Psychopharmacology (2004) 174:421–429
DOI 10.1007/s00213-003-1759-5

ORIGINAL INVESTIGATION

Stefan Cohrs · Andrea Rodenbeck · Zhenghua Guan · Kathrin Pohlmann · Wolfgang Jordan · Andreas Meier · Eckart Rüther

Sleep-promoting properties of quetiapine in healthy subjects

Received: 27 October 2003 / Accepted: 8 December 2003 / Published online: 17 March 2004

Abstract The aim of this study was to investigate the effects of quetiapine, an atypical antipsychotic, on polysomnographic sleep structure and subjective sleep quality. This double-blind, placebo-controlled, randomized cross-over study investigated the polysomnographic sleep structure and subjective sleep quality of 14 healthy male subjects given placebo, quetiapine 25 mg or quetiapine 100 mg. Volunteers were studied 3 times for 3 consecutive nights (N0, adaptation; N1, standard sleep conditions; N2, acoustic stress) 4 days apart. Treatment was administered orally 1 h before bedtime on nights 1 and 2. Quetiapine 25 mg and 100 mg significantly improved sleep induction and continuity under standard and acoustic stress conditions. Increases in total sleep time, sleep efficiency, percentage sleep stage 2 and subjective sleep quality were seen. A significant increase in periodic leg movements during sleep was observed with quetiapine 100 mg. The sleep-improving properties of quetiapine may be important in counteracting different aspects of psychopathology in schizophrenia and other disorders. These sleep-inducing and sleep-modifying properties are probably related to quetiapine's receptor-binding profile, including its antihistaminergic, antidopaminergic and antiadrenergic properties. Other mechanisms might be relevant as well and further investigation is required.

Keywords Quetiapine · Antipsychotic · Sleep · Polysomnography · EEG

S. Cohrs (✉) · A. Rodenbeck · Z. Guan · K. Pohlmann · W. Jordan · A. Meier · E. Rüther
Department of Psychiatry and Psychotherapy,
Georg-August-University of Göttingen,
von-Siebold Strasse 5, D-37075 Göttingen, Germany
e-mail: scohrs@gwdg.de
Tel.: +49-551-396761
Fax: +49-551-393887

Introduction

Disturbed sleep is highly prevalent among patients with schizophrenia. Polysomnographic sleep studies in such patients have consistently documented changes in a variety of sleep parameters, including reduced total sleep time (TST), sleep efficiency, increased sleep fragmentation, sleep latency, and, more variably, reduced slow wave sleep and rapid eye movement (REM) sleep (Caldwell and Domino 1967; Zarcone et al. 1987; Bench et al. 1992; Lauer et al. 1997; Keshavan et al. 1998). So far, few studies have investigated the influence of antipsychotics on polysomnographically recorded sleep, despite altered sleep in schizophrenia and the widespread off-label use of such drugs for the treatment of sleep disturbance (Linden and Thiels 2001). Conventional antipsychotics, such as chlorpromazine, pimozide and haloperidol, generally improve measures of sleep continuity in schizophrenia (Kaplan et al. 1974; Gillin et al. 1977; Keshavan et al. 1996; Maixner et al. 1998) but frequently demonstrate extrapyramidal side effects.

Limited information concerning sleep is available on the influence of atypical antipsychotics, which are associated with fewer extrapyramidal side effects and a more favorable outcome for cognitive deficits and negative symptomatology (Bilder et al. 2002). Clozapine has consistently been reported to improve sleep continuity and increase sleep stage 2 in particular (overview in Hinze Selch et al. 1997), while olanzapine also improves sleep continuity but appears to increase slow wave sleep specifically (Salin Pascual et al. 1999; Sharpley et al. 2000).

The influence of the atypical antipsychotic quetiapine on sleep has yet to be clarified. Its good tolerability and placebo-like level of extrapyramidal side effects have stimulated research on possible further treatment indications. Encouraging preliminary results have been presented for positive effects on depressive symptomatology, aggression, hostility, mania, anxiety, delirium, and post-traumatic stress disorder (PTSD) (Adityanjee and Schulz 2002; Nemeroff et al. 2002). All these disorders have in

common sleep disturbance. In PTSD the administration of 100 mg quetiapine was associated with a marked improvement in subjective sleep time (Hamner et al. 2003).

