

## Circadian distribution of sleep phases after major abdominal surgery

I. Gögenur<sup>1\*</sup>, G. Wildschjötz<sup>2</sup> and J. Rosenberg<sup>1</sup>

<sup>1</sup>Department of Surgical Gastroenterology D, University of Copenhagen, Gentofte Hospital, Niels Andersen Vej 65, DK-2900 Hellerup, Denmark. <sup>2</sup>Department of Psychiatry, Centre of Expertise, Oringe Hospital, Færggårdsvej 15, DK-4760 Vordingborg, Denmark

\*Corresponding author. E-mail: ig@dadlnet.dk

**Background.** It is believed that the severely disturbed night-time sleep architecture after surgery is associated with increased cardiovascular morbidity with rebound of rapid eye movement (REM). The daytime sleep pattern of patients after major general surgery has not been investigated before. We decided to study the circadian distribution of sleep phases before and after surgery.

**Methods.** Eleven patients undergoing elective major abdominal surgery were included in the study. Continuous ambulatory polysomnographic monitoring was made 24 h before surgery and 36 h after surgery, thus including two nights after operation. Sleep was scored independently by two blinded observers and the recordings were reported as awake, light sleep (LS, stages I and II), slow wave sleep (SWS, stages III and IV), and REM sleep.

**Results.** There was significantly increased REM sleep ( $P=0.046$ ), LS ( $P=0.020$ ), and reduced time awake ( $P=0.016$ ) in the postoperative daytime period compared with the preoperative daytime period. Five patients had REM sleep during the daytime after surgery. Three of these patients did not have REM sleep during the preceding postoperative night. There was significantly reduced night-time REM sleep for two nights after surgery compared with before surgery ( $P=0.001$ ).

**Conclusions.** Patients have significantly increased REM sleep, LS, and reduced time awake during the daytime period after surgery compared with before surgery. Disturbances in the circadian regulation of the sleep–wake cycle may be involved in the development of postoperative sleep disturbances.

*Br J Anaesth* 2008; **100**: 45–9

**Keywords:** sleep, circadian; surgery, abdominal

Accepted for publication: October 1, 2007

Owing to changes in the autonomic nervous system tone and ventilation, it is believed that sleep and especially certain sleep stages may be particularly stressful for patients at risk of cardiovascular disease.<sup>1,2</sup> Particularly, rapid eye movement (REM) sleep has been linked to activation of the sympathetic nervous system, occurrence of ventilatory disturbances with episodes of arterial hypoxaemia resulting in higher incidence of cardiovascular events.<sup>3–5</sup> Severe changes in sleep architecture occur after major general surgery with reduced or lack of REM sleep and slow wave sleep (SWS) the first one to three nights and a subsequent rebound of REM sleep and gradual

increase in SWS on the third and fourth night.<sup>6–8</sup> The highest incidence of postoperative myocardial ischaemia is within the first 3 days after surgery with a maximum on the third day after surgery<sup>9</sup> where there is rebound of REM sleep.

Circadian disturbances occur in the secretion of hormones,<sup>10</sup> in the regulation of core body temperature,<sup>10,11</sup> and in the activity of the autonomic nervous system after major surgery.<sup>12,13</sup> Circadian distribution of the sleep–wake cycle is also changed with increased daytime sleep for 1 week after minimal invasive surgery and 4 weeks after major surgery.<sup>14</sup> All previously published studies on postoperative

sleep pattern in the general surgical ward have only reported night time sleep stages.<sup>15</sup> Thus, it is not known how the sleep architecture evolves in the daytime period. We set out to study the circadian distribution of sleep stages by continuous ambulatory polysomnography (PSG) in the daytime and night time before and after surgery.

## Methods

Patients undergoing elective major surgery were asked for participation and all patients entered the study after written informed consent. The study was approved by the regional ethics committee before initiation. Patients with known sleep disorders, preoperative treatment with hypnotics, neuroleptics, antidepressants, or  $\beta$ -adrenergic blockers were excluded from the study.

