Melatonin agonist tasimelteon (VEC-162) for transient insomnia after sleep-time shift: two randomised controlled multicentre trials

Shantha M W Rajaratnam, Mihael H Polymeropoulos, Dennis M Fisher, Thomas Roth, Christin Scott, Gunther Birznieks, Elizabeth B Klerman

Summary

Background **Circadian rhythm sleep disorders are common causes of insomnia for millions of individuals. We did a phase II study to establish efficacy and physiological mechanism, and a phase III study to confirm efficacy of the melatonin agonist tasimelteon (VEC-162) for treatment of transient insomnia associated with shifted sleep and wake time.**

Methods **We undertook phase II and phase III randomised, double-blind, placebo-controlled, parallel-group studies. In a phase II study, 39 healthy individuals from two US sites were randomly assigned to tasimelteon (10 [n=9], 20 [n=8], 50 [n=7], or 100 mg [n=7]) or placebo (n=8). We monitored individuals for 7 nights: 3 at baseline, 3 after a 5-h advance of sleep–wake schedule with treatment before sleep, and 1 after treatment; we measured plasma melatonin concentration for circadian phase assessment. In a phase III study, 411 healthy individuals from 19 US sites, who had transient insomnia induced in a sleep clinic by a 5-h advance of the sleep–wake schedule and a first-night effect in a sleep clinic, were given tasimelteon (20 [n=100], 50 [n=102], or 100 mg [n=106]) or placebo (n=103) 30 min before bedtime. Prespecified primary efficacy outcomes were polysomnographic sleep efficiency (phase II study), latency to persistent sleep (phase III study), and circadian phase shifting (phase II study). Analysis was by intention to treat. Safety was assessed in both studies. These trials are registered with ClinicalTrials.gov, numbers NCT00490945 and NCT00291187.**

Findings **In the phase II study, tasimelteon reduced sleep latency and increased sleep efficiency compared with placebo. The shift in plasma melatonin rhythm to an earlier hour was dose dependent. In the phase III study, tasimelteon improved sleep latency, sleep efficiency, and wake after sleep onset (ie, sleep maintenance). The frequency of adverse events was similar between tasimelteon and placebo.**

Interpretation **After an abrupt advance in sleep time, tasimelteon improved sleep initiation and maintenance concurrently with a shift in endogenous circadian rhythms. Tasimelteon may have therapeutic potential for transient insomnia in circadian rhythm sleep disorders.**

Funding **Vanda Pharmaceuticals Inc.**

Published Online
December 2, 2008
DOI:10.1016/S0140-6736(08)61812-7

See Online/Comment
DOI:10.1016/S0140-6736(08)61813-9

Division of Sleep Medicine, Harvard Medical School, Boston, MA, USA (S M W Rajaratnam PhD, E B Klerman MD); **Division of Sleep Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA** (S M W Rajaratnam, E B Klerman); **Vanda Pharmaceuticals, Rockville, MD, USA** (M H Polymeropoulos MD, C Scott MS, G Birznieks MS); **School of Psychology, Psychiatry, and Psychological Medicine, Monash University, Clayton, VIC, Australia** (S M W Rajaratnam); **"P Less Than" Company, San Francisco, CA, USA** (D M Fisher MD); **and Henry Ford Hospital, Detroit, MI, USA** (T Roth PhD)

Correspondence to:
Dr Elizabeth B Klerman, Division of Sleep Medicine, Brigham and Women's Hospital, Harvard Medical School, 221 Longwood Avenue, Boston, MA 02115, USA
ebklerman@hms.harvard.edu

Introduction

Circadian rhythm sleep disorders are common causes of insomnia that affect millions of individuals, including those who work at night or who cross multiple time zones during travel. These primary sleep disorders are characterised by persistent and recurrent sleep disturbances, insomnia when trying to sleep, and excessive sleepiness while trying to remain awake.[1] They occur when scheduled or desired sleep times are incompatible with endogenous circadian rhythms generated by the hypothalamic suprachiasmatic nuclei.[2] For example, when timing of sleep is advanced such that it occurs during the circadian forbidden zone for sleep (occurring a few hours before habitual bedtime),[3] sleep latency, duration, and efficiency are adversely affected.[4]

When timed appropriately, ocular light exposure and hypnotic drugs have been used as therapies for circadian rhythm sleep disorders, but both have limitations. Light exposure promotes circadian readjustment,[5] but guidelines for best possible dosing and treatment are scarce.[6] Furthermore, such treatment is often impractical because it requires a high degree of commitment and a strict regimen to which many patients are not willing to adhere. No evidence exists that hypnotics affect the underlying endogenous circadian mechanisms. The best possible treatment for patients with circadian rhythm sleep disorders would simultaneously improve sleep and facilitate circadian readjustment.

The pineal hormone melatonin—produced mainly during the biological night—is involved in circadian regulation of sleep and wake. Increased objective and subjective sleepiness coincide with high endogenous melatonin concentrations.[7–9] Exogenous melatonin can shift sleep time[10] and hormones,[11] and increase sleep propensity, particularly during times of day when endogenous melatonin production is low.[12] Melatonin effects are mediated by the melatonin MT_1 and MT_2 receptors,[13,14] although the precise role of each receptor subtype in circadian phase shifting and sleep promotion is unknown.

Although melatonin is a popular treatment for patients with circadian rhythm sleep disorders, two caveats exist. First, melatonin products available over the counter in the USA are not recommended because their potency, purity, and safety are not regulated by the US Food and Drug Administration.[15,16] Second, despite substantial evidence that exogenous melatonin[10,12,17–24] and melatonin agonists[25,26] promote sleep and entrain endogenous circadian rhythms,[27,28] a meta-analysis[29] concluded that melatonin is not efficacious for treatment of patients with secondary sleep disorders or sleep disorders accompanying sleep restrictions (eg, jet lag and shift-work disorder). This conclusion is controversial[30] and could have resulted from variations in quality and content of individual melatonin preparations, and absence of large randomised controlled trials. Other meta-analyses have shown that melatonin is effective in the treatment of jet lag[31] and reducing sleep complaints associated with delayed sleep phase syndrome,[32] which are two common circadian rhythm sleep disorders.

Tasimelteon (VEC-162) is a novel MT_1 and MT_2 agonist with high affinity for human melatonin receptors (Vanda Pharmaceuticals, Rockville, MD, USA, unpublished data). We hypothesised that this melatonin agonist would reduce sleep disruption and promote circadian readjustment in a standard model[33–35] of transient insomnia induced by an abrupt advance in sleep–wake time. Transient insomnia refers to impaired sleep initiation, sleep maintenance, or both, assessed in this study by latency to sleep onset and sleep efficiency in the middle of the sleep episode, respectively. This model is appropriate both for jet lag and early-riser shift workers—a rapidly increasing number of people[36] who have to awaken and work at times when their endogenous melatonin concentrations are high. We assessed the physiological mechanism and efficacy of tasimelteon in a phase II trial, and confirmed its efficacy in a phase III trial.