Due to the receptor-binding profile of quetiapine with antidopaminergic, antiadrenergic, strong antihistaminergic and 5-HT_2-blocking properties and its clinically well-known mild and transient sedative properties, quetiapine appears to be useful in the treatment of disease-associated sleep disturbance. The aim of this study was to determine the effects of two doses of quetiapine (25 mg and 100 mg) in comparison with placebo on polysomnographic and subjective sleep parameters in normal and experimentally disturbed sleep in a group of healthy male volunteers.

Materials and methods

Subjects

A total of 18 healthy male subjects (age 26.7±3.9 years, range 19–33) were included in the study after recording clinical history, physical examination, electrocardiogram and routine laboratory examinations (creatinine, urea, liver enzymes, blood cell count and electrolytes). Inclusion criteria were: age 18–65 years and absence of clinically relevant health problems. Exclusion criteria were one of the following disorders: insomnia, affective disorder, schizophrenia, delusions, epilepsy, obsessive-compulsive disorder, social phobia, alcohol or drug dependence, intolerance to quetiapine, cardiovascular disease (myocardial infarction, heart insufficiency, ECG-conduction abnormalities), concomitant psychotropic medication, serious medical problems requiring treatment, cerebrovascular disease, liver disease, and any condition predisposing to arterial hypotension: dehydration, hypovolemia, or antihypertensive medication. Volunteers with a sleep apnea-hypopnea syndrome or more than ten periodic leg movements per hour during the first recording were not included into the study.

Study design

This was a randomized, double-blind, cross-over, placebo-controlled, single-center study. Screening of volunteers preceded randomization by a maximum of 14 days. Randomization followed a Williams design (Fleiss 1999). Each subject was studied for a total of 9 nights. Sleep was polysomnographically monitored in the sleep laboratory for three sessions, each 3 consecutive nights, separated by a 4-day washout period. Each session started with an adaptation night (N0) with full montage followed by 2 nights (N1, N2) on medication (randomized application of placebo, 25 mg or 100 mg quetiapine). The medication was taken orally 1 h before the estimated bedtime during nights 1 and 2. The 8-h bedtime was kept as close as possible to lights-out-time of the first night throughout the study. During night 1 undisturbed sleep was monitored, whereas during night 2 acoustic stimuli were applied in order to evaluate sleep under external stress. This additional intervention was carried out to ensure sleep-improving properties of the drug in healthy good sleepers could be demonstrated, as has been done in a comparable manner in earlier studies (Cluydts et al. 1995). The volunteers filled out standard morning sleep questionnaires (Görtelmeyer 1981; Ott et al. 1986) for all recorded nights. Urine produced during the 8-h bedtime of night 1 and night 2 was collected to determine stress hormone secretion after administration of medication. These results will be presented elsewhere.

The study followed the declaration of Helsinki and was approved by the local ethics committee. Subjects gave written informed consent and were paid an honorarium of Euro 460.

