during rapid eye movement sleep [99]. Taking these facts together, it has been postulated that irregular sleep-wakefulness rhythm disturbs emotional control and sociability, due to decreased serotonergic activation in the lateral orbito- prefrontal circuit.

It is likely that circadian desynchronization results in unsatisfactory physical, mental and/or emotional conditions, presumably leading to decreased physical activity. If physical activity becomes too low, then the serotonergic system will not be activated. This is further confounded by a lack of morning light. The following negative cycles (solid filled lines in Figure 1) can be postulated in those with delayed wake-up times, delayed bedtimes, and an irregular lifestyle.

4-4. Reported disease conditions associated with circadian disruption

Miike *et al.* [100] described altered circadian rhythms in childhood chronic fatigue syndrome, and reported that these patients suffered from an atypical, but continuous, jet lag condition. A British cohort study over more than 30 years [101] revealed that sedentary behavior during childhood increased the risk of chronic fatigue syndrome/myalgic encephalomyelitis, for which depression is a major symptom. Selective serotonin reuptake inhibitors have been reported to be effective in treating chronic fatigue syndrome patients [102]. It has been assumed that decreased serotonergic activity is involved in the occurrence of this syndrome. Melatonin has also been shown to be effective for chronic fatigue syndrome patients with delayed circadian rhythm [103]. One third of children with chronic fatigue syndrome exhibited abnormal cardiovascular regulation during postural changes (orthostatic dysregulation), which is characterized by instantaneous orthostatic hypotension, postural, or neural-mediated syncope [104]. Orthostatic dysregulation is a well-established clinical concept among pediatricians in Japan.

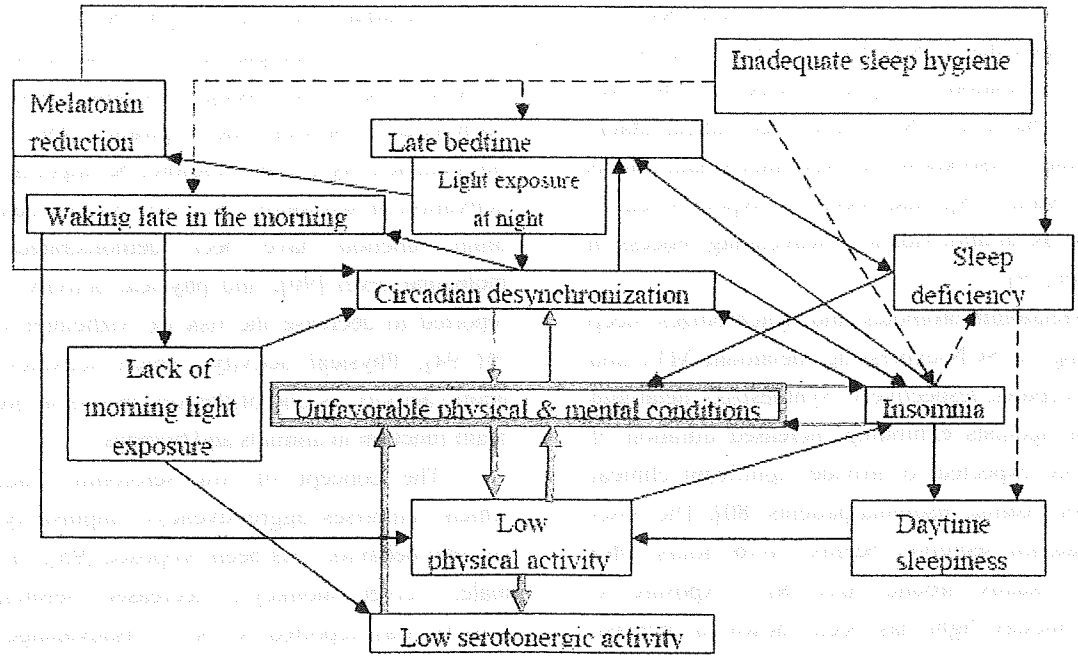

Figure 1 Schematic drawing of the development of asynchronization modified from Fig. 1 in reference 4.

The characteristic clinical burnout symptoms, first described in 1974 [105], comprise excessive and persistent fatigue, emotional distress, and cognitive dysfunction. These symptoms are common among disorders such as depression, chronic fatigue syndrome, and vital exhaustion [106]. Burnout is positively associated with poor sleep quality, a sensation of not feeling refreshed upon awakening,

and sleepiness and/or fatigue during daytime [107]. Burned-out subjects are reported to exhibit a higher frequency of arousal during sleep [106]. A study of University Hospital nurses revealed that daylight exposure for at least 3 hours per day resulted in reduced stress and greater job satisfaction, both of which were favorable factors for reducing burnout [108]. Because bright, midday light increases melatonin secretion during the night in elderly individuals [82], the melatonergic system, as well as the serotonergic system [109], might be involved in the pathogenesis of burnout.

Appels *et al.* introduced the terminology of vital exhaustion, which is conceptually akin to burnout [110]. In a prospective study of a large sample of healthy men, vital exhaustion was shown to comprise three factors - fatigue, depressive affect, and irritability - and the risk of subsequent myocardial infarction was attributed to fatigue from vital exhaustion [111]. Vital exhaustion is also associated with sleep disturbances. Polysomnographic recordings indicated that deep sleep stages were significantly reduced in exhausted subjects, compared with control subjects, suggesting that normal restoration processes, which occur while sleeping, are impaired in exhausted subjects [112]. In addition, exhausted subjects presented with a greater number of sleep complaints, shorter sleep duration, frequent napping, and poorer sleep quality [110, 113-115].