See Online for webappendix

Methods

Participants

Participants were men and women aged between 18 and 50 years (phase II study) or 21 and 50 years (phase III study), in good health (established by medical history, physical examination, electrocardiography, blood biochemistry, haematology, urinalysis, and urine toxicology), and without major sleep disorders (established by self-report and, in the phase II study, also by clinical polysomnography). We recruited participants by advertisements and interviewed them by telephone or email script. Those who passed this initial interview were invited to be screened for the study. Screening consisted of a visit to assess eligibility followed by an outpatient screening period (2–4 weeks in the phase II study or 2–5 weeks in the phase III study), followed immediately by the inpatient protocol.

In the phase II study, individuals were randomly assigned with a pre-set randomisation schedule. The randomisation schedule was constructed so that 32 individuals would receive tasimelteon (eight individuals per dose) and eight would receive placebo. Individuals were randomised into blocks of ten males and ten females; a block for each sex was finished before starting the next block. Participant codes were allocated sequentially as individuals enrolled. In this study, we excluded individuals who were pre-adapted to an early-sleep schedule (morningness–eveningness questionnaire[37] score >70).

In the phase III study, randomisation was done with an interactive voice response system to automate random assignment to treatment groups. When each individual started the study, the investigator or designee contacted the interactive voice response system to assign a randomisation and kit number. The kit number identified the capsule-containing bottle given to the individual. In this study, individuals who had previously slept in a sleep clinic were excluded to increase the first-night effect.[38,39]

Study design and procedure

Both studies had randomised, double-blind, placebo-controlled designs and were approved by human research ethics committees at all participating institutions. Participants provided written informed consent. The particle size for tasimelteon capsules (Vanda Pharmaceuticals) differed slightly between studies. Details of the pharmacokinetics of tasimelteon assessed in the phase II study are provided in the webappendix.

The phase II study was done between July 14, 2004, and April 1, 2005. Participants maintained a regular 8-h sleep schedule for 2 weeks before the inpatient study. The study was done at two US sites, each with a single-bed suite that was free of time cues and had controlled light intensity. Light intensities, assessed at the horizontal angle of gaze, were less than 25 lux during wake episodes, less than 2 lux during the first part of the circadian phase assessment (constant posture protocol), and 0 lux during sleep episodes. The 7-night protocol (figure 1) began with an adaptation night (lead-in day 1) followed by a baseline sleep recording night (lead-in day 2), and then a 19-h constant posture protocol for pretreatment assessment of plasma melatonin concentration. The constant posture protocol, starting at 1700 h, included semirecumbent posture and dim light.[40] The first three sleep episodes were scheduled from 2300 h to 0700 h, with administration of a single-blind placebo capsule 30 min before bedtime. After the constant posture protocol, the sleep episode was advanced by 5 h such that sleep was from 1800 h to 0200 h, remaining at this new time for 3 consecutive nights (treatment days 1, 2, and 3). Individuals were randomly assigned to double-blind study medication (10, 20, 50, or 100 mg) or matched placebo 30 min before bedtime on treatment days 1, 2, and 3 (webappendix). Placebo was the excipient for tasimelteon, and consisted

www.thelancet.com Published online December 2, 2008 DOI:10.1016/S0140-6736(08)61812-7

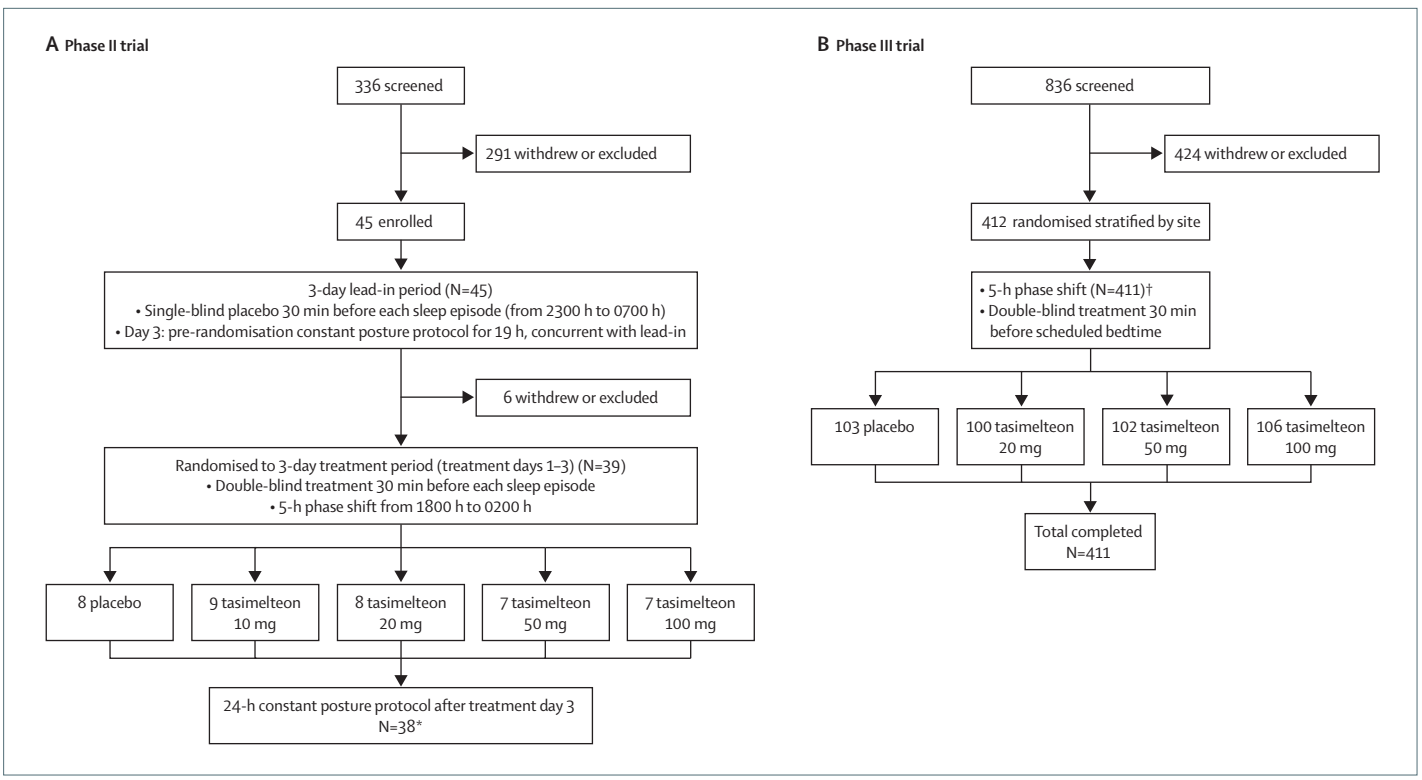

Figure 1: **Trial profiles for phase II (A) and phase III (B) studies**
*One participant in the tasimelteon 10-mg group withdrew on day 7 of the inpatient study, after 3 days of treatment and after key efficacy data had been obtained. This individual is included in all analyses. †One individual in the tasimelteon 50-mg group, who withdrew before receiving study drug and before collection of polysomnographic data, is not included.

mainly of lactose and cellulose. Treatment day 3 was followed by a 24-h constant posture protocol.