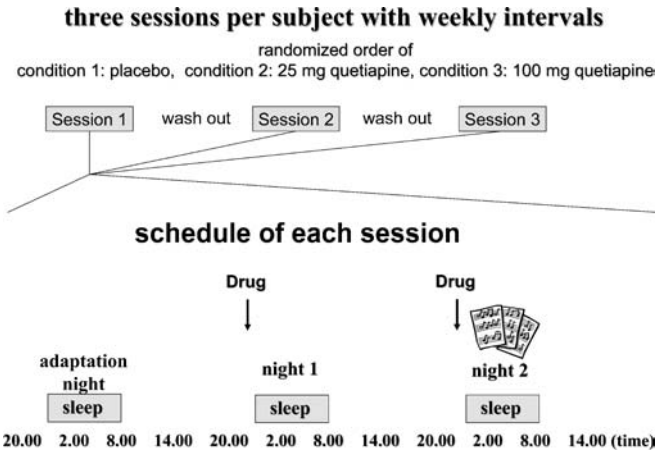

Fig. 1 Study design

Application of acoustic stress

The study participants were exposed to acoustic stress during night 2. For generation of tones the composition music software CUBASIS VST 3.0 was used. During the 8-h bedtime period groups of staccato piano tones were played through speakers into each volunteer's room. The tones lasted for 4–5 s, occurred irregularly (every 30–90 s), and ranged in pitch (880–3520 Hz) and tone intensity [55–85 dB(A)]. The same tone program was used each time the subject was exposed to acoustic stress. Tone application started at bedtime and ended on final awakening.

Polysomnography

Polysomnographic recordings for 3 consecutive nights followed standard criteria (Rechtschaffen and Kales 1968; Penzel et al. 1993). Sleep polygraphic recordings were obtained, including two electroencephalograms (EEG) (C3/A2 and C4/A1 according to the 10-20 EEG system), two electrooculograms (EOG), submental electromyogram (EMG), electrocardiogram (ECG) and EMGs of the anterior tibial muscles. During each adaptation night (N0), air flow and thoracic and abdominal excursion, as well as peripheral oxygen saturation, were recorded in order to exclude relevant periodic movement in sleep or sleep-related breathing disorders during the first adaptation night and to apply identical investigational procedures during the following study visits. Following polysomnographic screening, one subject was excluded because of sleep disordered breathing and one because of periodic limb movements in sleep. The subjects were allowed to go to bed at their usual bedtime (around midnight). Time in bed was restricted to 8 h. Sleep was recorded using Sagura Systems (Sagura Polysomnograph 2000; Sagura Medizintechnik GmbH, 63165 Mühlheim, Germany).

Sleep was scored according to the standardized criteria of Rechtschaffen and Kales (1968) in 30-s epochs by experienced sleep technologists and reviewed by two of the authors (S.C. and A.R.). Standard parameters calculated included: time in bed (TIB), sleep period time (SPT, time from sleep onset to final awakening), total sleep time (TST, SPT minus time spent awake), sleep efficiency (TST/TIB), percentage of sleep stage (stage 1, stage 2, slow wave sleep, REM sleep) of SPT, sleep latency to stage 1 and stage 2, REM latency (time from first epoch stage 2 until the first epoch of REM sleep), REM density (ratio of 3-s mini-epochs per REM epoch including at least one REM), and number of awakenings (at least one epoch of wake during SPT). In addition to these parameters, number of periodic leg movements in sleep (PLMS) was determined during all nights according to the Coleman criteria (Coleman 1982).

Subjects' self-ratings

Subjective sleep quality and daytime well-being were assessed daily, using standard visual analog scales and sleep questionnaires (SF-A, VIS-M) (Görtelmeyer 1981; Ott et al. 1986). Both questionnaires were filled out shortly after awakening in the morning. The VIS-M consists of two visual analog scales [How do you feel in the morning after getting up? (0, wonderfully fresh and energetic; 100, awfully tired and listless/apathetic); and How did you sleep last night? (0, very bad night; 100, very good night)]. Further questions include information about subjective sleep latency, number of awakenings, and subjective sleep time. The SF-A assesses general sleep quality, the degree of feeling refreshed in the morning, feelings of being well balanced in the evening, feelings of exhaustion in the evening, and psychosomatic complaints during the sleep phase.

Statistical analysis

Results were expressed as mean±SD. Multiple analyses of variance (MANOVA) with repeated measures were used to evaluate the main effects of treatment (placebo, quetiapine 25 mg or 100 mg) and intervention condition (undisturbed or acoustic stress) as well as interaction of treatment and intervention condition for each parameter. If the *F*-values were significant, post hoc *t*-tests were performed in order to compare the main treatment effect of 25 mg or 100 mg quetiapine with placebo. Additionally, post hoc *t*-tests were calculated to determine statistical differences between the undisturbed and acoustic stress condition in the placebo group and to compare the effects of quetiapine 25 mg and 100 mg with placebo for both conditions separately, where applicable. Level of significance was set at $P<0.05$. Significant outcomes of MANOVA were α-adjusted and expressed as overall significance (P) using the Cross and Chaffin method (Cross and Chaffin 1982).

