or serotonin-depleting condition is likely to be present in some of them. A novel clinical notion is needed to improve the understanding of the pathophysiology of the disturbances of these preschoolers/pupils/students. This new entity should contribute to both increased understanding and help ameliorate the problems of many preschoolers/pupils/students in Japan. The term "asynchronization" is meant to designate the conditions that many preschoolers/pupils/students in Japan with delayed wake-up times, delayed bedtimes, and an irregular lifestyle have displayed. Although asynchronization is a clinical-oriented term, this term was chosen in consideration of the recent discovery of a "singularity behavior" in mammalian circadian clocks [52].

In 1970, Winfree [107] reported that a specific dim blue light pulse stimulus with a unique stimulus time and duration resulted in unusual broadening of the daily eclosion peaks of the fruitfly, *Drosophila pseudoobscura*, even to the extreme of obscuring the circadian rhythm. This phenomenon is called "circadian singularity behavior", and has been shown in a range of organisms such as algae, plants, and mammals [108–113], suggesting that it is a shared phenomenon among all circadian clocks. In humans, Jewett et al. [110] reported that circadian rhythms in rectal temperature and plasma cortisol were abolished by a single, long duration, bright light pulse given during one or two successive circadian cycles. At the molecular level, Huang et al. [114] demonstrated that both temperature increase and light pulses can trigger singularity behavior in Neurospora circadian clock gene frequency. Ukai et al. [52] reported that a critical light pulse (3 h light pulses delivered at an approximately specific circadian time (CT) ~17 (near subjective midnight (=CT18))) drives cellular clocks into singularity behavior in mammals. Interestingly, this phenomenon is transient [114], although the removal of the stimulus is needed.

The essence of asynchronization is the disturbance of various aspects (e.g., cycle, amplitude, phase and interrelationship) of the biological rhythms that normally exhibit circadian oscillation, presumably involving decreased serotonergic system activity. The major trigger of asynchronization is hypothesized to be a combination of light exposure during the night and a lack of light exposure in the morning. Asynchronization results in the disturbance of variable systems. Thus, symptoms of asynchronization (Table 6) include disturbances of the autonomic nervous system (sleepiness, insomnia, disturbance of hormonal excretion, gastrointestinal problems, sympathetic nervous system predominance, etc.) and higher brain function (disorientation, loss of sociality, loss of will or motivation, impaired alertness and performance, etc.). Neurological (attention deficit, aggression, impulsiveness, hyperactivity, etc.), psychiatric (depressive disorders, personality disorders, anxiety disorders, etc.) and somatic (tiredness, fatigue, neck and/or back stiffness, headache, etc.) disturbances are also putative symptoms of asynchronization. The complaints introduced in this article (disturbances of higher brain function; memory problems, concentration problems, neurological disturbances; irritation, hypersensitivity, somatic disturbances; persistent yawn, desire for sleep, wish to lie down, inactivity, neck stiffness, lumbago) could be symptoms of asynchronization.

To detect the disturbance of the biological rhythms, actigraphic recordings [115] as well as the diurnal measuring of body temperature, corticosteroids and melatonin must be useful. Takimoto et al. monitored human clock genes in whole blood cells to evaluate internal synchronization [116].

The early phase of asynchronization is hypothesized to be very similar to desynchronization. During this phase, disturbances are functional and can be resolved relatively easily by the establishment of a regular sleep–wakefulness cycle; however, without adequate intervention disturbances can gradually worsen, involving a decrease in serotonergic activity, and can become difficult to resolve. In Fig. 1, red lines, especially the broad ones, are hypothesized to be involved in asynchronization. A portion of the patients with chronic fatigue syndrome, orthostatic dysregulation, burnout, vital exhaustion, fibromyalgia, and depression are suggested to be suffering from asynchronization.

Circadian singularity behaviors are similar to the concept put forward here, asynchronization. The early phase of asynchronization is hypothesized to be a very similar condition to desynchronization. Ukai et al. [52] also demonstrated that desynchronization of individual

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cellular clocks underlies singularity behavior. Although it is hypothesized that asynchronization is difficult to resolve, circadian singularity behavior has been shown to be reversible. According to Ukai et al. [52], a light pulse at CT 9–15 (transition from subjective day to night) reversed circadian singularity behavior. In addition to removing stimuli that induce circadian singularity behavior, an investigation to identify adequate stimuli to reverse circadian singularity behavior in the clinical setting should be undertaken.