The phase III study was done from Feb 9, 2006, to Aug 21, 2006. Participants maintained a regular 8-h sleep schedule for at least 1 week followed by a 9-h sleep schedule for 1 week before inpatient study (figure 1). The study was initiated at 20 US sites, 19 of which did assessments. Participants were monitored during 8 h in bed, with bedtime advanced by 5 h compared with habitual bedtime. Participants were randomly assigned to double-blind medication (20, 50, or 100 mg) or placebo 30 min before bedtime (webappendix).

Assessments

Sleep was assessed by polysomnography, scored in 30-s epochs by blinded experienced scorers using standard criteria.[41] In the phase II study, polysomnographic data were analysed for the baseline sleep episode and treatment days 1, 2, and 3. Treatment day 1 was of main interest because deterioration of sleep was expected to be worse on the first night of the sleep–wake shift than on days 2 and 3. In the phase III study, polysomnographic data were analysed for the single inpatient night. Self-assessed latency to sleep onset and total sleep time were measured in exploratory analyses, because the study was not powered to detect differences in self-reported measures.

Prespecified primary polysomnographic efficacy outcome measures were sleep efficiency (phase II study) and latency to persistent sleep (phase III study). Wake after sleep onset was a secondary outcome measure in both studies, and latency to sleep onset was a secondary outcome measure in the phase II study. Total sleep time—defined as rapid eye movement (REM) sleep plus non-REM sleep stages 1, 2, 3, or 4—was prespecified in both trials to measure sleep efficiency. Sleep efficiency was the percentage of total sleep time divided by the total scored data for the entire sleep episode in both trials and also for one-third segments of the sleep episode in the phase II study. Latency to persistent sleep was defined as the interval between bedtime and the first 10 consecutive minutes of any stage of sleep. Wakefulness after sleep onset was defined as minutes of wakefulness after sleep onset. Latency to sleep onset was defined as the interval between bedtime and the first epoch of any stage of sleep.

In the phase II study, the primary outcome measure for circadian timing was dim-light melatonin onset ($DLMO_{25\%}$) and the secondary outcome measure was percentage of REM sleep relative to total scored data. $DLMO_{25\%}$ was defined as the time of the first of two successive datapoints greater than 25% of the peak melatonin values for each individual.[27,42] To quantify the peak melatonin values for each individual, we calculated

	Phase II study					Phase III study			
	Placebo (n=8)	Tasimelteon (mg)				Placebo (n=103)	Tasimelteon (mg)		
		10 (n=9)	20 (n=8)	50 (n=7)	100 (n=7)		20 (n=100)	50 (n=102)*	100 (n=106)
Age (year)	27·5 (6·7)	31·8 (7·4)	32·5 (9·6)	27·4 (6·2)	30·4 (9·5)	30·9 (7·3)	30·8 (8·4)	31·0 (8·5)	31·2 (8·2)
Sex (male)	3 (38%)	6 (67%)	4 (50%)	3 (43%)	3 (43%)	35 (34%)	38 (38%)	44 (43%)	33 (31%)
Ethnic origin									
White	4 (50%)	6 (67%)	4 (50%)	5 (71%)	5 (71%)	78 (76%)	79 (79%)	74 (73%)	80 (76%)
Black	2 (25%)	2 (22%)	2 (25%)	0 (0%)	0 (0%)	20 (19%)	12 (12%)	20 (20%)	19 (18%)
Asian	1 (13%)	1 (11%)	1 (13%)	1 (14%)	1 (14%)	2 (2%)	5 (5%)	1 (1%)	1 (1%)
Other	1 (13%)	0 (0%)	1 (13%)	1 (14%)	1 (14%)	3 (3%)	4 (4%)	6 (6%)	6 (6%)
BMI (kg/m²)	23·0 (2·3)	25·3 (5·4)	24·7 (3·4)	23·9 (2·0)	23·3 (2·1)	26·0 (4·3)	25·6 (3·9)	25·7 (4·1)	25·7 (3·8)
MEQ† (score)	57·5 (9·5)	59·7 (8·5)	51·6 (9·8)	54·4 (5·8)	57·2 (6·9)	..	..	..	..

Data are mean (SD) or number (%). BMI=body-mass index. MEQ=morningness–eveningness questionnaire.[37] *Tasimelteon 50 mg, n=101 (data not available for one individual). †Possible MEQ scores range from 16 to 86. Individuals are classified as definitely morning type (70–86), moderately morning type (59–69), neither type (42–58), moderately evening type (31–41), or definitely evening type (16–30). MEQ score more than 70 was an exclusion criterion for phase II enrolment.

Table 1: **Baseline demographic and clinical characteristics**

the mean of the highest recorded melatonin concentration during pretreatment and post-treatment constant posture protocols. In post-hoc analyses to examine the effects of tasimelteon on REM sleep (the timing of which is strongly regulated by the circadian system),[4] we assessed (1) accumulated REM sleep per hour and (2) REM sleep as a percentage of total sleep time during treatment day 1. This second measure indicated whether REM sleep was disproportionately affected relative to other sleep stages. Furthermore, we expected sleep to be most disturbed during the middle third of the night in individuals whose circadian rhythms had not shifted, because this time would correspond with the wake maintenance zone.[3,4]

In the phase II trial, blood was sampled for melatonin every 30 min for 14 h, then every hour during constant posture protocols, and again every 30 min from 1600 h to 0200 h (the times during which $DLMO_{25\%}$ was expected) during treatment days 1, 2, and 3. Blood was also sampled at specified intervals to measure plasma tasimelteon concentrations. Samples were centrifuged within 1 h of collection; plasma was stored at –20°C until melatonin or tasimelteon concentration was assayed by liquid chromatography/mass spectroscopy (Exygen Research, State College, PA, USA). Limits of quantification were 10 pg/mL for melatonin and 100 pg/mL for tasimelteon. The respective coefficients of variation of the assays were <15% and <5%.

Safety assessments for both studies included daily queries about adverse events, daily vital signs (except during constant posture protocols of phase II study), and physical examinations at admission and discharge. For the phase II study, a physical examination was done before randomisation, and electrocardiography, blood haematology, and biochemistry were assessed on the day after treatment day 1. The phase III study also had electrocardiography, blood haematology, and biochemistry at admission and discharge.

For **more information on R** see www.r-project.org

Statistical analysis

For hypothesis testing in the phase II trial, a sample size of eight individuals per treatment group was estimated to provide 99% power to detect a difference of about 30 min in $DLMO_{25\%}$ between the treatment group and placebo, assuming a SD of 10 min and a two-tailed test with $\alpha=0\cdot05$. For hypothesis testing in the phase III trial, a sample size of 100 individuals per treatment group was estimated to provide 85% power to detect a difference of about 10 min in latency to persistent sleep between the treatment group and placebo, assuming a SD of 23 min (estimated from the phase II study) and a two-tailed test with $\alpha=0\cdot05$.

