Psychiatry and Clinical Neurosciences (1996), **50**, 203–209

Regular Article

A multicenter study of sleep–wake rhythm disorders: Therapeutic effects of vitamin B_{12}, bright light therapy, chronotherapy and hypnotics

HIROSHI YAMADERA, MD,[1] KIYOHISA TAKAHASHI, MD[2] AND MASAKO OKAWA, MD[3]
[1]*Department of Neuropsychiatry, Nippon Medical School, Tokyo,* [2]*National Center Hospital for Psychiatry, Neurological and Muscular Disorders, NCNP, Kodaira and* [3]*National Institute of Mental Health, NCNP, Ichikawa, Tokyo, Japan*

Abstract One hundred and six subjects with primary sleep–wake rhythm disorders [13 non-24 hour sleep–wake syndrome (non-24), 76 delayed sleep phase syndrome (DSPS), 11 irregular sleep–wake pattern (irregular) and six long sleepers] were treated with vitamin B_{12}, bright light, chronotherapy and/or hypnotics. These therapies caused moderate or remarkable improvement in 32% of the non-24, 42% of DSPS, 45% of irregular and 67% of long sleepers. A lack of adequate sleep, unpleasant feelings at waking and daytime drowsiness were also improved in DSPS.

Key words bright light therapy, chronotherapy, hypnotics, sleep–wake rhythm disorders, vitamin B_{12} (methylcobalamin).

INTRODUCTION

Clinical features and treatments for sleep–wake rhythm disorders [e.g. non-24 hour sleep–wake syndrome (non-24); delayed sleep phase syndrome (DSPS); irregular sleep–wake pattern type (irregular) and long sleepers] have been reported.[1–16] In order to treat such disorders, bright light therapy, chronotherapy (therapeutic approach to correct abnormal phase-shift of sleep by gradual shifting), and vitamin B_{12} have been used as novel treatments. The bright light therapy has been shown to have phase-shifting effects on circadian rhythms in humans.[2,4,5] Rosenthal *et al.* reported the efficacy of bright light therapy for sleep–wake rhythm disorders.[14] Czeisler *et al.* reported re-setting effects of chronotherapy in subjects with DSPS.[1] However, it has been reported that it is often difficult to maintain the phase of sleep–wake rhythm normalized by chronotherapy.[8] Administration of triazolam as a treatment for DSPS was also reported by several Japanese physicians but it was concluded that subjects are often reluctant to take hypnotics.[7,9,11] Efficacy of vitamin B_{12} was first reported by Kamgar-Parsi *et al.*[3] They used vitamin B_{12} for the treatment of hypothyroidism in a subject with non-24 and found that vitamin B_{12} improved the non-24 sleep disorder. Subsequently, several researchers studied the efficacy of vitamin B_{12} and reported good results.[11–13] In particular, Okawa *et al.* demonstrated a non-24 case who showed a dramatic benefit from vitamin B_{12}.[6,13] Therefore, vitamin B_{12} is suggested to play a certain role in the improvement of sleep–wake rhythm disorders. If vitamin B_{12} and bright light therapy and chronotherapy are truly efficacious, these methods will be welcomed by subjects as therapies that do not employ hypnotics. We reported the clinical features of non-24, DSPS, irregular and long sleepers.[15,17] Although several reports concerning the treatment of sleep–wake rhythm disorders have been shown, there was no study on large numbers of subjects. Therefore, this study was undertaken in order to investigate the efficacy of vitamin B_{12}, bright light therapy, chronotherapy and hypnotics by employing a sufficient number of subjects to draw some definite conclusions. The subjects in this study were the same as adopted in our previous study.[17]

PATIENTS AND METHODS

Patient selection

Patients selection and diagnosis were made by methods which have already been stated in our previous study.[17] After receiving a response from the subject to an advertisement in the mass media, The National Center of Neurology and Psychiatry sent a sleep–wake self-record form to be completed by the subject for 4 consecutive weeks and a questionnaire on the quantity and quality of sleep, psychosocial problems (in this paper we did not refer to the analysis of psycho-social factor influences on improvement), the

Correspondence address: Hiroshi Yamadera, MD, Department of Neuropsychiatry, Nippon Medical School, 1-1-5 Sendagi, Bunkyo-ku, Tokyo 113, Japan.
Received 26 September 1995; revised 10 November 1995; accepted 7 February 1996.

circadian pattern of their activity, educational levels, and past disease histories. After preliminary screening, the subjects were interviewed by one of our study doctors.