5.3. Presumable potential therapeutic approaches for asynchronization

5.3.1. Basic principles

Based on the knowledge of the functioning of the circadian clock, morning light and an avoidance of nocturnal light are the essential activities for synchronizing the biological clock to the 24 h cycle of the earth. Therefore, these two behaviors are the basic ways to avoid falling into asynchronization. In addition to light, food [117], and social factors [87] are known to affect the circadian clock. Regarding the food-anticipatory activity rhythms, the dorsomedial hypothalamic nucleus was found to be a putative food-entrainable circadian pacemaker in mice, and the oscillation of this pacemaker was found to persist for at least 2 days even when mice were given no food during the expected feeding period after the establishment of food-entrained behavioral rhythms [54]. Regular mealtimes as well as participation to social activities are also likely essential factors to prevent from falling into asynchronization. The social promotion of favorable sleep hygiene is also important [118,119].

A daytime nap is known to show favorable effects on performance [120]. However, adolescents of evening types were reported to nap more frequently during school days than those with other chronotypes [37], although the improvement of school performance after introducing a 15-min-nap in the afternoon was suggested in a high school in Japan [121]. The therapeutic way of napping to cure patients from asynchronization or to prevent preschoolers/pupils/students from falling into asynchronization should be studied.

5.3.2. Conventional approaches

5.3.2.1. Light therapy. The effectiveness of light therapy has been reported, especially for patients with depression [122,123] and seasonal affective disorder [124]. The thrust of recent clinical trials has led to the recommendation that patients with seasonal affective disorder initially be given morning light shortly after awakening [60]. According to a cross-center analysis of more than 25 studies that included 332 patients with winter depression (seasonal affective disorder), 1 week of morning bright light (2500 lux) treatment was found to produce a significantly higher remission rate (53%) than did

Table 6
Asynchronization

Essence	Disturbance of various aspects (e.g., cycle, amplitude, phase and interrelationship) of the biological rhythms that indicate circadian oscillation
Presumable causes	Light exposure during the night. Lack of light exposure in the morning Decreased physical activities Disturbance of the biological clock and/or the serotonergic system
Symptoms	*Disturbances related to autonomic nervous system* Sleepiness, insomnia, disturbance of hormonal excretion, gastrointestinal problems, sympathetic nervous system predominance *Somatic disturbances* Tiredness, fatigue, neck and/or back stiffness, headache, persistent yawn, desire for sleep, wish to lie down, inactivity, lumbago *Disturbances related to higher brain function* Disorientation, loss of sociality, loss of will or motivation, impaired alertness and performance, hard to remember, hard to concentrate *Neurological disturbances* Attention deficit, aggression, impulsiveness, hyperactivity, irritated, hypersensitive *Psychiatric disturbances* Depressive disorders, personality disorders, anxiety disorders
Therapeutic approaches	Morning light, an avoidance of nocturnal light exposure, conventional approaches (light therapy, medications (hypnotics, antidepressants, melatonin, vitamin B12), physical activation, chronotherapy) and alternative ones (kampo, pulse therapy, direct contact, control of the autonomic nervous system, respiration (qigong, tanden breathing), chewing, crawling)
Prognosis	*Early phase:* disturbances are functional and can be resolved relatively easily e.g., by the establishment of a regular sleep–wake cycle *Chronic phase:* without adequate intervention the disturbances can gradually worsen, involving the loss of serotonergic activity, and difficult to resolve

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evening (38%) or midday (32%) treatment [125]. A clinical trial [60] giving 5 weeks of morning bright light therapy (10,000 lux, 60 min) to out patients with chronic major depression lasting 2 years or longer obtained a remission rate of 50%, while a control-group showed only minor improvement. Light therapy also reduced the depression scores in patients with fibromyalgia [126].

As shown previously, exposure to daylight at least 3 h a day is suggested to produce favorable effects on burnout [95]. Although Williams et al. [127] reported no favorable effects of light therapy on chronic fatigue syndrome, Miike [128] did report approximately 60% effectiveness by means of high intensity light therapy on child patients with chronic fatigue syndrome.