Fibromyalgia is characterized by widespread pain and muscle tenderness lasting at least three months, as determined by palpation [32]. Patients with fibromyalgia commonly complain of light and non-refreshing sleep, fatigue, cognitive difficulties, and psychological distress, including symptoms of depression and anxiety. Interestingly, a serotonin and norepinephrine-reuptake inhibitor has been reported to be successful in these patients [116], as well as melatonin for treating the pain associated with fibromyalgia [117].

Decreased circadian rhythm amplitude has also been reported in a more common condition - depression [118]. Moreover, decreased amplitude in circadian core body temperature changes was reported in delinquent student patients diagnosed with a desynchronized condition [119]. External and internal desynchronizations were two of the three major components of jet lag [120]. Another major component was sleep deprivation [120]. External desynchronization refers to the conflict between the internal clock and external time cues. As an individual is exposed to new, external, time cues, the internal clock adjusts to the new time zone, which may take several days. Internal desynchronization, a loss of phase coupling between phenolmena revealing circadian oscillation, takes place during readjustment of internal clocks, and each system adjusts itself differently. Internal desynchronization can also be induced by acute manipulation resulting in phase alteration [121], which is the case in jet lag. As a result of internal and external desynchronization, sleep loss occurs, which decreases the quality and quantity of various activities [29, 33-38]. This ultimately results in decreased serotonergic activity. For the trans-meridian traveler, both physical cues such as daylight and darkness, and social cues, such as mealtimes and noise, encourage realignment of the circadian system.

In contrast, for the shift worker, physical cues are resolutely opposed to nocturnal alignment, as are most social cues stemming from a day-oriented society. Therefore, circadian realignment of shift workers takes longer than realignment from jet lag [122]. In addition, a forced, extraordinary schedule can also induce desynchronization [123]. As previously mentioned, alcoholics have been reported to display an inversion of melatonin circadian rhythm secretion, which could be respon- sible for their desynchronization [85].

As described in this review, chronic fatigue syndrome, orthostatic dysregulation, burnout, vital exhaustion, fibromyalgia, depression, jet lag, and shift work are likely to be a result of desynchronization and decreased serotonergic, as well as decreased melatonergic activity, although each of these disease conditions possesses its own specific origin, major symptoms, and course. There is a similar pathophysiology between these disease conditions and the condition that many Japanese preschoolers/students are currently suffering from.

5. Asynchronization

More than half of the preschoolers/students in Japan complained of daytime sleepiness, while about one quarter of junior high school students in Japan suffer from insomnia. Moreover, as shown in Table 2, frequent complaints of students in Japan were

compatible with associated features of behavioral-induced sleep-deficient syndrome [32], most likely due to inadequate sleep hygiene. If this were the case, these symptoms should be ameliorated following adequate sleep (by exclusion of dotted lines in Figure 1). However, such therapeutic approaches often fail. The students cannot fall asleep, despite sleep loss, and this is partly due to inadequate sleep hygiene consistent with excessive media exposure and low-level physical activity. Indeed, delayed wake-up times and bedtimes could be symptoms of a delayed sleep phase form of circadian rhythm sleep disorder. Although this article does not discuss this disorder in detail, it should be noted that there is confusion between this disorder and the biological- and lifestyle-related sleep phase delays that are especially common during adolescence [124]. It is possible that certain factors other than simple sleep loss and inadequate sleep hygiene are involved in many of the young people in Japan that exhibit delayed wake-up times, delayed bedtimes, and an irregular lifestyle. It has been assumed that decreased activity in the melatonergic and serotonergic systems, as well as desynchronization, are candidates for explaining pathophysiology.

5-1. Presumable pathophysiology

In 1976, Aschoff and Wever described [125] that activity rhythm (wakefulness and sleep) and other rhythmic variables (*e.g.*, temperature) often have similar circadian periods of approximately 25 hours. However, on occasions, the activity period may become substantially longer (*e.g.*, 33 hours), while other rhythms continue with a period of about 25 hours. Such a state is termed internal desynchronization. Thus circadian desynchronization is used to indicate a loss of phase coupling between certain phenomena, which lead to circadian oscillation. It should be noted that this term arose from basic studies, and was not originally a clinical-related term.

Individuals with delayed wake-up times, delayed bedtimes, and an irregular lifestyle may also exhibit a loss of phase coupling between phenomena, circadian oscillation, and decreased amplitudes of other phenomena, although no concrete evidence has obtained to date. Desynchronization alone is not adequate to describe the clinical conditions that many young people in Japan are suffering from. In addition, many of these individuals likely display reduced serotonergic and/or melatonergic activity. I wonder a novel, clinical entity is required to improve understanding of the pathophysiology of these disturbances [3, 4].

In 1970, Winfree [5] 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 circadian rhythm. This phenomenon was termed "circadian singularity behavior", and has been described in a range of organisms, such as algae, plants, and mammals [126-131]. In humans, Jewett *et al.* [128] reported circadian rhythms of rectal temperature and plasma cortisol were abolished by a single, long duration, bright-light pulse administered during one or two successive circadian cycles. Huang *et al.* [132] demonstrated that temperature increases and light pulses can trigger singularity behavior in Neurospora circadian clock gene frequency. In addition, Ukai *et al.* [58] reported that a critical light pulse (3-hour light pulses delivered at a specific circadian time (CT) ~17 (near subjective midnight (=CT18))) drives cellular clocks to singularity behavior in mammals. Interestingly, this phenomenon is transient [132], although removal of the stimulus is needed.