Diagnosis

The diagnosis of non-24, DSPS or long sleepers was made on the basis of the ICSD.[18] For a diagnosis of irregular, because the ICSD criteria were not practical, the following criteria were used:

(i) there are large variations concerning intervals between sleep-onset time and waking time (usually over 12 h) as determined from the subject's 4 week self-kept record;
(ii) the total sleep time for one 24-h period varies remarkably (usually the variation ranged over 12 h, and as the total sleep time, 0 h and over 12 h are seen often); and
(iii) these irregular patterns are not induced by any other pathology.

Subject's background

The total number of subjects who were diagnosed by the study doctors as having sleep–wake rhythm disorders was 168. Among these, 121 were classified as having primary sleep–wake rhythm disorders not associated with some other pathology, and 106 received treatment(s) ('treated' cases; Table 1). Most (89%) of the subjects were outpatients: 13 non-24 subjects, 76 DSPS, 11 irregular and six long sleepers.

Treatment

In most cases the first treatment choice was vitamin B_{12} (methylcobalamin). A daily dose of 1.5 or 3.0 mg in three divided doses per day was orally administered for more than 3 weeks. However, when it was not sufficiently effective, other treatments were added. Three subjects had bright light therapy only (one non-24, one DSPS, one irregular sleeper) and three patients who had bright light therapy concomitantly received hypnotics (one non-24 and two DSPS). The following treatments were used as an alternative to vitamin B_{12}.

Table 1. Breakdown of subjects by disease category and by treatment. Among 121 subjects, 106 received treatment(s) (mean ± s.d.)

Disease category	Not treated	Treated	Total
Non-24 (19.8 ± 6.2)	0	13	13
DSPS (21.9 ± 10.3)	14	76	90
Irregular (18.0 ± 4.3)	1	11	12
Long sleeper (21.5 ± 10.1)	0	6	6
Total	15	106	121

Bright light therapy

Bright light irradiation device (Koden Medical), which has 12 cool-white luminant bulbs and provides bright light with approximately 2500–3000 lux from a distance of 1 meter it was used. In this study, subjects received bright light illumination for 2 h at home soon after waking, and during the irradiation, subjects were instructed to look at the light source for several seconds per minute. Their eyes were checked periodically by ophthalmologists for possible damage to their eyes caused by illumination.

Chronotherapy

Patients were requested to delay their time of going to bed and of waking, 3 or 4 h every day until their day and night rhythms were shifted completely to the desired phase. Afterwards, the subject's time of going to bed and of waking were fixed to that phase.

Administration of hypnotics

Although a variety of hypnotics were adopted, triazolam was the treatment of choice.

Evaluation

Efficacy was evaluated by each doctor based on the more than 3 weeks' consecutive sleep–wake rhythm records in vitamin B_{12}; the records of those in chronotherapy and hypnotics were recorded by the subjects and their families for more than 2 weeks. The efficacy was divided into six grades: remarkable, moderate, mild, slight improvement, not effective, becoming worse and not evaluable. The following are the criteria adopted:

(i) remarkable improvement: sleep phase is completely normalized in each sleep–wake rhythm disorder;
(ii) moderate improvement: the sleep phase advanced 1–2 h after treatment in DSPS, the free-running pattern changed incompletely in non-24, the irregular pattern changed to a DSPS-like pattern, the sleep phase is still delayed by 1–2 h in irregular sleepers, sleep duration is shortened by 1–2 h in long sleepers, but the subjects with each sleep–wake rhythm disorder is able to adjust to the normal lifestyle;
(iii) mild improvement: sleep phase advanced 1 h–30 min in DSPS, free-running pattern apparently changed in non-24, irregular sleep pattern changed incompletely in irregular sleepers, sleep duration is shortened by 1 h–30 min in long sleepers, but the subject has some difficulty in adjusting to a normal lifestyle; and
(iv) slight improvement: sleep phase changed slightly in each sleep–wake rhythm disorder and the subject has some difficulty in adjusting to a normal lifestyle.

The doctor evaluated the expectation for therapy in three grades: high, moderate and low expectation by checking the subjects' attitudes to receiving treatment.