Patients were admitted to the general surgical ward in the morning, 1 day before surgery. Polysomnographic recording was initiated in the morning 24 h before surgery and continued until next morning. No recordings were made during surgery and in the postoperative recovery unit. The recording was resumed when the patient arrived at the general surgical ward and was continued until the morning on the second postoperative day. Thus, the postoperative recording included the first postoperative night (23:00–07:00 h), the first postoperative daytime (07:00–23:00 h), and the second postoperative night (23:00–07:00 h). All patients had a private room during the entire study period. Blood samples were drawn every hour from an extended i.v. line, to minimize patient disturbance,<sup>10</sup> and continuous Holter-monitoring and core body temperature monitoring were also made with minimal disturbance for the patient, as described previously.<sup>10</sup> Patients were prohibited to drink any stimulating beverages or alcohol during the study period. The patients were not otherwise restricted in their activities during the daytime (07:00–23:00 h), but in the night (23:00–07:00 h), the patients were in their rooms placed in a supine position in darkness. Light intensity (lux) reading was made every hour (Elma 1335 luxmeter; Elmanet, Greve, Denmark) making sure that light exposure at the level of gaze did not exceed 10 lux.

All patients had a thoracic epidural catheter placed before surgery and underwent general anaesthesia depending on the preference of the attending anaesthesiologist and surgeon. The epidural catheter was maintained for postoperative analgesia (infusion of a mixture of bupivacaine and morphine) for the total study period. The patients did not receive acetaminophen or a non-steroidal anti-inflammatory drug during the study period. I.V. or i.m. morphine (2.5–10 mg) was administered for rescue analgesia. Ondansetron was used for postoperative analgesia.

### *Sleep recording*

Ambulatory PSG (Embla A10, Medcare Flaga, Reykjavik, Iceland) recording was made by four channel bipolar

electroencephalography (C4–A1, C3–A2, F<sub>P2</sub>–A1, F<sub>P1</sub>–A2), two channel electrooculography, and two channel electromyography (submental).<sup>16</sup> Silver–silver chloride adhesive patch electrodes (Neuroline 720, Ambu Inc., Glen Burnie, MD, USA) were used at F<sub>P2</sub>, F<sub>P1</sub>, A1, A2 and at the electromyography and oculography positions after proper skin preparation (light abrasion after cleaning with alcohol-swap). Silver cup electrodes (Medcare Flaga) were placed at C3 and C4 after skin preparation and fixated with electrode paste (Elefix, Nihon Kohden, Tokyo, Japan). Electrodes were replaced after each 24 h period of measurement or if they accidentally fell off. The electrode wires were collected in a ‘ponytail’ arrangement at the back of the head and connected to the battery-driven ambulatory PSG unit, enabling the patient to move freely.

Two experienced scorers blinded for day of measurement, independently scored the patients sleep in 30 s epochs. In epochs where there was disagreement between the two scorers, a consensus was made after re-evaluation. The recordings were scored as awake, stages I–IV non-REM sleep, and REM sleep according to the criteria by Rechtschaffen and Kales.<sup>16</sup> The software platform used for manual scoring was Somnologica Studio (Medcare Flaga). Sleep data are reported as minutes awake or sleep in the daytime recording period (07:00–23:00 h) and night-time recording period (23:00–07:00 h). Light sleep (LS) is defined as the sum of stages I and II non-REM sleep, and SWS is defined as the sum of stages III and IV non-REM sleep.

### *Statistical analysis*

Data are presented as median (range) unless stated otherwise. Daytime data are presented as minutes awake/sleep in the measurement period (07:00–23:00 h) and night-time data are reported as per cent sleep in the measurement period (23:00–07:00 h). Paired intragroup comparison was performed using Wilcoxon’s test and for repeated measures, we used the Friedman’s test. For correlation analysis, Spearman’s test was used. For statistical analyses, SPSS 14.0 (SPSS Chicago, IL, USA) was used.