Taken together with this basic entity – singularity -, I designed a novel clinical concept –asynchronizatiopn-. Asynchronization is the result of disturbed aspects (*e.g.*, cycle, amplitude, phase, and interrelationship) of biological rhythms that normally exhibit circadian oscillation, which presumably involves decreased serotonergic and/or melatonergic activity. The major trigger of asynchronization is hypothesized to be a combination of light exposure during nighttime, which reduces melatonin secretion, and a lack of morning light exposure, which decreases serotonergic activity. Thus asynchronization symptoms (Table 3) include disturbances of the autonomic nervous system (sleepiness, insomnia, disturbed hormonal excretion, gastrointestinal problems, sympathetic nervous system predominance, *etc.*), as well as higher brain functions (disorientation, loss of sociability, loss of will or motivation, impaired alertness and performance, *etc.*). Neurological (attention deficits, 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. Complaints introduced in this article (Table 2) could be symptoms of asynchronization.

To detect the disturbance of biological rhythms, actigraphic recordings [133], as well as diurnal measurements of body temperature, corticosteroids, and melatonin are useful. Takimoto *et al.* monitored human clock genes in whole blood cells to evaluate internal synchronization [134]. The early phase of asynchronization is hypothesized to be functional and can be relatively easily resolved by establishing a regular sleep-wakefulness cycle. However, without adequate intervention, disturbances can gradually worsen, resulting in decreased serotonergic and/or melatonergic activity, which can be difficult to resolve. In Figure 1, red lines, especially the broad ones, are hypothesized to be involved in asynchronization. A portion of patients with chronic fatigue syndrome, orthostatic dysregulation, burnout, vital exhaustion, fibromyalgia, and depression are thought to suffer from asynchronization.

5-2.Potential therapeutic approaches

5-2-1. Basic principles

For synchronization of the biological clock to a 24-hour cycle, morning light and avoidance of nocturnal light are essential. Therefore, avoidance of these two behaviors will result in asynchronization. Moreover, light-induced adrenal gene expression and corticosterone release have been demonstrated [135]. Under normal conditions, steroid secretion is greatest in the morning.

Table 3: Asynchronization

Essence	Disturbance of various aspects (*e.g.*, cycle, amplitude, phase, and interrelationship) of 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 the 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, difficulties to remember, difficulties to concentrate Neurological Disturbances attention deficit, aggression, impulsiveness, hyperactivity, irritated, hypersensitive Psychiatric Disturbances Symptoms observed in depressive disorders, personality disorders, and 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 relatively easily resolved, *e.g.*, through establishment of a regular sleep-wake cycle Chronic phase: Without adequate intervention, disturbances can gradually worsen involving loss of serotonergic activity, which is difficult to resolve.

In addition to light and social factors [123], food [136] is known to affect the circadian clock. The dorsomedial hypothalamic nucleus was determined to be a putative food-entrainable circadian pacemaker in mice, and oscillation of this pacemaker was found to persist for at least 2 days, even when mice received no food during the expected feeding period following establishment of food-entrained behavioral rhythms [61]. Regular mealtimes, as well as participation in social activities, are likely to prevent asynchronization.

A daytime nap is known to result in favorable

performance [137]. However, evening-type adolescents were reported to nap more frequently during school days than other chronotypes [44], although improved school performance after an afternoon 15-minute-nap was reported in a Japanese high school [138]. Further studies are needed to determine whether napping affects asynchronization.

Nevertheless, to prevent asynchronization, the social promotion of favorable sleep hygiene is important [139, 140].

5-2-2. Conventional approaches

5-2-2-1. Light therapy

Light therapy has been shown to effectively treat patients with depression [141, 142] and seasonal affective disorder [143]. It has been recommended that patients with seasonal affective disorder initially receive morning light shortly upon awakening [67]. In patients with winter depression (seasonal affective disorder), one week of bright, morning light (2500 lux) treatment produced significantly greater remission rates (53%) than evening (38%) or midday (32%) treatment [144]. A clinical trial [67] that administered 5 weeks of bright, morning light therapy (10000 lux, 60 minutes) to chronic (≥ 2 years) major depression out-patients resulted in a remission rate of 50%, while the control group showed only minor improvements. Light therapy also reduced depress- sion scores in patients with fibromyalgia [145].

The effects of light therapy on chronic fatigue syndrome have, however, been controversial [146, 147]. As described previously, exposure to at least 3 hours daylight per day was suggested to produce favorable effects on burnout patients [108], and light therapy was used to treat patients with shift work and jet lag disorders [148]. However, in animals and humans, short nights attenuate both evening light-induced circadian phase delays and morning light-induced circadian phase advances [149, 150]. In addition, circadian clocks advance phases by inducing earlier waking time and bedtime, while circadian clocks delay phases by pushing waking and bedtime later [151, 152]. Although these light effects should be clues for treating patients with early phase asynchronization, attenuation of light-induced circadian phase delays during short nights results in decreased light therapy effects on individuals suffering from jet lag and night workers engaged in a nocturnal life with a long nocturnal photoperiod (= short nights) [150].