RESULTS

Subject 1: A 16-year-old male, senior high school student, non-24 type

The subject had sleep–wake rhythm disorder since 13 years of age (Fig. 1). He was often unable to attend classes in junior high school, and required 2 years to progress to the 8th grade. He visited one of the study doctors for consultation in January 1992. Vitamin B_{12} (1.5 mg/day) was prescribed to the subject as of 1 February 1992. His non-24 disorder improved and he was able to attend high school.

Subject 2: An 18-year-old male, preparing for university entrance examinations, DSPS type

The subject withdrew from high school at the age of 17 years because of sleep–wake rhythm disorder (Fig. 2). He obtained a certificate that enabled him to sit college/university entrance examinations. He was unable to wake up on the morning of his university entrance examination. He visited one of the study hospitals in October 1990 and was diagnosed as DSPS. Vitamin B_{12} (3 mg/day) was prescribed commencing 8 December. His rhythm disorder has since improved; he became able to get up early in the morning to attend lectures at a preparatory school, and finally sat and passed some entrance examinations.

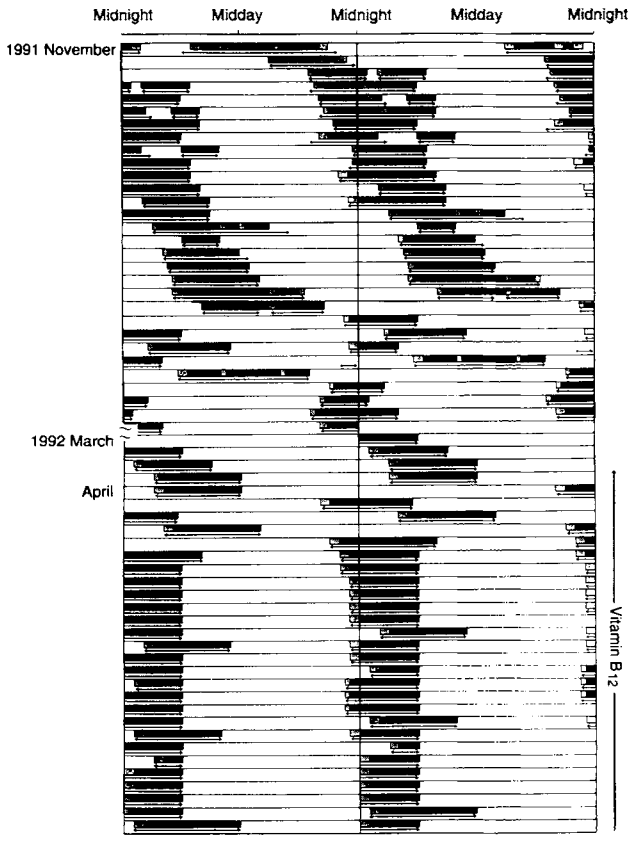

Figure 1. Sleep–wake rhythm of a 16-year-old male, non-24 type subject. Each horizontal row represents 2 days. Black bar represents the period when subject slept well, and the shaded bar when the subject felt drowsy. The thin bars represents total period in bed. The subject received vitamin B_{12} administration (1.5 mg/day) starting 1 February. Shortly after commencement of vitamin B_{12} treatment, the rhythm disorder improved.