## Results

Twelve patients were initially enrolled in the study. One patient did not complete postoperative monitoring because of psychological reasons (unexpected finding of disseminated disease in a 44-yr-old female). One patient was not monitored the second postoperative night because of acute delirium. Patient demographics and operative data are listed in Table 1. Nine patients were operated for colorectal cancer (four low anterior rectal resections, two rectosigmoid resections, two right-sided hemicolectomies, and one left-sided hemicolectomy) and two patients were operated for gastric cancer (subtotal gastric resection). None of

**Table 1** Baseline and perioperative characteristics. Values are given as frequencies or median (range). ASA, American Society of Anesthesiologists

Patient characteristics	
Sex (male/female)	9/2
Age	61 (38–82)
ASA physical status class I/II/III	5/5/1
BMI (kg m <sup>-2</sup> )	28 (21–30)
Surgery start (hh:mm)	09:50 (09:10–12:58)
Surgery end (hh:mm)	13:00 (11:52–15:00)
Surgery duration (min)	150 (115–230)

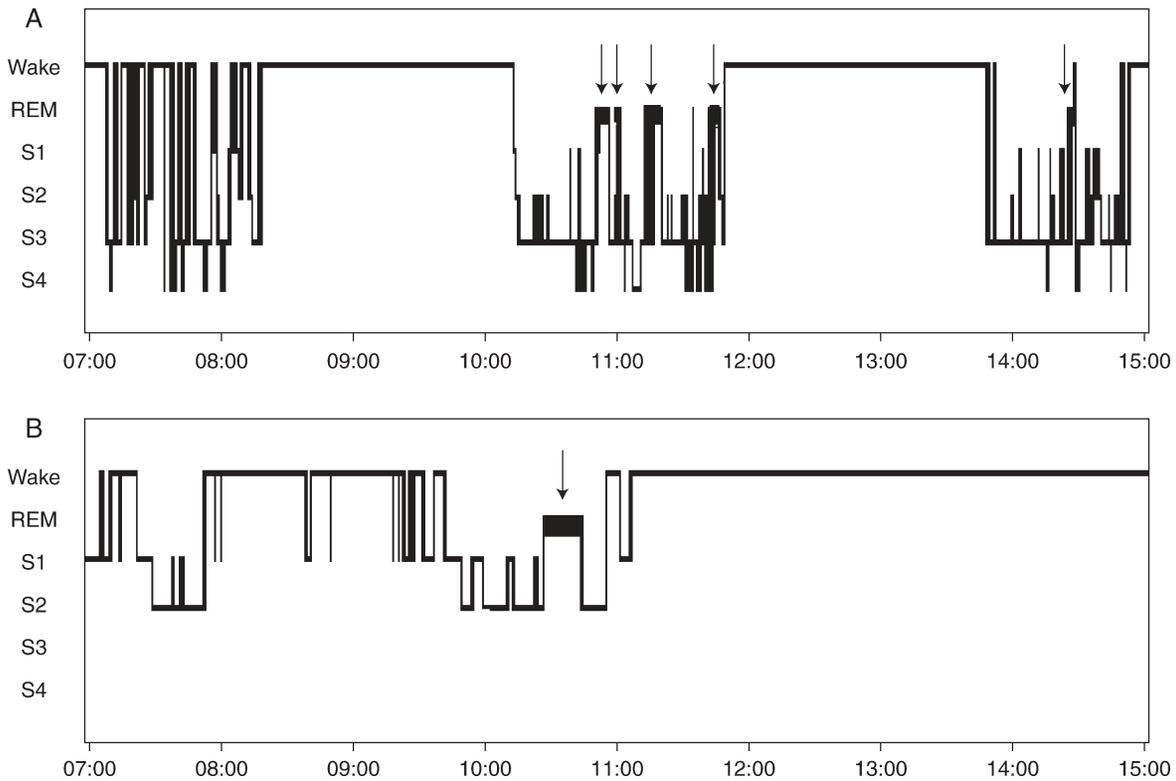
**Table 2** Sleep data (min) in the daytime measurement period (07:00–23:00 h). Data are presented as median (range). *P*-value indicated for paired intragroup comparisons (paired Student’s *t*-test or Wilcoxon’s signed rank test based on normality)

	Preoperative daytime	Postoperative daytime	<i>P</i> -value
Awake	936 (793–960)	819 (633–891)	0.017
LS	22 (0–147)	105 (6–69)	0.028
SWS	2 (0–27)	1 (0–337)	0.484
REM sleep	0 (0–2)	2 (0–17)	0.046

the patients was in regular treatment with drugs that are known to affect sleep.