5-2-2-2. Medications

5-2-2-2-1. Hypnotics

There is insufficient evidence to assess the safety and efficacy of hypnotic medication for delayed sleep phase disorder [153]. Data encompassing the safety and efficacy of hypnotics with other types of circadian rhythm sleep disorders are scant [153]. In addition, the effects of hypnotics on shift work disorder patients are inconsistent [148]. However, the use of hypnotics for jet lag-induced insomnia is a rational treatment and is consistent with standard recommendations for treating short-term insomnia. The efficacy of benzodiazepines on patients with fibromyalgia, together with non-steroidal anti-inflammatory drugs, has been inferior to amitriptyline [154]. In addition, ultra-short- or medium-acting hypnotics have been used in children with chronic fatigue syndrome [147], and are widely used to treat insomnia in depression patients [155]. It is likely that appropriate use of hypnotics should be taken into consideration for the management of asynchronization.

5-2-2-2-2. Antidepressants

The efficacy of antidepressants has been reported in depression, as well as chronic fatigue syndrome [102] and fibromyalgia [116, 154]. These agents could also be promising for treating depressive tendencies in asynchronization patients. However, because asynchronization involves serotonin depletion, the use of selective serotonin reuptake inhibitors or serotonin and norepinephrine-reuptake inhibitors should not be used as the first agent of choice for treating asynchronization.

5-2-2-2-3. Melatonin and its agonists

The effects of melatonin in patients with delayed sleep phase disorder and free-running disorder have been established [153]. Afternoon or evening melatonin administration would be expected to shift rhythms earlier, thereby correcting pathological phase delay. Appropriately timed melatonin administration has been shown to entrain totally blind individuals with free-running disorder. Melatonin or melatonin agonists might benefit daytime sleep in night workers through their hypnotic, as well as phase-shifting, effects [148]. Melatonin, administered at the appropriate time, can reduce symptoms of jet lag and improve sleep following travel across

multiple time zones [148]. Melatonin is also effective treatment for some patients with chronic fatigue syndrome [103], as well as pain associated with fibromyalgia [117]. Interestingly, agomelatine, a compound with melatonin receptor agonist properties, has been reported to exert an antidepressant effect superior to selective serotonin reuptake inhibitors and selective serotonin and noradrenaline reuptake inhibitors [156]. However, because melatonin is not regulated by the U.S. FDA, there are a variety of preparations, and its usefulness has been limited [157].

In a 4-year-old boy diagnosed with Smith-Magenis syndrome, Carpizo *et al.* reported treatment with a beta (1)-adrenergic antagonist in the morning (to suppress diurnal melatonin secretion) and melatonin in the evening (to generate nocturnal melatonin peak), which resulted in improved sleep quality, as evaluated by polysomnographic methods [158]. This approach could be beneficial for asynchronization patients that exhibit altered diurnal melatonin secretion.

5-2-2-2-4. Vitamin B12

Vitamin B12 has been shown to enhance light pulse-induced phase shifts and thus augment entrainability of the circadian clock to light in rats [159]. In fact, high-dose vitamin B12 (3 g/day) proved to be effective in childhood chronic fatigue syndrome patients with free-running disorder [147]. An association between low vitamin B12 status and depression in elderly individuals has been suggested [160]. Because vitamin B12 deficiency causes decreased remethylation of homocysteine and is, therefore, most likely contributing to increased homocysteine levels, Regland *et al.* [161] measured homocysteine and vitamin B12 levels in cerebrospinal fluid of patients that fulfilled criteria for both fibromyalgia and chronic fatigue syndrome. They measured increased homocysteine concentrations, as well as a correlation between vitamin B12 levels and clinical variables. In other words, decreased vitamin B12 levels resulted in more severe clinical conditions. However, a recent review suggested that vitamin B12 was not an effective treatment for delayed sleep phase disorder [153]. Also, vitamin B12 was not recommended for treating jet lag or shift work disorders [148].

5-2-2-3. Physical activity

Physical activity is associated with an antidepressant effect in clinical depression [162]. Exercise leads to improved physical and mental health in fibromyalgia patients [163] and was shown to re-time circadian rhythm in individuals suffering from jet lag or shift work [164]. In patients with chronic fatigue syndrome, graded exercise therapy was shown to be valuable in randomized controlled trials [165]. Exercise induces these effects not only through the serotonergic systems, which is activated by rhythmic movements, such as gait, chewing, and respiration [89], but also through other molecules, such as brain-derived neurotrophic factor [90]. Physical activity or exercise could be potentially used to relieve asynchronization. Each morning in Japan, we have a 10-minute radio program of gymnastic exercises with piano accompaniment. This set of exercises is very familiar to almost all people in Japan, especially those older than twenty years of age. The efficacy of these exercises should be re-evaluated for physical and mental health.

5-2-2-4. Chronotherapy

To resynchronize the circadian clock with the desired 24-hour cycle, chronotherapy has been used in patients with circadian rhythm sleep disorder. This approach assumes that the circadian clock cycle of the majority of people is longer than 24 hours. In a case of delayed sleep phase, a successive delay of sleep onset by 3 hours each day, over a 5-6-day period, is required to achieve desired sleep onset [166]. This shift should be rigidly adhered to establish a set sleep-wake schedule and proper sleep hygiene practice. However, the potential confounding effects of light exposure at inappropriate circadian times might limit the effectiveness and practicality of this approach [167].

5-2-3. Alternative approaches

The following are potential approaches to manage asynchronization, although the diagnostic standards and methodology, in terms of applicability, remain to be determined.

5-2-3-1. Kampo

Kampo medicine is a traditional Japanese herbal medicine that originated from traditional Chinese medicine. Examples for prescription are listed in Table 4 [168-170]. In addition to these prescriptions, Kanbaku-taisou-to (72) and Yoku-kan-san (54) is the author's preference for patients with early-phase asynchronization and presumed elevated sym-

pathetic nerve activity (the value in parentheses is the standardized number for prescription in Japan). I also use Dai-saiko-to (8) to treat insomnia due to hypertension or tinnitus. In patients with depression [171] and fibromyalgia [172], Kampo or traditional Chinese medicine have been commonly used.