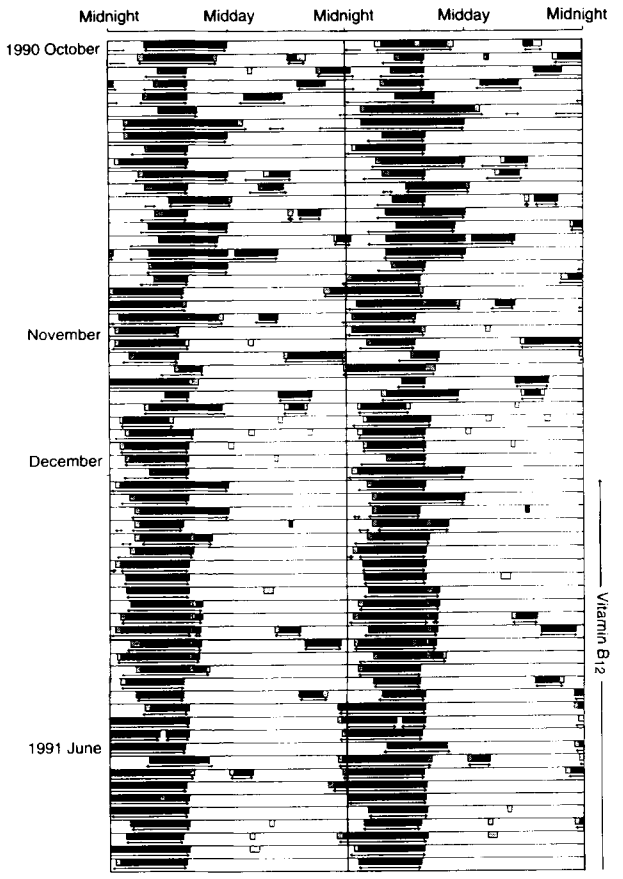

Figure 2. Sleep–wake rhythm of an 18-year-old male, DSPS type. Vitamin B_{12} (3 mg/day) administration from 8 December improved the subject's rhythm disorder.

Subject 3: A 20-year-old female, university student, DSPS type

The subject had shift work in which she had to work from 00.00–14.00 h in early April. She became unable to get up in the morning. She was diagnosed as DSPS, and vitamin B_{12} was prescribed but this failed to advance her sleep phase to the desired level, although a training camp transiently advanced her sleep phase. Bright light therapy was added to her treatment starting 13 March. The combination of vitamin B_{12} and bright light therapy made the onset time and offset time of her sleep uniform.

We found it difficult to evaluate objectively the efficacy of the treatment, assuming that a given treatment was effective when the study doctors judged the results of treatment as moderate or as marked. As shown in Table 2,

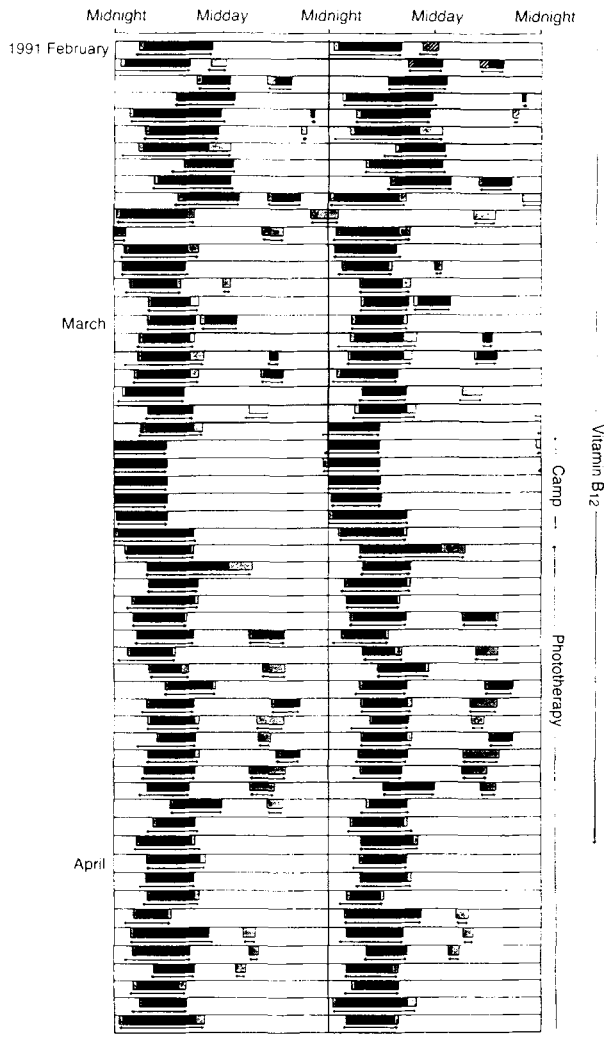

Figure 3. Sleep–wake rhythm of a 20-year-old female, DSPS type. The subject received vitamin B_{12} but sufficient improvement was not obtained. Bright light therapy was added to the treatment (right of the figure) and resulted in a good improvement.

Table 2. Breakdown of subjects by effectiveness of treatment

	Non-24 (%)	DSPS (%)	Irregular (%)	Long sleeper (%)	Total (%)
Effective[a]	4 (31)	32 (41)	5 (45)	4 (67)	45 (48)
Others[b]	9 (69)	44 (59)	6 (55)	2 (33)	61 (52)
Total	13	76 (41)	11	6	106

[a]Effective, markedly and moderately improved patients; [b]others, slightly improved, not effective, became worse, and patients not evaluable.