Results

Of the 18 healthy male volunteers included in the trial, two slim Asian subjects (weight 65 kg, 62 kg, respectively) were withdrawn from the study because of orthostatic hypotension after the first intake of 100 mg quetiapine resulted in brief fainting with total recuperation. One subject withdrew from the study for personal reasons. For another volunteer, the results of the acoustic stress condition had to be discarded because of technical problems during application of acoustic stimuli. Therefore, the analysis is based on 14 volunteers.

Table 1 shows polysomnographic sleep variables for all conditions, as well as *F*- and *P*-values according to MANOVA. MANOVA showed significant effects for intervention (undisturbed versus acoustic stress) on SPT, TST, sleep efficiency, latencies to sleep stage 1 and 2, percentage of time awake, sleep stage 1, slow wave sleep, REM density, and number of awakenings. The overall significance (10 out of 15 tests) was $P<0.0001$.

Furthermore, significant effects for treatment condition (placebo, quetiapine 25 mg or 100 mg) were detected for SPT, TST, sleep efficiency, latency to sleep stage 1 and 2, percentage of time awake, sleep stage 2, REM sleep, and number of PLMs as reported in Table 2. The overall significance was $P<0.0001$. Compared with placebo, both 25 mg and 100 mg quetiapine significantly increased SPT, TST, sleep efficiency, and percentage sleep stage 2. Both doses decreased latencies to sleep stage 1 and 2, and percentage of time awake. A significant increase in PLMs and a reduction in percentage REM were observed only with the quetiapine 100 mg dose.

Additionally, MANOVA revealed significant interactions of treatment (placebo, quetiapine 25 mg or 100 mg) with intervention condition (undisturbed versus acoustic stress) for SPT, TST, sleep efficiency, latency to sleep stage 2, and percentage of time awake. The overall significance was $P<0.001$. For the placebo treatment, subsequent t-tests revealed significant effects of acoustic stress (N2) compared with undisturbed sleep (N1), with a significant reduction of SPT, TST, sleep efficiency, and a significant increase in latency to sleep stage 2 and percentage of time awake. Compared with undisturbed nights (N1), stronger effects of quetiapine were observed during the acoustic stress night (N2) for SPT, TST, sleep efficiency, latency to sleep stage 2 and percentage of time awake. The reduction of percentage REM in the quetiapine 100 mg group compared with placebo tended to be more pronounced on N1 than on N2.

Subjects' self-ratings

The results for the subjective sleep variables, including *F*- and *P*-values according to MANOVA, are presented in Tables 3 and 4. Significant main effects for intervention condition (undisturbed versus acoustic stress) were detected for the VIS-M items sleep quality, number of awakenings and subjective sleep time, and the SF-A items sleep quality, feeling refreshed, well balanced in the evening, and exhaustion in the evening. The overall significance was $P<0.0001$.

In addition, significant effects for treatment condition (placebo, 25 mg or 100 mg quetiapine) were detected for the VIS-M items sleep quality and subjective sleep time and the SF-A items sleep quality, exhaustion in the evening, and psychosomatic complaints. The overall significance was $P<0.0001$. In comparison with placebo, both quetiapine 25 mg and 100 mg significantly increased subjective sleep time, sleep quality (SF-A), and reduced psychosomatic complaints. Additionally, quetiapine 100 mg increased sleep quality (VIS-M) and exhaustion in the evening.

Significant interactions of treatment (placebo, quetiapine 25 mg or 100 mg) and intervention condition (undisturbed versus acoustic stress) were found for the items being refreshed, tiredness in the morning, and subjective sleep latency. The overall significance was $P<0.05$. Subsequent *t*-tests revealed significant effects of acoustic stress (N2) compared with undisturbed sleep (N1) under placebo with a significant increase in tiredness and sleep latency and a reduction in feeling refreshed.