Table 4 Presumable Kampo prescriptions for asynchronization

		weakness in the lower extremities	systemic hypothermia and or coldness	glowing (or heat sensation in the palm or foot)	apathy	aggressiveness or impulsiveness	depressive tendency	anemia	GI disturbance	fatigue after some infection
fatigue syndrome	Rokumi-gan (87), Hochu-ekki-to (41), and Sho-Saiko-to (9) [168]									
chronic fatigue syndrome	Ninjin-yoei-to (108) [168] [169]	Hachimi-jiou-gan (7) [170]	Saiko-to (30) or Ougiken-chu-to (98) and Ninzu-to (52) [170]	Rokumi-gan (87) [170]				Zyuzen-taiho-to (48) and or Ninjin-yoei-to (108) [170]	or insomnia Kihi-to (65) or fatigue Hochu-ekki-to (41) [170]	Saiko-keishi-to (20) [170]
child patients with school refusal				Rokumi-gan (87) [170]	Saiko-ekki-to (136) [170]	Saiko-keiryu-kotsoboreo-to (12) [170]	Kami-shoyo-san (24) [170]	Zyuzen-taiho-to (48) and or Ninjin-yoei-to (108) [170]	or insomnia Kihi-to (65) Hochu-ekki-to (41) [170]	

Number in the parenthesis is the standardized number for prescription in Japan

5-2-3-2. Rhythmic movements

As described in the former section, exercise could produce favorable effects on depression [162], fibromyalgia [163] jet lag, shift work [164], and chronic fatigue syndrome [165], presumably not only through the activation of serotonergic system [89] but also by the induction of other molecules [90]. Among rhythmic movements which activate serotonergic system [89], gait must be a part of exercise. In this section, rhythmic movements other than gait –respiration and chewing- will be introduced.

Qigong is an ancient, oriental, mindful exercise [173], also described as a mind-body, integrative exercise or traditional Chinese medicine intervention that is used to prevent and cure ailments, as well as to improve health and energy levels [174]. Qigong (or ch'i kung) refers to a wide variety of traditional "cultivation" practices that involve movement and/or regulated breathing [175]. Qigong has recently been designated as an alternative therapy to help meet the increasing demand of non-pharmacologic modalities for achieving bio-psycho-social health in patients suffering from anxiety [173] or pain [176]. Although the meta-analyses to date have been based on low-quality studies and small numbers of hypertensive participants, Qigong and Zen meditation have been shown to significantly reduce blood pressure [177].

Tanden breathing involves slow breathing (range of 0.05-0.15 Hz) into the lower abdomen, and was found to affect cardiac variability, which is controlled by the autonomic nervous system [178]. Although rhythmic respiration has been reported to activate serotonergic activity [89], Arita and Takahashi [179] preliminarily determined that tanden respiration also elevates serotonergic activity. Chewing has also been reported to activate the serotonergic system [89, 180]. This behavior could be used to manage asynchronization by deliberately activating serotonergic activity.

Locomotion is a sort of rhythmic movements. Failed locomotion (crawling) during infancy (lack of interlimb coordination between upper and lower extremities) has been reported to be due to hypofunctioning serotonergic and/or noradrenergic neurons [181]. This results in postural atonia by disfacilitating postural augmentation pathways and/or disinhibiting the postural suppression path- way and preventing locomotion [182]. Forced-crawl training has been described as relieving symptoms resulting from low serotonergic activity [183].

5-2-3-3. Direct contact

An older generation Japanese pediatrician [184] was quoted to say, "Holding a baby in the arms

("dakko" in Japanese) is the most effective tranquilizer for a baby." Although therapeutic touch is now receiving attention as a method to manage anxiety disorders, including depression [185], dakko is a typical and classic daily behavior that involves direct contact between caretakers and youngsters. With the rapid spread of various types of media, including mobile phones, one concern is that direct contact between people is rapidly diminishing. In fact, concurrent television exposure is reported to correlate with fewer social skills [186]. In addition, hugging and intimate, face-to-face conversations are expected to be promising in the effort to manage and/or prevent asynchronization.

5-2-3-4. Control of the autonomic nervous system

To provide adequate cues for the circadian clock, morning activation of the sympathetic nervous system and evening stimulation of the parasympathetic system might be helpful to manage asynchronization. In Japan, some pediatricians recommend scrubbing the skin with a dry towel or cold water in the morning to train the autonomic nervous system in patients with orthostatic dysregulation [187]. However, this approach has not been covered in the recently published guideline [188].

5-2-3-5. Pulse light

In addition to the removal of stimuli that induce singularity effects, adequate stimuli (light pulse at CT 9-15 (transition from subjective day to night) [58]) could also reverse singularity. Further studies are needed to identify adequate stimuli for reversing circadian singularity behavior in asynchronization.

6. Conclusion

Many young people in Japan suffer from daytime sleepiness and nocturnal insomnia, and are persistently tired and inactive. This review focused on the association between nocturnal lifestyle and biological clock disorders, as well as the melatonergic and serotonergic systems. However, involvement of dopamine [189] and opioid peptides [100] are also possible. A novel clinical concept – asynchronization - has been proposed, and a similar basic concept - singularity - was also introduced.