In the daytime period after surgery, there was a significant increase in REM sleep and LS, and the total duration of time spent awake was reduced (Table 2). Number of minutes spent in SWS was unchanged. Only two patients

had REM sleep the first night after surgery. These two patients also had REM sleep during the following daytime period. Three patients who did not have REM sleep the first postoperative night had REM sleep in the following daytime period. Thus, five of the 11 patients had REM sleep in the daytime period after surgery. The hypnogram for two patients visualizing the period of REM sleep in the postoperative daytime period is presented in Figure 1A and B. The first patient was a 68-yr-old female who was operated for colon cancer by right-sided hemicolectomy. The patient had 39 min of REM sleep the day before surgery and no REM sleep the first night after surgery but several fragmented and shorter periods of REM sleep during the day. The second patient was a 38-yr-old male who was operated for gastric cancer by subtotal gastrectomy. The patient had 61 min of REM sleep the night before surgery and 26 min of REM sleep the first night after surgery and also a single longer period of REM sleep during the day. The per cent time spent in REM sleep was significantly lower in the night time period after operation compared with the preoperative night, but per cent time spent awake in LS and SWS was unchanged after surgery (Table 3). There was a positive correlation between minutes spent in REM sleep in the postoperative daytime and REM sleep in the first postoperative night ( $r=0.747$ ,  $P=0.013$ ), but no significant correlation to REM sleep in the preoperative night ( $r=0.588$ ,  $P=0.073$ ).



**Fig 1** (A) postoperative hypnogram (07:00–15:00 h) for a 68-yr-old female patient who was operated for colon cancer by right-sided hemicolectomy. Arrows represent REM sleep. (B) Postoperative hypnogram (07:00–15:00 h) for a 38-yr-old male patient who was operated for gastric cancer by subtotal gastrectomy. Arrow represents REM sleep.

**Table 3** Sleep data (%) in the night-time measurement period (07:00–23:00 h). Data are presented as median (range). *P*-value indicated for repeated measures intragroup comparison (Friedman test)

	Preoperative night	First postoperative night	Second postoperative night	<i>P</i> -value
Awake	37 (29–71)	36 (10–76)	30 (11–43)	0.082
LS	41 (11–53)	46 (3–82)	52 (1–84)	0.150
SWS	9 (5–48)	4 (0–84)	9 (0–74)	0.656
REM sleep	8 (1–13)	0 (0–6)	1 (0–13)	0.001

The total dose of morphine used as rescue analgesia and ondansetron for nausea on postoperative day 2 was 0 (0–45) and 0 (0–4) mg, respectively. There was no significant correlation between the dose of morphine required for rescue analgesia and the time spent awake or sleep stages during daytime. A significant correlation was found between dose of morphine and per cent time spent awake during the night ( $r=0.829$ ,  $P=0.003$ ), but no significant correlations to the duration of sleep stages during night.

## Discussion

As expected, sleep is severely disturbed after major surgery. In this study, we have supplemented previous studies by examining daytime sleep with PSG and have shown that circadian distribution of sleep is disturbed the first day after surgery with an increase in REM sleep and LS and a decrease in time spent awake during the daytime.

To our knowledge, the only other study where sleep has been continuously recorded by PSG after surgery is by Aurell and Elmquist,<sup>17</sup> who examined the sleep in nine patients admitted to the intensive care unit after surgery. The patient population was diverse with both elective and acute operations, and for various different conditions such as pelvic fracture or intestinal obstruction. The PSG recordings were made in the ICU environment where environmental factors and medications are very different from the surgical ward. The diverse population and different study setting do not permit any comparison between the studies.

We have, to our knowledge, for the first time in the literature described the sleep pattern of patients during daytime after elective major general surgery. Previous reports and the present study have shown that REM sleep is diminished or abolished the first nights after surgery.<sup>6–8 17–19</sup> Rebound of REM sleep with increased intensity and duration has been described on the following nights.<sup>6–8 15 18</sup> This rebound phenomenon has been described as particularly stressful for patients after surgery. REM sleep is associated with increased autonomic nervous system instability with intense sympathetic activity and increases in arterial pressure and heart rate.<sup>20</sup> Another marker of increased sympathetic activity is excretion of norepinephrine in urine, which is shown to be