Further evaluation of the interaction of treatment (placebo, 25 mg or 100 mg quetiapine) and intervention condition (undisturbed versus acoustic stress) revealed that subjects felt more tired after quetiapine 100 mg than after placebo treatment after N1, whereas after N2 under

Table 1 MANOVA of polysomnographic sleep parameters. *PLM* periodic leg movement, *REM* rapid eye movement, *S1* sleep stage 1, *S2* sleep stage 2, *SE* sleep efficiency, *SPT* sleep period time, *SWS* slow wave sleep, *Wake* percentage wake. Presented are means and SDs for sleep parameters

Intervention	N1 (standard sleep laboratory conditions)			N2 (acoustic stress)			Intervention effect (N1 vs N2)	Treatment effect (placebo vs 25 mg vs 100 mg quetiapine)	Interaction of treatment and intervention
							MANOVA	MANOVA	MANOVA
Treatment	Placebo	25 mg quetiapine	100 mg quetiapine	Placebo	25 mg quetiapine	100 mg quetiapine	$F(1,13)$, $p<$	$F(2,26)$, $p<$	$F(2,26)$, $p<$
SPT	461.4 (10.5)	468.0 (6.9)+	468.4 (8.6)*	446.0 (24.9)[a]	465.5 (7.6)#	464.1 (10.1)#	12.95, 0.005	11.07, 0.0005	3.87, 0.05
TST	433.4 (15.7)	449.9 (7.4)**	446.0 (26.5)	389.4 (40.8)[c]	430.0 (24.7)**	436.9 (19.8)**	27.16, 0.0005	15.89, 0.0001	7.63, 0.005
SE	90.5 (3.3)	93.8 (1.6)**	92.9 (5.5)	81.2 (8.5)[c]	89.7 (5.0)**	91.2 (3.9)**	26.53, 0.0005	15.58, 0.0001	7.92, 0.005
S1- latency	12.3 (6.6)	7.4 (4.7)	6.0 (6.2)	18.6 (16.1)	9.0 (5.7)	8.9 (5.0)	5.38, 0.05	9.63, 0.001	0.68, 0.51
S2- latency	15.0 (7.1)	11.6 (6.4)	11.6 (8.3)	30.8 (22.8)[a]	12.8 (5.9)*	14.9 (8.8)+	10.2, 0.01	10.09, 0.001	5.19, 0.05
SWS- latency	17.4 (9.6)	15.8 (6.8)	34.4 (32.8)	22.4 (13.0)	35.4 (49.5)	56.7 (117.8)	1.05, 0.32	2.70, 0.09	0.33, 0.7
REM- latency	89.7 (31.3)	86.2 (28.9)	117.8 (45.7)	90.5 (33.0)	91.4 (50.1)	96.3 (43.3)	0.35, 0.56	2.10, 0.14	0.89, 0.42
Wake (%SPT)	6.0 (2.9)	3.9 (1.6)*	4.8 (4.6)	12.8 (6.6)[b]	7.7 (4.3)*	5.9 (3.2)**	17.69, 0.001	9.54, 0.001	6.32, 0.01
S1 (%SPT)	6.2 (1.7)	5.0 (1.6)	4.9 (1.3)	8.5 (2.9)	7.5 (2.8)	7.4 (4.0)	17.03, 0.005	2.39, 0.11	0.02, 0.98
S2 (%SPT)	49.5 (7.1)	55.1 (7.1)	58.7 (9.9)	51.5 (7.0)	56.0 (7.3)	61.1 (11.1)	2.59, 0.13	19.89, 0.0001	0.39, 0.68
SWS (%SPT)	16.8 (5.4)	17.3 (6.7)	16.7 (7.0)	9.5 (5.6)	10.4 (5.4)	10.2 (6.7)	65.93, 0.0001	0.36, 0.70	0.12, 0.88
REM (%SPT)	21.5 (4.0)	18.7 (3.2)	14.9 (3.5)	17.7 (4.0)	18.5 (3.9)	15.3 (6.0)	1.85, 0.20	28.99, 0.0001	3.16, 0.06
REM density	1.8 (0.7)	1.7 (0.6)	1.8 (0.7)	1.9 (0.6)	2.1 (0.9)	2.2 (1.0)	11.64, 0.005	0.49, 0.62	0.70, 0.51
Number awake	25.1 (7.1)	24.9 (5.5)	22.0 (8.0)	34.9 (12.9)	29.1 (9.1)	27.7 (11.5)	32.41, 0.0001	2.57, 0.10	1.66, 0.21
Number PLM	34.3 (65.0)	57.4 (78.0)	154.6 (170.4)	48.1 (62.4)	67.0 (81.0)	122.2 (139.9)	0.10, 0.76	8.35, 0.005	2.10, 0.14