We defined the intention-to-treat population as all randomised individuals receiving at least one dose of double-blind study medication who had at least one subsequent polysomnographic assessment. For the phase II study, change from baseline (treatment day 1 minus baseline) for all polysomnographic sleep parameters and $DLMO_{25\%}$ time were compared between groups by one-way analysis of variance (ANOVA) with linear contrasts to placebo. We also compared baseline with treatment day 1 within groups with repeated measures ANOVA followed by Tukey HSD. Change in $DLMO_{25\%}$ time was analysed with Spearman's non-parametric regression and ANOVA with linear contrasts to placebo. For the phase III study, treatment groups were compared with ANOVA followed by linear contrasts. Unless otherwise stated, values were reported as mean (SE). Analyses by intention to treat were done with R, version 2.5.1. We report only adverse events observed in five or more individuals in either study after the first dose of placebo or tasimelteon.

Role of funding source

The sponsor designed the study, in consultation with SMWR and EBK, but did not participate in data collection. Data monitoring was done by a contract research

organisation. DMF, SMWR, and EBK did data analysis. All authors, including those representing the sponsor, contributed to data interpretation and writing of the report. SMWR and EBK had full access to all data. All authors had final responsibility for the decision to submit for publication.

Results

In the phase II study, 336 individuals were screened, 39 were randomised, and 38 completed the trial (figure 1). Randomised patients were the intention-to-treat population. The webappendix lists major reasons for exclusion or withdrawal. In the phase III study, 836 individuals were screened, 412 enrolled and randomised, and 411 completed the study (figure 1). Randomised patients were the intention-to-treat population. Table 1 shows demographic and clinical characteristics of patients.

In the phase II study, sleep efficiency during treatment day 1 decreased by 20% (95% CI –38% to –3%, p=0·007) and total sleep time decreased by 113 min (–208 to –18, p=0·006) in the placebo group compared with baseline (webappendix).

The reduction in sleep efficiency took place mainly during the middle third of the night (figure 2). During this period, sleep efficiency was significantly higher in the tasimelteon groups (10 mg, p=0·049; 20 mg, p=0·008; 50 mg, p=0·002; 100 mg, p=0·002) than that in the placebo group. The first and final thirds of the sleep episode were not different between treatment and placebo groups (figure 2). In the placebo group, wake after sleep onset on treatment day 1 increased compared with baseline (p=0·033).

In individuals treated with tasimelteon, the reduction in sleep efficiency and total sleep time from baseline to treatment day 1 was greatly attenuated compared with that in individuals given placebo: mean values for each of the tasimelteon groups on treatment day 1 did not differ significantly from baseline (preshift). The tasimelteon groups slept 35 to 104 min (10 mg, 34·8 min, 95%CI –54 to 123; 20 mg, 71·4 min, –13 to 156; 50 mg, 85·6 min, 7 to 164; and 100 mg, 104·1 min, 28 to 181) more than did the placebo group (*vs* tasimelteon 20 mg, p=0·03; 50 mg, p=0·013; 100 mg, p=0·003). Similarly, compared with placebo, treatment with tasimelteon attenuated the increase in latency to sleep onset (10 mg, p=0·025; 20 mg, p=0·023; 50 mg, p=0·018; 100 mg, p=0·01) and latency to persistent sleep (10 mg, p=0·003; 50 mg, p=0·019; 100 mg, p=0·021) from baseline to treatment day 1. Results from treatment days 2 and 3 are reported in the webappendix.

In the phase III study, individuals on treatment had increased sleep efficiency (20 mg, p=0·002; 50 mg, p<0·001; 100 mg, p=0·005), increased total sleep time (20 mg, p=0·002; 50 mg, p<0·001; 100 mg, p=0·005), reduced wake after sleep onset (20 mg, p=0·02; 50 mg, p=0·001), and shorter latency to sleep onset (20 mg, p=0·006; 50 mg, p<0·001; 100 mg, p=0·002) and latency to persistent sleep (all doses, p<0·001) compared with those on placebo (table 2). In a post-sleep questionnaire,

	Phase II study*						Phase III study			
	Baseline (all groups) (N=39)	Placebo (N=8)	Tasimelteon (mg)				Placebo (N=103)	Tasimelteon (mg)		
			10 (N=9)	20 (N=8)	50 (N=7)	100 (N=7)		20 (N=100)	50 (N=102)	100 (N=106)
Polysomnography										
Sleep efficiency (%)	90·0%(0·9%) (n=39)	70·9%(6·1%)† (n=7)	79·9%(4·0%) (n=8)	82·5%(4·4%) (n=8)	85·5%(3·0%)‡ (n=7)	89·3% (2·5%)‡ (n=7)	66·1% (1·7%)	73·2 (1·6)§	76·0 (1·4)§	72·3 (1·5)§
Total sleep time (min)	429·9 (4·6) (n=39)	323·9 (33·0)† (n=7)	358·8 (24·3) (n=8)	395·3 (21·0)‡ (n=8)	409·6 (14·4)‡ (n=7)	428·1 (11·9)§ (n=7)	317·0 (8·2)	350·5 (7·8)§	364·9 (6·8)§	347·0 (7·3)§
Wake after sleep onset (min)	34·5 (4·2) (n=39)	106·7 (31·5)¶ (n=7)	79·8 (21·3) (n=8)	71·9 (21·6) (n=8)	56·6 (16·1) (n=7)	41·8 (11·5) (n=7)	140·3 (7·9)	116·2 (7·3)‡	106·3 (6·6)§	122·3 (7·0)
Latency to sleep onset (min)	10·7 (1·4) (n=38)	21·8 (8·8) (n=8)	10·2 (1·6)‡ (n=8)	10·0 (2·4)‡ (n=8)	11·6 (5·3)‡ (n=7)	6·8 (3·1)§ (n=7)	21·9 (4·5)	10·9 (3·1)§	7·8 (0·7)§	9·7 (1·1)§
Latency to persistent sleep (min)	16·2 (2·1) (n=38)	28·5 (8·9) (n=8)	14·8 (3·3)§ (n=8)	18·8 (4·4) (n=8)	14·6 (5·7)‡ (n=7)	9·4 (4·5)‡ (n=7)	44·6 (6·5)	23·1 (3·7)§	18·5 (2·1)§	22·0 (2·9)§
Self-report‖										
Latency to sleep onset (min)	..	..	..	..	..	..	39·0 (5·7)	28·5 (4·0)	17·4 (1·9)§	22·5 (3·6)§
Total sleep time (min)	..	..	..	..	..	..	395·9 (9·7)	418·8 (8·7)	430·7 (8·6)§	410·3 (9·4)

Data are mean (SE). Sleep parameters are derived from polysomnography recordings scored as wake, non-REM sleep stages 1, 2, 3, or 4, or REM sleep, with standard criteria[41] (both studies), and from self-report questionnaire given after the sleep episode (phase III study). Polysomnographic sleep parameters are shown for baseline and treatment day 1 in the phase II study, and for the single treatment day in the phase III study. For the phase II study, sleep parameters on the baseline night did not differ significantly between placebo and treatment groups, or between treatment groups. Therefore, all values were pooled as the baseline value. Baseline values were not obtained in the phase III study. *Numbers of participants are indicated in parentheses. †p<0·01 *vs* baseline. ‡p<0·05 *vs* placebo. §p<0·01 *vs* placebo. ¶p<0·05 *vs* baseline. ‖Self-reported latency to sleep onset data were missing for one participant in the tasimelteon 50-mg group, reducing the sample size to 101. Self-reported total sleep time data were missing for two participants in the tasimelteon 50-mg group, reducing the sample size to 100.