significantly elevated in nights with postoperative REM sleep.<sup>21</sup> A high constant level of sympathetic activity and lack of increase in parasympathetic activity probably based on circadian dysfunction in the autonomic system have also been shown in patients after major general surgery.<sup>13</sup> During REM sleep, the tidal volume, minute ventilation, and hypoxic ventilatory drive are at their lowest level. The combination of the above mentioned factors adds to the assumption that REM sleep is a period of cardiovascular and respiratory instability with possibly increased cardiovascular morbidity and mortality. Thus, the rebound of REM sleep on the third and fourth nights after surgery have resulted in focus on these nights as particularly stressful for the patients and there have been several studies with emphasis on morbidity related to sleep disturbances during these nights.<sup>8 22–24</sup> However, our results show that REM sleep is not completely abolished in the first days after surgery and that patients can have REM sleep in the daytime period. In patients at increased risk of cardiovascular and respiratory events in the postoperative period,<sup>25</sup> daytime REM sleep may thus be adding to their risk. This, however, remains to be proven.

The regulation of the sleep–wake cycle is controlled by homeostatic mechanisms and circadian regulation.<sup>26</sup> The homeostatic drive is based on increased sleep propensity as the wake period increases. The circadian system is controlling arousal systems, with high activity during the day resulting in wakefulness and low activity during the late evening resulting in increased sleep propensity.<sup>26</sup> Whether the REM sleep during the daytime after surgery represents a homeostatically driven REM sleep or it represents a result of circadian dysfunction after surgery is not known. We found a positive relation between REM sleep in the first postoperative night and REM sleep in the daytime after surgery, indicating that it is probably not a homeostatic mechanism. The distribution and facilitation of REM sleep is known to be regulated by the circadian pacemaker in the hypothalamus.<sup>27 28</sup> Previous studies have shown that disturbances in the circadian regulation of melatonin release, core body temperature, and autonomic nervous system activity exist after major surgery.<sup>10 11 13</sup> REM sleep occurring in the daytime might be another aspect of circadian dysfunction in the postoperative period. This, however, needs to be investigated further, especially with respect to restoration of normal postoperative sleep pattern with chronobiotics. Melatonin, which is an endogenous circadian regulator hormone, is known to be effective in REM sleep disorders.<sup>29</sup> Whether melatonin can restore normal sleep–wake pattern after surgery remains to be proven.

In conclusion, we have shown that the circadian distribution of sleep phases is disturbed after surgery with REM sleep occurring in the daytime almost in half of the patients. LS is also increased and time spent awake is reduced. Although the results are based on a study with a relatively small number of patients, the findings suggest the hypothesis that the sleep architecture changes may be

partly explained by a circadian dysfunction in the regulation of the sleep–wake cycle. This, however, should be confirmed in future studies.

## Funding

University of Copenhagen, Denmark; The Danish Medical Research Council (Journal no. 22-04-0430).