Significance level of differences between night 1 (*N1* undisturbed) and night 2 (*N2* acoustic stress) calculated for placebo if interaction was significant: [a]$p<0.01$, [b]$p<0.005$, [c]$p<0.001$
Significance level of differences between treatment with quetiapine (25 mg or 100 mg) and placebo for each night separately if interaction was significant: +$p<0.05$, #$p<0.01$, *$p<0.005$, **$p<0.001$

Table 2 Treatment effect of two doses of quetiapine on polysomnographic sleep parameters. PLM, periodic leg movement. *REM* rapid eye movement, *S1* sleep stage 1, *S2* sleep stage 2, *SE* sleep efficiency, *SPT* sleep period time, *SWS* slow wave sleep, *Wake* percentage wake. Presented are means and SDs for sleep parameters. 'Treatment effect' presents the average of N1 and N2 found under placebo, quetiapine 25 mg and 100 mg. Significance level of differences between quetiapine (25 mg or 100 mg) and placebo

	Treatment effect (averaged values from night 1 and night 2)			MANOVA
	Placebo	25 mg quetiapine	100 mg quetiapine	$F(2,26)$, $p<$
SPT	453.7 (20.3)	466.7 (7.2)**	466.3 (9.4)**	11.07, 0.0005
TST	411.4 (37.7)	439.9 (20.5)**	441.4 (23.4)**	15.89, 0.0001
SE	85.8 (7.9)	91.8 (4.2)**	92.0 (4.8)**	15.58, 0.0001
S1- latency	15.4 (12.5)	8.2 (5.2) #	7.4 (5.7) *	9.63, 0.001
S2- latency	22.8 (18.4)	12.2 (6.1)*	13.3 (8.5)*	10.09, 0.001
SWS- latency	19.9 (11.5)	25.6 (36.0)	45.5 (85.6)	2.70, 0.09
REM- latency	90.4 (32.1)	88.9 (40.9)	107.0 (45.1)	2.10, 0.14
Wake (%SPT)	9.4 (6.1)	5.8 (3.7)**	5.4 (3.9)*	9.54, 0.001
S1 (%SPT)	7.4 (2.6)	6.2 (2.6)	6.2 (3.2)	2.39, 0.11
S2 (%SPT)	50.5 (7.0)	55.6 (7.1)**	59.9 (10.4)**	19.89, 0.0001
SWS (%SPT)	13.1 (6.5)	13.9 (6.9)	13.5 (7.5)	0.36, 0.70
REM (%SPT)	19.6 (4.4)	18.6 (3.5)	15.1 (4.8)**	28.99, 0.0001
REM density	1.8 (0.6)	1.9 (0.8)	2.0 (0.9)	0.49, 0.62
Number awake (*n*)	30.0 (11.3)	27.0 (7.7)	24.9 (10.1)	2.57, 0.10
Number PLM	41.2 (63.2)	62.2 (78.1)	138.4 (153.8)**	8.35, 0.005

#$p<0.01$
*$p<0.005$
**$p<0.001$

acoustic stress they felt less tired after quetiapine 100 mg than after placebo. Reciprocal results were found for the item feeling refreshed in the morning (SF-A), i.e. feeling more refreshed after quetiapine 100 mg after N2.