In this review, studies that recommended morning-type behavior to reduce behavioral/ emotional problems were introduced [28, 47, 52]. Ayurveda, an ancient system of health care that is native to the Indian subcontinent, suggests that, in addition to good conduct, thought, diet, interpersonal dealings, physical activity, early rising, and early bedtimes are good for a healthy life [190]. Ekken Haibara wrote in his essay, Youzyoukun (1713), that one should awake early in the morning and avoid late bedtime to live a healthy life [191]. Byoukesuchi (Hirano, 1832), a book describing medical practices for the home, stated that one should go to bed early at night and awake before dawn for a healthy life [192]. Thus both traditional wisdoms and recent researches recommend morning-type behavior, and this article reviewed the possible background mechanisms for the favorable effects on physical and mental health.

Senior high school students in Korea are reported to go to bed (0:54 on school nights) [193] later than those in Japan (0:06 [11] or 23:50 [12]). Although Chinese senior high school students in Hong Kong went to bed earlier (23:24) than those in Japan, it was concluded that they did not receive sufficient sleep [194]. Many young people not only in Japan but also in the other countries might be potential patients with asynchronization. In addition, some NEET (Not in Employment, Education, or Training) [195] individuals might also suffer from asynchronization.

Now we are living in the society with 24-hour activity. I am afraid that this type of society might produce unfavorable effects on the SCN. A quarter of the world's population is subjected to a 1 hour time change twice a year (daylight saving time; DST) [196]. DST is now known to disturb normal seasonality seen in sleep timing assessed by mid—sleep times [196]. In addition, at the beginning of DST (=spring), the rates of traffic accidents [197] and the attacks of myocardial infarction [198] are reported to increase. I wonder we should be more careful on the property of the biological clock. I hope a novel concept of asynchronization to contribute to noticing the significance of the SCN, and to helping patients suffering from circadian disruptions.

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研究報告

うつ病におけるfluvoxamine投与前後の睡眠ポリグラフ所見と治療反応性予測

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抄録：大うつ病性障害患者8名にfluvoxamineを単剤投与し，投与前（drug free下）と投与4週時に睡眠ポリグラフ検査（PSG）を行い，PSG所見の変化から12週時の抗うつ効果を予測できるかどうかを検討した。
投与12週時の最終評価時点で，ハミルトンうつ病評価尺度（HRSD）の改善率が50％以上のresponder群は8名中5名（62.5％），改善率が50％未満のnon-responder群は3名（37.5％）であった。PSG上のREM潜時変化量（投与前，4週）と12週時のHRSD改善率は強い正の相関を示し，4週時のREM潜時変化量から12週時の治療効果を予測できる可能性が示唆された。一方，4週時の臨床症状の改善度からは，12週時の治療効果の予測は困難であった。以上より，大うつ病性障害のfluvoxamine療法において，PSGを導入することにより，より早期に治療効果を予測できる可能性が示唆された。

臨床精神医学38：1073～1081

Key words：うつ病（depression），睡眠ポリグラフ検査（polysomnography），治療反応性予測（treatment prediction），レム潜時（REM latency）

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1 緒言

現在，大うつ病性障害の薬物療法においてはいくつかの治療ガイドラインが存在し[1,4,17]，そのいずれにおいても選択的セロトニン再取り込み阻害薬（selective serotonin reuptake inhibitor；以下SSRI）あるいはセロトニン・ノルアドレナリン再取り込み阻害薬（serotonin noradrenalin reuptake inhibitor；以下SNRI）が第一選択薬として推奨されている。しかしこれら薬物療法の大きな問題点の一つは，効果発現までに2～4週間を要すること，最終的な効果判定までには十分量の抗うつ薬を8～10週間は投与して経過をみる必要があることである[16,21]。さらに初回の抗うつ薬に効果を示すうつ病患者は50～75％であることが，多くのプラセボ対照の二重盲検比較試験により確認されている[1,8]。初回抗うつ薬が無効であった場合には，別の抗うつ薬に切り替え，さらに8～10週間後に治療効果を判定する必要があり，各患者に効果的な薬剤決定までに相当の時間を要してしまう。また治療の長期化は，うつ病の遷延化や慢性化にもつながりかねない。

しかしながら現時点では，抗うつ効果を判定・予測できるような客観的な生物学的指標が存在しないため，薬剤の選択や効果判定に関しては各臨床医の裁量や主観的判断に委ねられているのが現状である。これまでにうつ病の生物学的研究に関

Polysomnographic findings before and after the administration of fluvoxamine and treatment prediction in depression
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しては，睡眠脳波でのレム(rapid eye movement；以下REM)睡眠の異常(特にREM潜時の短縮)[9]，内分泌検査での視床下部－下垂体－副腎系の異常(コルチゾールの過剰分泌とデキサメサゾン抑制試験でのコルチゾールの非抑制)[3]などが示唆されてきたが，実際の臨床現場で診断や治療効果の判定・予測を行える生物学的マーカーにはなりえていない。

今回われわれは，ほとんどの抗うつ薬が強力なREM睡眠抑制作用(REM潜時の延長，% Stage REMの減少)を有すること，それらの変化は比較的早期に出現すること[19]，SSRIやSNRIでの初回抗うつ薬療法に反応する患者は50～75%前後であること[1,8]，われわれの予備的研究では同一のSSRIを投与しても顕著にREM潜時が延長する症例としない症例が存在することに注目し，SSRI投与前後におけるREM睡眠指標(特にREM潜時)の変化からその後の治療反応性を予測できるのではないかという仮説を立てた。

本研究では，大うつ病性障害患者にSSRIであるfluvoxamineを単剤で投与し，投与前(drug free下)と投与4週時に睡眠ポリグラフ検査(polysomnography；以下PSG)を行い，fluvoxamine投与4週時のPSG所見の変化から投与12週時の抗うつ効果を予測できるかどうかを検討した。