45/106 (48%) subjects with sleep–wake rhythm disorders benefited from some individual treatments or by a combination of treatments employed in the present study. Among four different types of disorders, the long sleeper group showed the highest rate (67%) of effective response to treatment while the non-24 subjects showed the least rate (31%) of effectiveness.

It was shown that among the subjects there were two constructive subjects groups, those who came to the clinic willingly with high expectations and those with low expectations who were persuaded by their families to attend the clinic. In order to investigate how such psychological conditions affected the results of the treatment, each study doctor evaluated roughly the degree of subjects' expectations. Patients with moderate or high enthusiasm tended to show better results compared with those with low enthusiasm (Table 3).

Moderate or marked improvement of symptoms was recorded in 28/99 subjects (28%) who received vitamin B_{12} (Table 4). Twenty-nine subjects benefited from this substance, 16 were treated with only vitamin B_{12}, while others also had bright light therapy and/or hypnotics. No side-effects were reported in any subject who was given vitamin B_{12}. The rate of effectiveness of bright light therapy was 29% (12/41 subjects; Table 5). Only one subject who benefited from light therapy was treated by light only, others were treated in combination with vitamin B_{12}. Various hypnotics, though mainly triazolam, were adopted to treat 25 subjects. Therapeutic effects were seen in 7/20 (34%) subjects with DSPS (Table 6). Chronotherapy was undertaken in 11 subjects without any effect at all.

With regard to the therapeutic effect of various treatments adopted for specific symptoms in DSPS, 30% showed improvement of disturbed nocturnal sleep (shallow sleep and discomfort at waking), and 26% showed amelioration of daytime sleepiness (Table 7).

DISCUSSION

The present study demonstrated several ways to treat rhythm disorders that see beneficial effects. It is noteworthy that 48% of subjects showed moderate or marked improvement. Because the number of subjects in each disorder category varied widely, it is difficult to compare the rate of therapeutic efficacy among the categories. However, in general, the long sleepers showed a high rate of marked improvement, and the irregular group showed similar results by treatment. Improvement of the symptoms was observed in only 31% of non-24 subjects. That suggests that this

Table 3. Level of expectation for the efficacy of treatments and therapeutic effects

	Moderate and high (%)	Low (%)
Moderate/marked improvement	43 (43)	1 (14)
Others[a]	57 (57)	6 (86)
Total	100	7

[a]Others, slightly improved, not effective, became worse, and patients not evaluable. Three patients data were not available for evaluation of enthusiasm for treatments.

Table 4. Efficacy of vitamin B_{12} therapy by disease category

	Non-24 (%)	DSPS (%)	Irregular (%)	Long sleeper (%)	Total (%)
Effective[a]	2 (20)	21 (29)	3 (27)	2 (40)	28 (28)
Others[b]	8 (80)	52 (71)	8 (73)	3 (60)	71 (72)
Total	10	73	11	5	99

[a]Effective, markedly and moderately improved patients; [b]others, slightly improved, not effective, became worse, and patients not evaluable.

Table 5. Efficacy of bright light therapy with/without other therapy by disease category

	Non-24 (%)	DSPS (%)	Irregular (%)	Long sleeper (%)	Total (%)
Effective[a]	1 (13)	7 (25)	3 (75)	1 (100)	12 (29)
Others[b]	7 (87)	21 (75)	1 (25)	0 (0)	29 (71)
Total	8	28	4	1	41

[a]Effective, markedly and moderately improved patients; [b]others, slightly improved, not effective, become worse, and patients not evaluable.

Table 6. Efficacy of hypnotics with/without other therapy by disease category

	Non-24 (%)	DSPS (%)	Irregular (%)	Long sleeper (%)	Total (%)
Effective[a]	0 (0)	7 (34)	0 (0)	0 (0)	7 (28)
Others[b]	3 (100)	13 (66)	1 (100)	1 (100)	18 (72)
Total	3	20	1 (100)	1	25

[a]Effective, markedly and moderately improved patients; [b]others, slightly improved, not effective, became worse, and patients not evaluated.

category of subjects may be the most difficult to be treated; in other words, it might be the most severe rhythm disorder.

It was natural to expect treatment in those who had a strong enthusiasm in any disorder category to show better therapeutic efficacy than those with low enthusiasm. This suggests that for treatment of rhythm disorders, a subject's motivation or mental attitude toward treatment is a very important factor.