Discussion

Significant sleep-promoting effects of quetiapine resulted from both the 25 mg and the 100 mg dosages. In this group of healthy volunteers, quetiapine accelerated the initiation of sleep, increased the duration of TST and enhanced sleep efficiency, with a parallel reduction in time spent awake. Furthermore, a highly significant dose-dependent increase in percentage sleep stage 2 was observed. The application of acoustic stimuli during N2 proved to be successful in inducing sleep disturbance similar to that observed in patients with a variety of disorders including schizophrenia. Pronounced sleep-improving effects of quetiapine were observed during N2 under external stress conditions. A significant decrease of percentage REM sleep occurred only after the administration of quetiapine 100 mg and appeared to be less pronounced during N2.

The results for objective sleep measures were paralleled by an increase in subjective sleep quality and sleep time, and a reduction in psychosomatic complaints for both nights after quetiapine administration. Differential effects of quetiapine for the items "feeling refreshed in the morning" and "tiredness" were detected for N1 and N2. After N1, the subjects felt less refreshed and more tired after administration of quetiapine 100 mg compared with placebo, whereas after N2 they felt more refreshed and less tired in the morning after quetiapine 100 mg than after placebo.

Our results confirm the effects of various typical and atypical antipsychotics observed in other studies in patients with schizophrenia as well as healthy subjects for some, but not all, of the observed sleep parameters. Subchronic treatment of patients suffering from schizophrenia with typical antipsychotics increases TST and sleep efficiency and reduces sleep latency in most of the studies but leaves percentage sleep stage 2 and REM unchanged (Taylor et al. 1991; Wetter et al. 1996; Maixner et al. 1998).

The atypical antipsychotic clozapine showed little effect on sleep measures other than an increase in TST and decrease of sleep stage 4 and a trend towards an increase in percentage sleep stage 2 in a small study (n=7) investigating a low dose of 25 mg in healthy subjects (Touyz et al. 1977). In patients with schizophrenia, treatment with clozapine was consistently associated with an increase in TST, sleep efficiency and a strong increase in percentage sleep stage 2, while percentage REM was unchanged (Wetter et al. 1996; Hinze Selch et al. 1997; Lee et al. 2001). The atypical antipsychotic olanzapine shares the increase in TST and sleep efficiency and appears to increase slow wave sleep in healthy subjects as well as patients with schizophrenia (Salin Pascual et al. 1999; Sharpley et al. 2000). Risperidone given to healthy subjects, on the other hand, shows no significant effects on these standard sleep parameters with the exception of decreased REM percentage (Sharpley et al. 2003). While quetiapine shares the increase of TST and sleep efficiency with other typical and atypical neuroleptics, the pronounced increase in sleep stage 2 seen with quetiapine in our study was only observed in association with the treatment of clozapine.

The receptor-binding properties of quetiapine are complex, and it appears unlikely that a single mechanism could explain the observed influence on sleep parameters. The drug shows strong binding to histamine H_1, α_1 adrenergic receptors, and serotonergic 5-HT_{2A} receptors, low affinity for the dopamine D_2 and D_1 receptors, and some α_2 adrenergic-blocking qualities, with little binding to muscarinic and 5-HT_{1A}, 5-HT_{1D}, and 5-HT_{2C} seroto-

Table 3 MANOVA of subjects' self-ratings. *Refreshed* feeling refreshed in the morning, *Well balanced* feeling well balanced in the evening, *Exhaustion* feeling exhausted in the evening, *Psychosom. compl.* psychosomatic complaints during the sleep phase, *Tiredness* feeling tired in the morning, *n awake* number of awakenings, *subj.* subjective. Presented are means and SDs for subjects' self-ratings