Table 2: **Sleep efficacy measures**

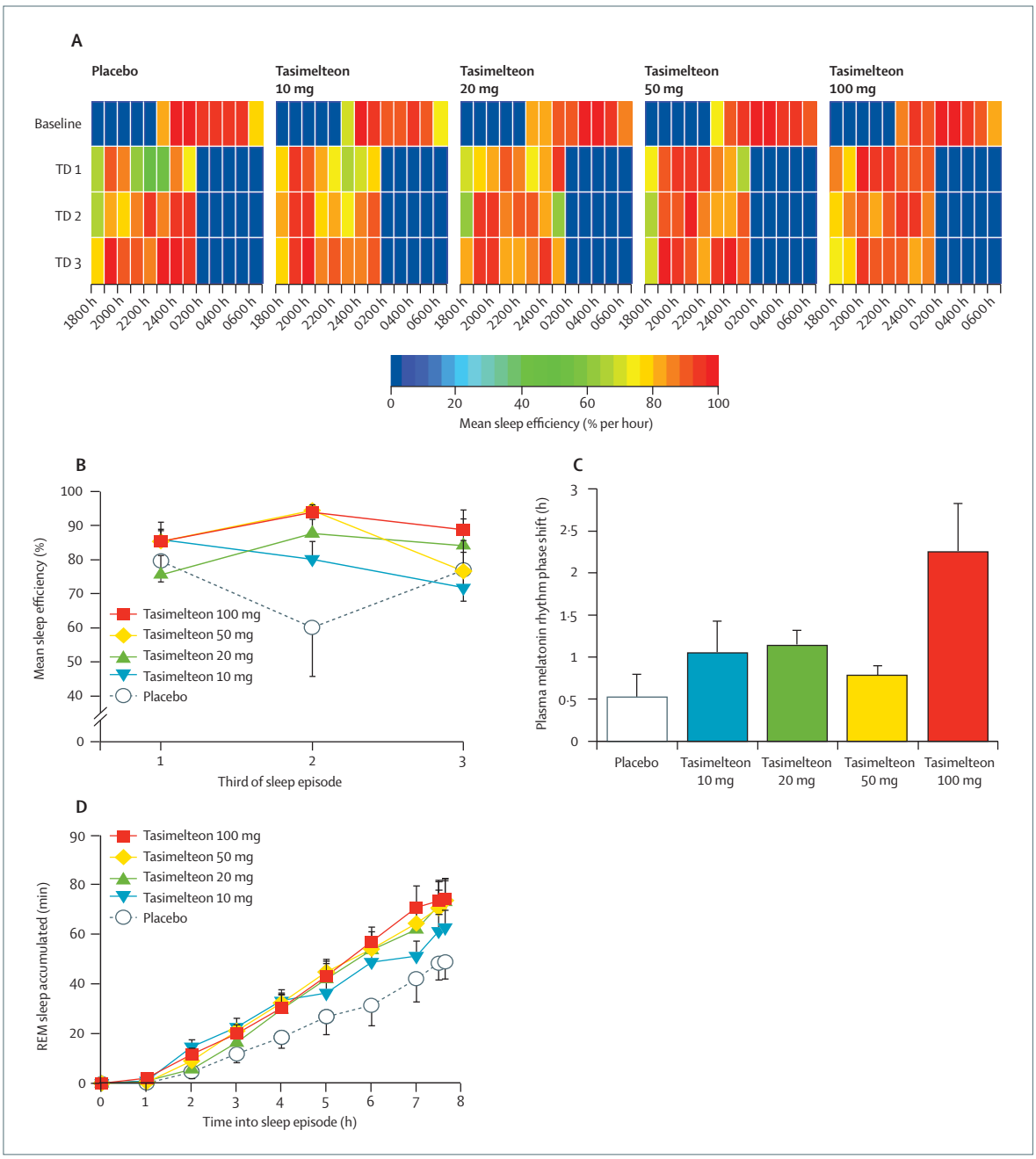

Figure 2: **Sleep-promoting and circadian rhythm phase-shifting effects of tasimelteon**
(A) Sleep efficiency data (mean values at hourly intervals) are presented as colour-contour plots, with 0% sleep efficiency shown in dark blue and 100% in red, for inpatient days baseline, treatment day 1, 2, and 3. The baseline sleep episode was from 2300 h to 0700 h; sleep episodes during treatment days were from 1800 h to 0200 h. Outside the sleep episodes, wakefulness was confirmed by continuous observation. TD=treatment day. (B) Mean sleep efficiency for each third of the sleep episode on treatment day 1. (C) Mean shift in the plasma melatonin rhythm. Values for plasma melatonin rhythm phase shift are the difference between dim-light melatonin onset ($DLMO_{25\%}$) time on treatment day 1 and baseline (a positive value indicates earlier $DLMO_{25\%}$, ie, a phase-advance shift). (D) Accumulation of REM sleep as a marker of circadian regulation of sleep on treatment day 1. Cumulative REM-sleep data are displayed at each hour (up to 7 hours); then, at 7·50 h and 7·62 h, for each treatment group. Assessment was only up to 7·62 h because data collection for some individuals was stopped before 8 h. Error bars show SE. REM=rapid eye movement.

participants receiving tasimelteon reported shorter sleep latency (50 mg, p<0·001; 100 mg, p=0·004) compared with those receiving placebo, and those receiving tasimelteon (50 mg, p=0·009) reported longer total sleep time compared with those receiving placebo (table 2).

In the phase II study, $DLMO_{25\%}$ was earlier on treatment day 1 than on baseline for all treatment groups, indicating that the circadian melatonin rhythm had advanced. Although there was a dose–response relation (p=0·008, by Spearman rank correlation), only tasimelteon 100 mg

www.thelancet.com **Published online December 2, 2008 DOI:10.1016/S0140-6736(08)61812-7**

	Placebo	Tasimelteon (mg)				Total
		10	20	50	100	
Phase II study						
Participants who received treatment	8	9	8	7	7	39
Participants with ≥1 adverse events	8 (100%)	8 (89%)	7 (88%)	7 (100%)	7 (100%)	37 (95%)
Number of adverse events*	38	38	37	39	33	185
Adverse events						
Haematocrit decreased	3 (38%)	4 (44%)	3 (38%)	4 (57%)	4 (57%)	18 (46%)
Somnolence	4 (50%)	3 (33%)	2 (25%)	5 (71%)	2 (29%)	16 (41%)
Haemoglobin decreased	2 (25%)	3 (33%)	0 (0%)	2 (29%)	3 (43%)	10 (26%)
Headache	2 (25%)	1 (11%)	1 (13%)	1 (14%)	2 (29%)	7 (18%)
Site irritation (iv)†	3 (38%)	1 (11%)	2 (25%)	0 (0%)	0 (0%)	6 (15%)
Site pain (iv)†	1 (13%)	1 (11%)	1 (13%)	2 (29%)	1 (14%)	6 (15%)
Site bruising (iv)†	1 (13%)	1 (11%)	2 (25%)	1 (14%)	0 (0%)	5 (13%)
Phase III study						
Participants who received treatment	103	..	100	102	106	411
Participants with ≥1 adverse events	7 (7%)	..	11 (11%)	14 (14%)	8 (8%)	40 (10%)
Number of adverse events*	10	..	18	19	10	57
Adverse events						
Nausea	3 (3%)	..	3 (3%)	3 (3%)	3 (3%)	12 (3%)
Headache	3 (3%)	..	0 (0%)	1 (1%)	1 (1%)	5 (1%)

Data are number (%). iv=intravenous. *All adverse events arising in five or more individuals in either study are listed. In both studies, the frequency of adverse events in any treatment group did not exceed twice that in the placebo group (when frequency in the placebo group was 0, frequency in the treatment group never exceeded 2). †All dosing was oral; therefore, these events only relate to the intravenous catheter used for blood sampling.