Light therapy is also known as promising method to treat patients with both shift work disorder and jet lag disorder [129]. However, night length (photoperiod) is also known to impact circadian phase shifts to light. Not only in non-human animals but also in humans, short nights attenuate both evening light-induced circadian phase delays and morning light-induced circadian phase advances [130,131]. Also, circadian clocks advance their phases by making waking time and bedtime earlier, while circadian clocks delay their phases by making waking time and bedtime later [132,133]. Although these effects of light therapy must be basic clues to treat patients who are in the early phase of asynchronization, an attenuation in light-induced circadian phase delays during short nights produce less light therapy effect on jet travelers and night workers who are now generally engaged in a nocturnal life with a long photoperiod (=short nights) [131].

5.3.2.2. Medications. Hypnotics: In the treatment of delayed sleep phase disorder, it is concluded that there is insufficient evidence to assess the safety and efficacy of hypnotic medication [134]. As for the treatment of other types of circadian rhythm sleep disorders, data to evaluate the safety and efficacy of hypnotics are scant [134]. The effects of hypnotics for shift work disorder patients are inconsistent [129]; some reports indicate that hypnotics increase daytime sleep, while others indicate that treatment improves nighttime alertness. The use of hypnotics for jet lag-induced insomnia is a rational treatment and consistent with the standard recommendations for the treatment of short-term insomnia. The efficacy of benzodiazepines with non-steroidal anti-inflammatory drugs on patients with fibromyalgia is inferior to that of amitriptyline [135]. Miike [128] described the use of hypnotics of ultra-short acting or medium-acting type for child patients with chronic fatigue syndrome. Hypnotics are widely used for insomnia in patients with depression [136].

It is likely that an appropriate use of hypnotics should be taken into consideration in managing asynchronization.

Antidepressants: The efficacy of antidepressants has been reported not only in depression but also in chronic fatigue syndrome [89] and fibromyalgia [103,135]. These agents must be considered promising in managing depressive tendencies in patients with asynchronization. However, since a serotonin-depleting condition is assumed in asynchronization, it does not seem good practice to recommend the use of selective serotonin reuptake inhibitors or serotonin and norepinephrine-reuptake inhibitors as the first agent of choice for asynchronization.

Melatonin: The effects of melatonin in patients with delayed sleep phase disorder and free-running disorder are established [134]. Melatonin administration in the afternoon or evening would be expected to shift rhythms earlier, thereby correcting a pathological phase delay. Appropriately timed melatonin has been shown to entrain totally blind people who had free-running disorder. According to a recent review [129], melatonin or melatonin agonists might benefit daytime sleep in night workers through their hypnotic as well as phase-shifting effect. Melatonin, administered at the appropriate time, can reduce the symptoms of jet lag and improve sleep following travel across multiple time zones [129]. Melatonin is reported to be an effective treatment for patients with chronic fatigue syndrome with delayed circadian rhythmicity [137]. Melatonin is also reported to be effective in treating the pain associated with fibromyalgia [138]. Interestingly, agomelatine, a compound with agonist properties at melatonin receptors, has been reported to exert an antidepressant effect superior to that of selective serotonin reuptake inhibitors and selective serotonin and noradrenaline reuptake inhibitors [139]. However, since melatonin is not regulated by the US FDA, there have been a variety of preparations, and its usefulness so far has been limited [140].

Vitamin B12: Vitamin B12 is reported to enhance light pulse-induced phase shifts and thus augment the entrainability of the circadian clock to light in rats [141]. In fact, Miike [128] described the efficacy of high dose vitamin B12 (3 g/day) for patients with childhood chronic fatigue syndrome who showed free-running disorder. An association between low vitamin B12 status and depression in older adults has been suggested [142]. Since vitamin B12 deficiency causes a deficient remethylation of homocysteine and is therefore probably contributing to increased homocysteine levels, Regland et al. [143] measured homocysteine and vitamin B12 levels in the cerebrospinal fluid in patients who fulfilled the criteria for both fibromyalgia and chronic fatigue syndrome. They found an increased concentration of homocysteine, and a correlation between the vitamin B12 level and clinical variables; the lower the vitamin B12, the more severe the clinical condition. However, a recent review has indicated that vitamin B12 is not an effective treatment for delayed sleep phase disorder

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