We found that about one-third (28%) of subjects benefited from vitamin B_{12} treatment with or without bright light therapy. The success rate of treatment among different disorder group was almost similar ranging between 20 and 40%. Previous reports demonstrated the effect of this compound.[3,6,12,13] This study confirmed previous findings; however, it is too early to conclude the definite effect of vitamin B_{12} as the placebo effect of vitamin B_{12} remains to be dissolved. However, the double blind test undertaken

Table 7. Efficacy of all treatments on improvement of specific symptoms in DSPS patients

	Overnight sleep[b]	Daytime drowsiness
Moderate/Marked Improvement	13 (30%)	11 (26%)
Others[a]	31 (70%)	31 (74%)
Total	44	42

[a]Others, slightly improved, not effective, became worse, and patients not evaluable. [b]Improvement of overnight sleep was considered to be feeling of deep-sleep and pleasant feeling when waking.

here suggested that methylcobalamin might have some therapeutic effect on sleep–wake rhythm disorders, although its results were not sufficiently conclusive due to insufficient number of subjects.[16] Okawa *et al.* also demonstrated a remarkable efficacy of vitamin B_{12} on non-24 subjects which may have excluded the possibility of placebo effect of this compound.[6,13] They administered vitamin B_{12} to the subjects who had free-running patterns of sleep–wake rhythm for over 15 years. This subject's rhythm which had been entrained to a 24 h cycle during the vitamin B_{12} administration period, returned to a free-running pattern when vitamin B_{12} treatment was ceased, and the pattern's rhythm was restored after vitamin B_{12} was re-started.

Investigators have raised three possible modes of vitamin B_{12} action on sleep–wake rhythm disorders. Two studies have suggested the increase of sensitivity to light by vitamin B_{12} in humans to be a factor.[20,21] Subjects treated with vitamin B_{12} showed more marked suppression of melatonin levels by bright light compared with the levels before administration of vitamin B_{12}. Such action may enable the subject to be entrained to a 24 h cycle. The second possibility was that vitamin B_{12} shortens the period of free-running rhythm which might make entrainment to a 24 h cycle easier. Several investigators attempted without success to prove this using rats.[22,23] Vitamin B_{12} given orally or by injection did not cause any change to the free-running period of locomotor activity. The third possibility was demonstrated by Inoue and Honda who showed vitamin B_{12} to increase slow wave and REM sleep in animals.[24] Administration of vitamin B_{12} into the third ventricle in rats caused increments of slow wave and REM sleep together with a reduction in brain temperature. In human subjects vitamin B_{12} administration tended to increase slow wave sleep.[25] Thus, we are able to assume two possible modes of vitamin B_{12} action: increase sensitivity to light or an increase in sleep. It is to be determined which factor is truly responsible for therapeutic benefit of vitamin B_{12}.

In this study, bright light therapy also seemed to be effective. The rate of beneficial effect of bright light therapy was 29%, although it is likely that light therapy acts as placebo. However, it is impossible to exclude the placebo effect of bright light therapy by use of a double blind test. Effectiveness of bright light therapy has been seen in DSPS

subjects. Some investigators reported that the phase of sleep–wake rhythm can be advanced not only in animals but also in humans when bright light therapy is given to the subjects in the late resting or early active period. Rosental *et al.* reported advanced body temperature rhythm when 2500 lux of bright light was administered to 20 DSPS subjects.[14] Another study reported that light therapy improved daytime drowsiness in winter insomnia subjects residing in northern Europe.[26] More recent studies reported that shift-workers working under bright light can synchronize sleep–wake rhythm effortlessly.[27–29] These studies also introduced the interesting findings that physical symptoms in the daytime (e.g. headache and nausea), were improved by bright light therapy. Because of the small number of cases subjected to only bright light therapy in this study, efficacy should be further investigated.

In conclusion, this study showed vitamin B_{12} to be effective in some subjects with sleep–wake disorders. We also demonstrated the significant effectiveness of bright light therapy. The rate of therapeutic success for each treatment is relatively low and the placebo effect of these treatments could not be excluded. However, the possible therapeutic benefit by vitamin B_{12} and/or bright light therapy for sleep–wake rhythm disorders is encouraging as to date there has been no useful treatment established for rhythm disorders. Further studies should be conducted in order to clarify the usefulness and efficacy of vitamin B_{12} and bright light therapy.