Table 3: **Adverse events**

shifted $DLMO_{25\%}$ significantly earlier than did placebo (p=0·001, ANOVA with linear contrasts, figure 2).

On treatment day 1, REM sleep accumulated more rapidly in individuals given tasimelteon 20 mg, 50 mg, and 100 mg (figure 2) than in those given placebo or tasimelteon 10 mg. With placebo (p=0·001) and tasimelteon 10 mg (p=0·004), REM sleep, expressed as a percentage of all scored data (ie, all sleep stages plus wake), decreased from baseline to treatment day 1. Similarly, REM sleep, expressed as a percentage of total sleep time, decreased on treatment day 1 with placebo (p=0·014) and tasimelteon 10 mg (p=0·01). These two REM sleep measures did not differ between treatment day 1 and baseline in the groups receiving tasimelteon 20 mg, 50 mg, or 100 mg.

The frequency and severity of adverse events were similar across treatment groups (table 3). Most adverse events were mild. The most frequent adverse events were decreased haemoglobin concentration and haematocrit (phase II study), intravenous site pain, irritation, and bruising (phase II study), somnolence (phase II study), nausea (phase III study), and headache (both studies, table 3). No serious adverse events were present in the intention-to-treat populations. In the phase II study, one person on tasimelteon discontinued treatment because of an adverse event; however, the event was deemed unrelated to study drug by the investigator. In this study, mean haemoglobin and haematocrit values decreased to slightly less than normal for all groups (including placebo), consistent with the roughly 780 mL of blood sampled.

To assess the possibility that a sleep-promoting treatment might affect wake in the day after treatment, performance was assessed the next morning relative to baseline for each individual with the psychomotor vigilance test in the phase II study and the digit symbol substitution test in the phase III study. Neither study showed any difference between treatment groups and placebo (data not shown).

Discussion

Tasimelteon reduced transient insomnia that is induced by an abrupt shift in the sleep–wake cycle. We have shown that a melatonin agonist can improve established measures of sleep initiation and maintenance, enabling sleep latency and efficiency to remain mainly unaffected after an abrupt change in sleep schedule. In both studies, 50-mg tasimelteon was consistently efficacious in improving polysomnographic and self-reported sleep initiation and maintenance parameters. The tasimelteon 100-mg dose achieved maximal circadian phase shifting of the plasma melatonin rhythm.

As expected, an untreated (as in the placebo group) 5-h advance in the sleep–wake schedule substantially disrupted sleep, with increased latency to sleep onset and wake after sleep onset, and decreased sleep efficiency

and total sleep time. Disruption in sleep efficiency was most prominent in the middle third of the sleep episode, indicating impaired sleep maintenance. Tasimelteon reduced disruption to sleep, so that sleep initiation and maintenance were restored to values similar to those before the 5-h shift in sleep–wake time. Participants on tasimelteon had 30–104 min (range for all doses in both studies) more sleep than did those on placebo.

In the phase II study, effects of the study drug on sleep were most evident on treatment day 1, which was expected because sleep disruption induced by this phase-advance model of transient insomnia peaked on this day. On subsequent nights, sleep patterns in the placebo group may have recovered because of the eventual shift of the circadian pacemaker and because sleep debt taking place after treatment day 1 could increase sleep on treatment day 2, independent of circadian shift. Immediate (ie, first-night) improvement of sleep after a shift in sleep–wake schedule could have practical implications because deficits in cognitive processes are most pronounced on the first night of a series of night shifts.[43]

A useful treatment for patients with circadian rhythm sleep disorders would be one that promotes sleep by adjusting the endogenous circadian rhythm of sleep. Tasimelteon 100 mg advanced the melatonin rhythm by an average of 2–3 h within hours of administration. This finding is consistent with that in a report[44] showing that melatonin immediately shifted the circadian rhythm of light-induced expression of the immediate early gene *c-fos* in the suprachiasmatic nuclei of rats, and with that in a report[45] in human beings showing that the melatonin agonist S20098 (agomelatine) advanced timing of the melatonin rhythm on the first treatment day.

Many previous studies have indicated that, in human beings, REM sleep is strongly regulated by the circadian pacemaker.[4] Rapid recovery of REM sleep relative to total sleep time in individuals given tasimelteon further lends support to the hypothesis that this drug might improve sleep, at least partly, by shifting the circadian pacemaker. REM sleep also increases after evening phase advance administration of melatonin and the melatonin agonist S20098.[46]

Potential limitations of this study should be noted. Sample size in the phase II study was small and, although the study was powered to detect changes in sleep and plasma melatonin rhythm, it was not sufficiently powered to detect changes in performance or mood. Findings of this study were confirmed in the phase III trial, with exposure to standard environmental conditions immediately before and after the shift in sleep–wake schedule. However, efficacy of tasimelteon in patients with chronic circadian rhythm sleep disorders remains to be tested.

Traditionally, studies of either pharmacological or behavioural treatment of insomnia have focused on nocturnal sleep, not daytime effect. Daytime effects should be investigated, especially because some studies[47–49] have shown increased sleepiness and impaired neurobehavioural performance immediately after administration of melatonin or a melatonin agonist. Daytime performance and alertness should be tested to detect both carryover sedative effect as an adverse side-effect and improved daytime performance secondary to improved sleep. In both our protocols, we measured performance to examine possible carryover effect, but none was present. However, the appropriate model for studying daytime effects secondary to improved sleep would be in a protocol with chronic circadian rhythm sleep disorder, not with a transient condition as in this protocol, and would include several days of study.

The frequency of adverse events was similar between tasimelteon and placebo, suggesting that the compound was well tolerated in a short-term treatment regimen (ie, 1–3 days). These data are consistent with previous indications that melatonin[29,31] and a melatonin agonist[50] are safe during occasional, short-term use.