2 研究対象および研究方法

【対象】

久留米大学精神神経科を受診した大うつ病性障害患者8名(女性6名，男性2名，平均年齢27.9±12.8歳)を対象とした。大うつ病性障害の診断はDSM-Ⅳ-TR[18]を用いた構造化面接にて行い，双極性障害，不安障害，物質乱用／依存，人格障害など他の精神疾患を併発する患者は除外した。

【方法】

1)初診時(ベースライン時)に17項目Hamiltonうつ病評価尺度(Hamilton rating scale for depression；以下HRSD)[6]と21項目Beckうつ病調査票(Beck Depression Inventory；以下BDI)[2]を用いてうつ病症状の重症度を，ピッツバーグ睡眠質問票(Pittsburgh sleep quality index；以下PSQI)[5]を用いて主観的な睡眠の質の重症度を評価した。

2)全患者に対し，fluvoxamine投与前(ベースライン時)にdrug-free下に睡眠ポリグラフ検査(PSG)を施行した。PSGは4端子の脳波(C3, C4, O1, O2)，2端子の眼球運動，頤筋電図，両側前脛骨筋の筋電図，鼻口気流，胸腹部呼吸運動，酸素飽和度を測定した。PSGでの就床時刻はAM1：00を超えない時刻で，患者の普段の就床時刻に合わせ，起床は自然覚醒を原則とfした。睡眠段階判定は，Rechtschaffen and Kalesの手法[14]に従い，20秒1エポックで視察にて行った。PSG解析後の客観的睡眠指標として，総睡眠時間(分)，睡眠効率(%)，睡眠潜時(分)，中途覚醒時間(分)，各睡眠段階(Stage 1, 2, 3＋4, REM)が占める割合(%)，REM潜時，REM密度を用いた。入眠はstage 1睡眠以外の睡眠段階(stage 2, 3, 4, REM睡眠)が出現した時点とし，睡眠潜時は就床から入眠までの時間(分)と定義した。REM潜時は入眠から最初のREM睡眠出現までの時間から，その間の覚醒時間を除外した時間(分)と定義した。REM密度は，REM期間全体を2秒間隔のエポックに分け，少なくとも1つの眼球運動を含むエポックがREM期間に占める割合を算出した。

3)ベースライン時(drug-free下)のPSG終了後，全患者にfluvoxamine 50mg/日の単剤投与を開始し，2～4週は100mg/日を投与した。投与4週の時点で，再度PSGを施行した。その後の4～12週は臨床的なうつ病症状に応じて，忍用性が許す範囲で最高150mg/日まで増量した。

4) fluvoxamine投与後，初診時同様に，うつ病症状の重症度をBDI，HRSDにて2週間毎(投与2週，4週，6週，8週，10週，12週)に，主観的な睡眠の質の重症度をPSQIにて4週間毎(投与4週，8週，12週)に評価し，投与12週時を最終評価時点とした。

5)データ解析は，まずはfluvoxamine投与前後での抑うつ症状(HRSD，BDI)および主観的な睡眠の質(PSQI)の経時的変化を，期間を要因とする1要因分散分析(被験者内)にて統計学的に検討した。多重比較検定にはLSD法を用いた。

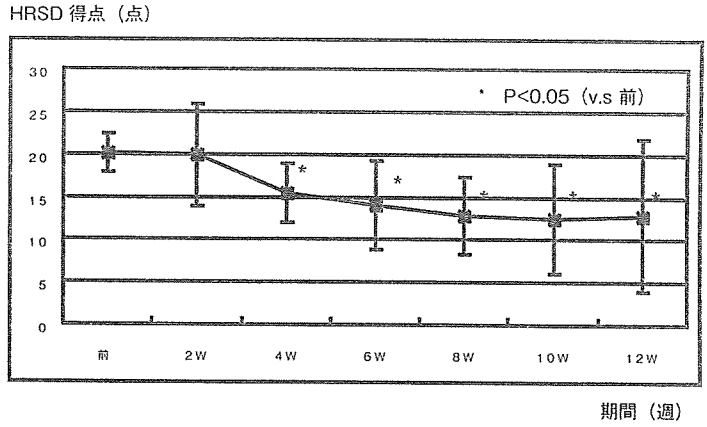

図1　fluvoxamine 投与前後の Hamilton うつ病評価尺度（HRSD）の変化（N=8）

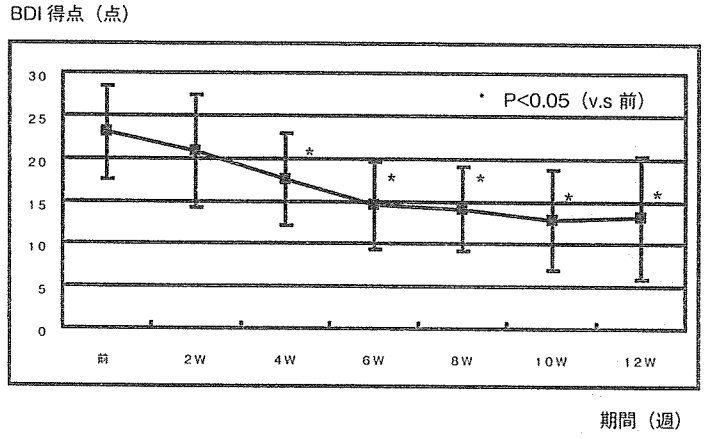

図2　fluvoxamine 投与前後の Beck うつ病調査票（BDI）の変化（N=8）

fluvoxamine投与前と4週時のPSG上の各睡眠指標の比較は，対応のあるt検定を用いて行った。

6)次にfluvoxamine投与4週時のPSG所見の変化および臨床症状の変化から最終評価時点の抗うつ効果を予測できるか否かを知るために，投与4週時のPSG上の各睡眠指標の変化，臨床症状の変化(4週時のHRSD改善率)と投与12週時のHRSD改善率との相関をSpearmanの順位相関係数を用いて検討した。なお統計解析にはJavaScript-STAR（version4.4.4j)を用いた。