## References

- 1 Bonsignore MR, Smirne S, Marrone O, Insalaco G, Salvaggio A, Bonsignore G. Myocardial ischemia during sleep. *Sleep Med Rev* 1999; **3**: 241–55
- 2 Lavery CE, Mittleman MA, Cohen MC, Muller JE, Verrier RL. Nonuniform nighttime distribution of acute cardiac events: a possible effect of sleep states. *Circulation* 1997; **96**: 3321–7
- 3 Nowlin JB, Troyer WG, Collins WS, et al. The association of nocturnal angina pectoris with dreaming. *Ann Intern Med* 1965; **63**: 1040–6
- 4 Murao S, Harumi K, Katayama S, Mashima S, Shimomura K. All-night polygraphic studies of nocturnal angina pectoris. *Jpn Heart J* 1972; **13**: 295–306
- 5 King MJ, Zir LM, Kaltman AJ, Fox AC. Variant angina associated with angiographically demonstrated coronary artery spasm and REM sleep. *Am J Med Sci* 1973; **265**: 419–22
- 6 Cronin AJ, Keifer JC, Davies MF, King TS, Bixler EO. Postoperative sleep disturbance: influences of opioids and pain in humans. *Sleep* 2001; **24**: 39–44
- 7 Knill RL, Moote CA, Skinner MI, Rose EA. Anesthesia with abdominal surgery leads to intense REM sleep during the first postoperative week. *Anesthesiology* 1990; **73**: 52–61
- 8 Rosenberg J, Wildschjødtz G, Pedersen MH, von Jessen F, Kehlet H. Late postoperative nocturnal episodic hypoxaemia and associated sleep pattern. *Br J Anaesth* 1994; **72**: 145–50
- 9 Mangano DT, Wong MG, London MJ, Tubau JF, Rapp JA. Perioperative myocardial ischemia in patients undergoing noncardiac surgery—II: Incidence and severity during the 1st week after surgery. The Study of Perioperative Ischemia (SPI) Research Group. *J Am Coll Cardiol* 1991; **17**: 851–7
- 10 Gögenur I, Ocak U, Altunpinar O, Middleton B, Skene DJ, Rosenberg J. Disturbances in melatonin, cortisol and core body temperature rhythms after major surgery. *World J Surg* 2007; **31**: 290–8
- 11 Gögenur I, Eversbusch A, Achiam M, Sølvig P, Rosenberg J. Disturbed core body temperature rhythm after major surgery. *Sleep Biol Rhythms* 2004; **2**: 226–8
- 12 Backlund M, Toivonen L, Tuominen M, Pere P, Lindgren L. Changes in heart rate variability in elderly patients undergoing major noncardiac surgery under spinal or general anesthesia. *Reg Anesth Pain Med* 1999; **24**: 386–92
- 13 Gögenur I, Rosenberg-Adamsen S, Lie C, Rasmussen V, Rosenberg J. Lack of circadian variation in the activity of the autonomic nervous system after major abdominal operations. *Eur J Surg* 2002; **168**: 242–6
- 14 Gögenur I, Rosenberg-Adamsen S, Kiil C, Kjaersgaard M, Kehlet H, Rosenberg J. Laparoscopic cholecystectomy causes less sleep disturbance than open abdominal surgery. *Surg Endosc* 2001; **15**: 1452–5
- 15 Gögenur I, Rosenberg J. Sleep disturbances after non-cardiac surgery. In: Lee-Chiong T, ed. *Sleep: A Comprehensive Handbook*. Hoboken, NJ: Wiley, 2006; 913–25
- 16 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
- 17 Aurell J, Elmqvist D. Sleep in the surgical intensive care unit: continuous polygraphic recording of sleep in nine patients receiving postoperative care. *Br Med J* 1985; **290**: 1029–32
- 18 Ellis BV, Dudley HA. Some aspects of sleep research in surgical stress. *J Psychosom Res* 1976; **20**: 303–8
- 19 Kavey NB, Ahshuler KZ. Sleep in herniorrhaphy patients. *Am J Surg* 1979; **138**: 683–7
- 20 Somers VK, Dyken ME, Mark AL, Abboud FM. Sympathetic-nerve activity during sleep in normal subjects [see comments]. *N Engl J Med* 1993; **328**: 303–7
- 21 Knill RL, Skinner MI, Novick T, Vandenberghe HM, Moote CA. The night of intense REM sleep after anesthesia and surgery increases urinary catecholamines. *Can J Anaesth* 1990; **37**: S12
- 22 Gögenur I, Rosenberg-Adamsen S, Lie C, Carstensen M, Rasmussen V, Rosenberg J. Relationship between nocturnal hypoxaemia, tachycardia and myocardial ischaemia after major abdominal surgery. *Br J Anaesth* 2004; **93**: 333–8
- 23 Rosenberg J, Pedersen MH, Ramsing T, Kehlet H. Circadian variation in unexpected postoperative death. *Br J Surg* 1992; **79**: 1300–2
- 24 Rosenberg J, Kehlet H. Postoperative mental confusion—association with postoperative hypoxemia. *Surgery* 1993; **114**: 76–81
- 25 Priebe HJ. Triggers of perioperative myocardial ischaemia and infarction. *Br J Anaesth* 2004; **93**: 9–20
- 26 Saper CB, Cano G, Scammell TE. Homeostatic, circadian, and emotional regulation of sleep. *J Comp Neurol* 2005; **493**: 92–8
- 27 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
- 28 Czeisler CA, Zimmerman JC, Ronda JM, Moore-Ede MC, Weitzman ED. Timing of REM sleep is coupled to the circadian rhythm of body temperature in man. *Sleep* 1980; **2**: 329–46
- 29 Kunz D, Mahlberg R, Muller C, Tilmann A, Bes F. Melatonin in patients with reduced REM sleep duration: two randomized controlled trials. *J Clin Endocrinol Metab* 2004; **89**: 128–34