ACKNOWLEDGMENTS

The following co-authors contributed substantially to this paper: Hisakazu Furuta (Department of Neuropsychiatry, Kanazawa University School of Medicine, Kanazawa); Yoshiaki Higashitani (Department of Neuropsychiatry, Yamagata University School of Medicine, Yamagata); Teruhiko Higuchi (Department of Neuropsychiatry, Showa University School of Medicine, Tokyo); Jun Horiguchi (Ehime University, Matuyama); Hironobu Ichikawa (Tokyo Metropolitan Umegaoka Hospital, Tokyo); Noriaki Koizumi) Department of Neuropsychiatry, Shinshu University School of Medicine, Matsumoto; Kenji Kamei (Department of Neuropsychiatry, Kagoshima University School of Medicine, Kagoshima); Young-do Kim (Department of Neuropsychiatry, Toyama Medical and Pharmaceutical University School of Medicine, Toyama); Tatayu Kotorii (Department of Neuropsychiatry, Kurume University, School of Medicine, Kurume); Hirobumi Mashiko (Department of Neuropsychiatry, Fukushima Medical College, Fukushima); Yasushi Mizuki (Department of Neuropsychiatry, Yamaguchi University School of Medicine, Ube); Kiyoshi Morimoto (Department of Neuropsychiatry, Okayama University Medical School, Okayama); Hiroshi Murase (Department of Neuropsychiatry, Tokai University School of Medicine, Isehara); Shuichi Nakamura (Department of Neuropsychiatry, Nippon Medical School, Tokyo); Tatsuo Ohta (Department of Psychiatry, Nagoya University School of Medicine, Nagoya); Norio Okamoto (Department of Psychiatry, Hamamatsu University School of Medicine, Hamamatsu); Kaoru Sakamoto (Department of Neuropsychiatry, Tokyo Women's College, Tokyo); Mitsuo Sasaki (Department of Psychiatry, Jikei University, School of Medicine, Tokyo); Hideaki Suzuki (Department of Neuropsychiatry, Nippon Medical School, Tokyo); Satoshi Tamiya (Department of Neuropsychiatry, Hiroshima University, School of Medicine, Hiroshima); Naoto Yamada (Shiga University of Medical Science, Ohtsu); Jun Yamazaki (Department of Neuropsychiatry, Saitama Medical School, Moro); Tomoyuki Yokoyama (Department of Neuropsychiatry, Niigata University School of Medicine, Niigata); and Reiji Yoshimura (Department of Neuropsychiatry, University of Occupational and Environmental for Health, Kitakyushu).

REFERENCES

1. Czeisler CA, Richadson CS, Richard M *et al.* Chronobiology: Resetting the circadian clock of patients with delayed sleep phase insomnia. *Sleep* 1981; **4**: 1–21.
2. Pittendrigh CS. Circadian systems: Entrainment. **In**: Schoff J (ed.). *Handbook of Behavioral Biology: Biological Rhythms*, Vol. 4. New York, Plenum, 1981; 95–124.
3. Kamgar-Parsi B, Wehr TA, Gillin JC. Successful treatment of human non-24 hour sleep–wake syndrome. *Sleep* 1983; **6**: 257–262.
4. Lewy AJ, Sack RL, Frederickson RH *et al.* The use of bright light in the treatment of chronobiologic sleep and mood disorders: The phase-response curve. *Psychopharmacol. Bull.* 1983; **19**: 523–525.
5. Eastman CI. Application of circadian rhythm principles. **In**: Rensing L, Heiden V, Mackey MC (eds). Temporal Disorder in Human Oscillatory System. Springer-Verlag, Berlin, 1987; 176–185.
6. Okawa M, Sugita Y. The treatment of sleep–wake rhythm disorder by vitamin B_{12}. *Rinsho Seishin Igaku*, 1988; **17**: 475–482 (in Japanese).
7. Uruha S, Mikami A, Teshima *et al.* The effect of triazolam on delayed sleep phase syndrome. *Jpn. J. Psychiatry Neurol.* 1988; **42**: 141.
8. Ohta T. Sleep-wake schedule disorders and treatment. *Seishin Igaku* 1989; **31**: 61–67 (in Japanese).
9. Ozaki N, Iwata T, Itoh A, Ohta T, Okada T, Kasahara Y. A trial treatment of delayed sleep phase syndrome with triazolam. *Jpn. J. Psychiatry Neurol.* 1989; **43**: 51.
10. Ando K, Ohta T, Iwata M, Trashima M, Ozaki N. A case of non-24 sleep–wake syndrome treated by vitamin B_{12} and phototherapy. *Seishin-ka Chiryo-gaku* 1990; **5**: 673–681 (in Japanese).
11. Matsumoto M, Miyagishi T, Mouri Y, Tanaka Y. A case of delayed sleep phase syndrome: The treatment effects of triazolam. *Seishin Igaku* 1990; **32**: 789–792 (in Japanese).
12. Ohta T, Ando K, Hayakawa T *et al.* Treatment of adolescent patients with sleep-wake schedule disturbances who complain of non-attendance at school. **In**: Hayes DJ *et al.* (ed). *Chronobiology: its Role in Clinical Medicine, General Biology, and Agriculture*, Part B. Wily Liss, 1990; 65–72.
13. Okawa M, Mishima K, Nanami T, Schimizu T, Iijima S, Hishikawa Y. Vitamin B_{12} treatment for sleep-wake rhythm disorders. *Sleep* 1990; **13**: 15–23.
14. Rosental NE, Joseph-Vanderpool Jr, Levendosky AA *et al.* Phase shifting effects of bright morning light as treatment for delayed sleep phase syndrome. *Sleep* 1990; **13**: 354–361.