We suggest that a phase-shifting drug such as tasimelteon has therapeutic potential for circadian rhythm sleep disorders, especially the jet-lag and shift-work types. In 2007, about 94 million passengers boarded aircraft in the USA to travel internationally.[51] Because many of these people probably cross time zones, and based on the estimate that about two-thirds of individuals have jet-lag symptoms,[52] the worldwide frequency of jet-lag disorder is likely to be substantial. Tasimelteon may be used not only to treat jet-lag disorder, but also to alleviate sleep complaints in individuals who start work at early hours. According to the US Bureau of Labour Statistics, about 20% of the total workforce (19·7 million workers in the USA) are early risers, who start work between 0230 h and 0700 h.[36] Most of these people probably experience chronic sleep restriction because they are unable to initiate and maintain sleep when they attempt to sleep in the early or late evening hours. Tasimelteon might alleviate this problem by advancing the sleep–wake cycle, by providing a direct sleep-promoting effect, or both. The melatonin agonist ramelteon is efficacious in the treatment of chronic primary insomnia;[26,50] however, the physiology underlying chronic primary insomnia is expected to differ from that of circadian rhythm sleep disorders.

By simultaneously improving sleep latency and sleep maintenance with a shift in circadian rhythms, tasimelteon has the potential for the treatment of patients with transient insomnia associated with circadian rhythm sleep disorders, including people affected by jet lag, or those who work at night, and early-riser workers.

Contributors

SMWR, MHP, TR, CS, GB, and EBK participated in the clinical study design. SMWR, TR, and EBK participated in data collection, and SMWR, DMF, and EBK in data analysis. SMWR, MHP, DMF, CS, GB, and EBK participated in interpretation of the results, and all authors were involved in clinical report development.

www.thelancet.com **Published online December 2, 2008 DOI:10.1016/S0140-6736(08)61812-7**

Study teams

Phase II study—E B Klerman, S M W Rajaratnam, Boston, MA; G S Richardson, Detroit, MI.

Phase III study—R K Bogan, Columbia, SC; S Brooks, San Francisco, CA; M A Cohn, Naples, FL; B C Corser, Cincinnati, OH; H A Emsellem, Chevy Chase, MD; N T Feldman, St Petersburg, FL; J Flescher, Raleigh, NC; P B Haberman, Santa Monica, CA; B A Harris, Phoenix, AZ; J D Hudson, Austin, TX; S G Hull, Overland Park, KS; A O Jamieson, Dallas, TX; G V Pegram, Birmingham, AL; M L Perlis, Rochester, NY; K M Rice, New York, NY; R Rosenberg, Atlanta, GA; M H Rosenthal, San Diego, CA; H I Schwartz, Miami, FL; D J Seiden, Pembroke Pines, FL; S G Thein, San Diego, CA.

Conflict of interest statement

SMWR has received grant support from Vanda, Takeda, the ResMed Foundation, and Philips Lighting. MHP is Chief Executive Officer of Vanda. DMF has served as a consultant for Vanda and is a stockholder. TR has served as a consultant to Acadia, Actelion, Arena, Cephalon, GlaxoSmithKline, Jazz, Merck, Neurim, Neurocrine Biosciences, Neurogen Corporation, Organon, Procter & Gamble, Pfizer, Sanofi-Aventis, Schering-Plough, Sepracor, Shire, Somaxon, Takeda, TransOral, Vanda, and Wyeth; has received grant support from Cephalon, Sanofi-Aventis, Schering-Plough, Somaxon, and TransOral; and has been a lecturer for Cephalon, Sanofi-Aventis, and Takeda. CS is an employee of Vanda and a stockholder. GB is an employee of Vanda and a stockholder. EBK has received grant support from Vanda and Takeda.

Acknowledgments

We thank the study teams; Charles A Czeisler, Joseph Ronda, Steven W Lockley, Melissa St Hilaire, Conor O'Brien, and the research staff and physicians of Brigham and Women's Hospital General Clinical Research Center and Henry Ford Hospital for their contribution to the research.

References

1 American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th edn, text revision. Washington, DC: American Psychiatric Association, 2000.

2 Klein DC, Moore RY, Reppert SM. Suprachiasmatic nucleus. The mind's clock. New York: Oxford University Press, 1991.

3 Lavie P. Ultrashort sleep-waking schedule. III. 'Gates' and 'forbidden zones' for sleep. *Electroencephalogr Clin Neurophysiol* 1986; **63:** 414–25.

4 Dijk DJ, Czeisler CA. Contribution of the circadian pacemaker and the sleep homeostat to sleep propensity, sleep structure, electroencephalographic slow waves, and sleep spindle activity in humans. *J Neurosci* 1995; **15:** 3526–38.

5 Czeisler CA, Johnson MP, Duffy JF, Brown EN, Ronda JM, Kronauer RE. Exposure to bright light and darkness to treat physiologic maladaptation to night work. *N Engl J Med* 1990; **322:** 1253–59.

6 Fahey CD, Zee PC. Circadian rhythm sleep disorders and phototherapy. *Psychiatr Clin North Am* 2006; **29:** 989–1007.

7 Dijk DJ, Shanahan TL, Duffy JF, Ronda JM, Czeisler CA. Variation of electroencephalographic activity during non-rapid eye movement and rapid eye movement sleep with phase of circadian melatonin rhythm in humans. *J Physiol* 1997; **505:** 851–58.

8 Lockley SW, Skene DJ, Tabandeh H, Bird AC, Defrance R, Arendt J. Relationship between napping and melatonin in the blind. *J Biol Rhythms* 1997; **12:** 16–25.

9 Wyatt JK, Ritz-de Cecco A, Czeisler CA, Dijk DJ. Circadian temperature and melatonin rhythms, sleep, and neurobehavioral function in humans living on a 20-h day. *Am J Physiol* 1999; **277:** R1152–63.

10 Rajaratnam SM, Middleton B, Stone BM, Arendt J, Dijk DJ. Melatonin advances the circadian timing of EEG sleep and directly facilitates sleep without altering its duration in extended sleep opportunities in humans. *J Physiol* 2004; **561:** 339–51.

11 Rajaratnam SM, Dijk DJ, Middleton B, Stone BM, Arendt J. Melatonin phase-shifts human circadian rhythms with no evidence of changes in the duration of endogenous melatonin secretion or the 24-hour production of reproductive hormones. *J Clin Endocrinol Metab* 2003; **88:** 4303–09.

12 Wyatt JK, Dijk DJ, Ritz-de Cecco A, Ronda JM, Czeisler CA. Sleep-facilitating effect of exogenous melatonin in healthy young men and women is circadian-phase dependent. *Sleep* 2006; **29:** 609–18.

13 Liu C, Weaver DR, Jin X, et al. Molecular dissection of two distinct actions of melatonin on the suprachiasmatic circadian clock. *Neuron* 1997; **19:** 91–102.

14 Reppert SM. Melatonin receptors: molecular biology of a new family of G protein-coupled receptors. *J Biol Rhythms* 1997; **12:** 528–31.

15 Naylor S, Gleich GJ. Over-the-counter melatonin products and contamination. *Am Fam Physician* 1999; **59:** 284, 287–88.

16 Williamson BL, Tomlinson AJ, Mishra PK, Gleich GJ, Naylor S. Structural characterization of contaminants found in commercial preparations of melatonin: similarities to case-related compounds from L-tryptophan associated with eosinophilia-myalgia syndrome. *Chem Res Toxicol* 1998; **11:** 234–40.

17 Arendt J, Bojkowski C, Folkard S, et al. Some effects of melatonin and the control of its secretion in humans. *Ciba Found Symp* 1985; **117:** 266–83.