全患者には，事前に研究主旨，副作用の出現の可能性や危険性，データの論文使用，プライバシーの保護について口頭・書面にて説明し，同意を得た。なお本研究は当院倫理委員会の承認を得ている。

3 結果

1. fluvoxamine 投与による抗うつ効果

最終評価時点(12週時)でのfluvoxamine平均投与量は135.7±24.4mgであった。図1にfluvoxamine投与前後のHamiltonうつ病評価尺度(HRSD)の変化を示した。投与前(ベースライン時)のHRSDは20.1±2.3点と中等症の抑うつ症状を示した。fluvoxamine投与後2週時は，HRSDが19.9±5.9点で治療前に比べ有意な改善がみられなかったが，4週時は15.5±5.5点，6週時は14.0±5.2点，8週時は12.9±4.5点，10週時は12.5±6.4点，12週時は12.9±9.0点と投与前に比べ，HRSD得点は有意に改善した(すべてp<0.05)(図1)。

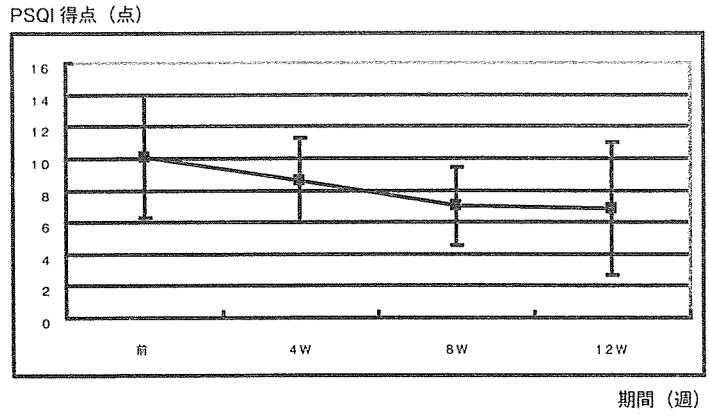

図3 fluvoxamine投与前後のピッツバーグ睡眠質問票（PSQI）の変化（N=8）

表1 fluvoxamine投与前後の睡眠ポリグラフ（PSG）所見（N=8）

	投与前（Drug free）	投与4W	P値
総睡眠時間（分）	427.6 ± 51.5	408.7 ± 67.3	n.s
睡眠効率（%）	85.7 ± 7.1	83.5 ± 7.7	n.s
睡眠潜時（分）	31.2 ± 27.9	27.3 ± 16.9	n.s
中途覚醒時間（分）	36.1 ± 26.8	50.5 ± 37.9	n.s
%Stage 1 睡眠（%）	9.0 ± 6.7	14.5 ± 6.5	<.05
%Stage 2 睡眠（%）	51.5 ± 9.2	47.0 ± 6.9	n.s
%Stage 3 + 4 睡眠（%）	11.8 ± 5.5	10.4 ± 7.1	n.s
%REM 睡眠（%）	19.8 ± 4.1	17.3 ± 3.5	n.s
REM 潜時（分）	87.4 ± 26.7	134.3 ± 26.5	<.01
REM 密度（%）	22.1 ± 8.7	23.3 ± 5.6	n.s

paired t-test

図2にfluvoxamine投与前後のBeckうつ病調査票(BDI)の変化を示した。BDIもHRSD同様の推移を示し，投与2週時には有意な改善は示さなかったが，4週，6週，8週，10週，12週と経時的に投与前に比べ有意に改善した(p<0.05)(図2)。

2. fluvoxamine投与による主観的な睡眠の質の変化

図3にfluvoxamine投与前後のピッツバーグ睡眠質問票(PSQI)の変化を示した。PSQIは投与前(ベースライン時)が10.1±3.8点で，投与4週時が8.6±2.6点，8週時が7.0±2.4点，12週時が6.9±4.2点と順次減少したが，統計学的に有意な改善には至らなかった。

3. fluvoxamine投与による客観的睡眠指標の変化

fluvoxamine投与前(drug free下)と投与4週時の睡眠ポリグラフ(PSG)所見の比較を表1に示した。最も顕著な睡眠指標の変化はREM潜時において認められ，投与前の87.4±26.7分から投与4週時には134.3±26.5分と有意な延長を認めた(P<0.01)。% REM，REM密度に関しては，投与前と投与4週後で有意な変化は認めなかった。

総睡眠時間，睡眠効率，睡眠潜時，中途覚醒時間などの入眠・睡眠維持指標と深睡眠の割合(% Stage 3 + 4)に関しては，fluvoxamine投与前後で統計学的に有意な差はなかったが，% Stage 1が9.0±6.7%から14.5±6.5%と有意に増加した(P<0.05)。

4. fluvoxamine投与4週時の睡眠ポリグラフ(PSG)変化および臨床症状変化と最終評価時（12週時）の抗うつ効果

最終評価時(12週時)のHRSD改善率が50%