15. Takahashi K, Morita N, Mishima K *et al.* A multiple center study on sleep-wake rhythm disorders in Japan (1): demographic feature. *Seishin Igaku* 1993; **35**: 605–614 (in Japanese).
16. Takahashi K, Okawa M, Shirakawa S. The therapeutic effects of methyl cobalamin and bright light on patients with sleep-wake rhythm disorders. **In**: Hiroshige T, Honnma K eds. Hokkaido-University Press, Sapporo, 1994; 369–382.
17. Yamadera H, Takahashi K, Okawa M *et al.* A multiple study of sleep-wake rhythm disorders: Clinical features of sleep–wake rhythm disorders. *Psych. Clin. Neurosci.* 1996; **50**: 195–201.
18. Thorpy MJ. *International Classification of Sleep Disorders.* American Sleep Disorders Association. Diagnostic classification steering committee. Allen Press Inc., Lawrence, 1990.
20. Yamazaki J, Sugishita T, Yanamuchi T, Takahashi K. Effects of vitamin B_{12} on the inhibitory action of bright light to melatonin release. *5th Workshop of Chronobiology* (Abstract in Japanese). Tokyo, 1990.
21. Honma KI, Honma S, Wada T. Entrainment of human circadian rhythms by artificial bright light. *Experientia* 1987; **43**: 572–574.
22. Takashima M, Sugishita M, Takeuchi Y *et al.* The effect of methylcobalamin on circadian rhythm of rats. *5th Workshop of Chronobiology* (abstract in Japanese). Tokyo, 1990.
23. Tsujimaru S, Ida Y, Satoh H *et al.* Vitamin B_{12} accelerates re-entrainment of activity rhythm in rats. *Life Science* 1992; **50**: 1843–1850.
24. Inoue S, Honda K. Sleep-promoting and temperature-modulatory activities of vitamin B_{12} in rat. *Jpn. J. Psychiatry Neurol.* 1991; **45**: 943.
25. Morita N, Kohsaka M, Honma K *et al.* Effect of vitamin B_{12} on biological rhythm in human (1): The change on sleep. *Jpn. J. Psychiatry Neurol.* 1994; 178.
26. Hansen T, Bratlid T, Lingjarde O, Brenn T. Midwinter insomnia in the sub-Arctic region: Evening levels of serum melatonin and cortisol before and after treatment with bright artificial light. *Acta. Psychiat. Scand.* 1987; **75**: 428–434.
27. Czeisler CA, Johnson MP, Duffy JF *et al.* Exposure to bright light and darkness to treat physiologic maladaptation to night work. *New Engl. J. Med.* 1990; **18**: 253–1259.
28. Minors DS, Waterhouse JM, Wirt-Justice A. A human phase-response curve to light. *Neurosci. Let.* 1991; **133**: 36–40.
29. Dawson D, Campbell SS. Timed exposure to bright light improves sleep and alertness during simulated night shifts. Sleep 1991; **14**: 511–516.