18 Dollins AB, Zhdanova IV, Wurtman RJ, Lynch HJ, Deng MH. Effect of inducing nocturnal serum melatonin concentrations in daytime on sleep, mood, body temperature, and performance. *Proc Natl Acad Sci USA* 1994; **91:** 1824–28.

19 Dijk DJ, Roth C, Landolt HP, et al. Melatonin effect on daytime sleep in men: suppression of EEG low frequency activity and enhancement of spindle frequency activity. *Neurosci Lett* 1995; **201:** 13–16.

20 Cajochen C, Krauchi K, von Arx MA, Mori D, Graw P, Wirz-Justice A. Daytime melatonin administration enhances sleepiness and theta/alpha activity in the waking EEG. *Neurosci Lett* 1996; **207:** 209–13.

21 Zhdanova IV, Wurtman RJ, Morabito C, Piotrovska VR, Lynch HJ. Effects of low oral doses of melatonin, given 2–4 hours before habitual bedtime, on sleep in normal young humans. *Sleep* 1996; **19:** 423–31.

22 Hughes RJ, Badia P. Sleep-promoting and hypothermic effects of daytime melatonin administration in humans. *Sleep* 1997; **20:** 124–31.

23 Lavie P. Melatonin: role in gating nocturnal rise in sleep propensity. *J Biol Rhythms* 1997; **12:** 657–65.

24 Stone BM, Turner C, Mills SL, Nicholson AN. Hypnotic activity of melatonin. *Sleep* 2000; **23:** 663–69.

25 Roth T, Stubbs C, Walsh JK. Ramelteon (TAK-375), a selective MT1/MT2-receptor agonist, reduces latency to persistent sleep in a model of transient insomnia related to a novel sleep environment. *Sleep* 2005; **28:** 303–07.

26 Erman M, Seiden D, Zammit G, Sainati S, Zhang J. An efficacy, safety, and dose-response study of ramelteon in patients with chronic primary insomnia. *Sleep Med* 2006; **7:** 17–24.

27 Sack RL, Brandes RW, Kendall AR, Lewy AJ. Entrainment of free-running circadian rhythms by melatonin in blind people. *N Engl J Med* 2000; **343:** 1070–77.

28 Lockley SW, Skene DJ, James K, Thapan K, Wright J, Arendt J. Melatonin administration can entrain the free-running circadian system of blind subjects. *J Endocrinol* 2000; **164:** R1–6.

29 Buscemi N, Vandermeer B, Hooton N, et al. Efficacy and safety of exogenous melatonin for secondary sleep disorders and sleep disorders accompanying sleep restriction: meta-analysis. *BMJ* 2006; **332:** 385–93.

30 Arendt J. Does melatonin improve sleep? Efficacy of melatonin. *BMJ* 2006; **332:** 550.

31 Herxheimer A, Petrie KJ. Melatonin for the prevention and treatment of jet lag. *Cochrane Database Syst Rev* 2002; CD001520.

32 Buscemi N, Vandermeer B, Hooton N, et al. The efficacy and safety of exogenous melatonin for primary sleep disorders. A meta-analysis. *J Gen Intern Med* 2005; **20:** 1151–58.

33 Erman MK, Erwin CW, Gengo FM, et al. Comparative efficacy of zolpidem and temazepam in transient insomnia. *Hum Psychopharmacol* 2001; **16:** 169–76.

34 Walsh JK, Schweitzer PK, Sugerman JL, Muehlbach MJ. Transient insomnia associated with a 3-hour phase advance of sleep time and treatment with zolpidem. *J Clin Psychopharmacol* 1990; **10:** 184–89.

35 Walsh JK, Deacon S, Dijk DJ, Lundahl J. The selective extrasynaptic GABA A agonist, gaboxadol, improves traditional hypnotic efficacy measures and enhances slow wave activity in a model of transient insomnia. *Sleep* 2007; **30:** 593–602.

36 Workers on flexible and shift schedules. Bureau of Labor Statistics, US Department of Labor, July 1, 2005. http://www.bls.gov/news.release/flex.toc.htm (accessed Jan 15, 2008).

37 Horne JA, Ostberg O. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. *Int J Chronobiol* 1976; **4:** 97–110.

38 Agnew HW Jr, Webb WB, Williams RL. The first night effect: an EEG study of sleep. *Psychophysiology* 1966; **2:** 263–66.

39 Roth T, Roehrs T, Vogel G. Zolpidem in the treatment of transient insomnia: a double-blind, randomized comparison with placebo. *Sleep* 1995; **18:** 246–51.

40 Duffy JF, Dijk DJ. Getting through to circadian oscillators: why use constant routines? *J Biol Rhythms* 2002; **17:** 4–13.

41 Rechtschaffen A, Kales A. A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. Washington, DC: US Government Printing Office, 1968.

42. Klerman EB, Gershengorn HB, Duffy JF, Kronauer RE. Comparisons of the variability of three markers of the human circadian pacemaker. *J Biol Rhythms* 2002; **17:** 181–93.

43 Santhi N, Horowitz TS, Duffy JF, Czeisler CA. Acute sleep deprivation and circadian misalignment associated with transition onto the first night of work impairs visual selective attention. *PLoS ONE* 2007; **2:** e1233.

44 Sumova A, Illnerova H. Melatonin instantaneously resets intrinsic circadian rhythmicity in the rat suprachiasmatic nucleus. *Neurosci Lett* 1996; **218:** 181–84.

45 Krauchi K, Cajochen C, Mori D, Graw P, Wirz-Justice A. Early evening melatonin and S-20098 advance circadian phase and nocturnal regulation of core body temperature. *Am J Physiol* 1997; **272:** R1178–88.

46 Cajochen C, Kräuchi K, Möri D, Graw P, Wirz-Justice A. Early evening melatonin and S-20098 advance circadian phase and nocturnal regulation of core body temperature *Am J Physiol* 1997; **272**: 1189–96.

47 Deacon S, Arendt J. Melatonin-induced temperature suppression and its acute phase-shifting effects correlate in a dose-dependent manner in humans. *Brain Res* 1995; **688**: 77–85.

48 Cajochen C, Kräuchi K, Wirz-Justice A. The acute soporific action of daytime melatonin administration: effects on the EEG during wakefulness and subjective alertness. *J Biol Rhythms* 1997; **12:** 636–43.

49 Graw P, Werth E, Kräuchi K, et al. Early morning melatonin administration impairs psychomotor vigilance. *Behav Brain Res* 2001; **121:** 167–72.

50 Zammit G, Erman M, Wang-Weigand S, et al. Evaluation of the efficacy and safety of ramelteon in subjects with chronic insomnia. *J Clin Sleep Med* 2007; **3:** 495–504.

51 Schedule T-100 Market and segment. US Bureau of Transportation Statistics. http://www.bts.gov/ (accessed July 22, 2008).

52 Rajaratnam SM, Arendt J. Health in a 24-h society. *Lancet* 2001; **358:** 999–1005.

www.thelancet.com **Published online December 2, 2008 DOI:10.1016/S0140-6736(08)61812-7**