Intervention	N1 (standard sleep laboratory conditions)			N2 (acoustic stress)			Intervention effect (N1 vs N2)	Treatment effect (placebo vs 25 mg vs 100 mg quetiapine)	Interaction of treatment and intervention
							MANOVA	MANOVA	MANOVA
Treatment	Placebo	25 mg quetiapine	100 mg quetiapine	Placebo	25 mg quetiapine	100 mg quetiapine	$F(1,13)$, $p<$	$F(2,26)$, $p<$	$F(2,26)$, $p<$
SF-A									
Sleep quality	3.5 (0.6)	3.9 (0.4)	4.0 (0.4)	2.5 (0.7)	2.9 (0.8)	3.2 (0.6)	47.07, 0.00005	16.14, 0.0001	0.98, 0.39
Refreshed	3.4 (0.5)	3.2 (0.6)	2.9 (0.7)+	2.7 (0.5)[c]	2.9 (0.5)+	3.1 (0.8)+	9.62,0 .01	0.49, 0.62	5.39, 0.05
Well balanced	3.8 (0.4)	3.9 (0.4)	3.7 (0.4)	3.4 (0.4)	3.6 (0.4)	3.5 (0.5)	24.01, 0.0005	0.61, 0.55	0.97, 0.39
Exhaustion	2.6 (0.7)	2.6 (0.7)	3.0 (0.5)	2.5 (0.5)	2.3 (0.6)	2.6 (0.5)	5.99, 0.05	4.76, 0.05	1.50, 0.24
Psychosom. compl.	1.4 (0.4)	1.2 (0.3)	1.3 (0.4)	1.7 (0.4)	1.5 (0.4)	1.3 (0.3)	4.51, 0.54	4.13, 0.05	1.55, 0.23
VIS-M									
Tiredness	39.7 (16.8)	49.2 (16.9)	52.7 (16.4)*	55.9 (13.6)[b]	51.4 (13.0)	43.4 (18.2)+	1.58, 0.23	0.21, 0.81	7.73, 0.005
Sleep quality	61.4 (18.7)	62.5 (18.3)	65.4 (17.2)	30.9 (13.6)[c]	37.2 (16.7)	52.8 (12.1)*	59.38, 0.00001	4.46, 0.05	3.02, 0.07
Sleep latency	22.8 (14.8)	14.4 (8.0)+	33.0 (46.0)	42.9 (29.1)[a]	22.3 (18.2)+	18.7 (14.0)+	0.91, 0.36	1.93, 0.17	5.71, 0.01
n awake	1.9 (1.7)	1.4 (1.5)	0.9 (0.9)	3.9 (3.4)	3.4 (3.7)	2.4 (1.7)	17.23, 0.005	3.29, 0.053	0.13, 0.88
Subj. sleep time	437.9 (30.3)	468.2 (15.3)	460.4 (38.2)	385.4 (70.1)	423.6 (50.9)	442.5 (32.9)	31.36, 0.0001	6.85, 0.005	2.20, 0.13

Significance level of differences between night 1 (N1=undisturbed) and night 2 (N2=acoustic stress) calculated for placebo if interaction was significant: [a]$p<0.01$, [b]$p<0.005$, [c]$p<0.001$
Significance level of differences between treatment with quetiapine (25 mg or 100 mg) and placebo for each night separately if interaction was significant: +$p<0.05$, #$p<0.01$, *$p<0.005$, **$p<0.001$

Table 4 Treatment effect of two doses of quetaipine on subjects' self-ratings. *Refreshed* feeling refreshed in the morning, *Well balanced* feeling well balanced in the evening, *Exhaustion* feeling exhausted in the evening, *Psychosom. compl.* psychosomatic complaints during the sleep phase, *Tiredness* feeling tired in the morning, *n* awake, number of awakenings, *subj.* subjective. Presented are means and SDs for subjects' self-ratings. *Treatment effect* presents the average of N1 and N2 found under placebo, quetiapine 25 mg and 100 mg

	Treatment effect (averaged values from night 1 and night 2)			MANOVA
	Placebo	25 mg quetiapine	100 mg quetiapine	$F(2,26)$, $p<$
SF-A				
Sleep quality	3.0 (0.8)	3.4 (0.8)**	3.6 (0.6)**	16.14, 0.0001
Refreshed	3.0 (0.6)	3.1 (0.6)	3.0 (0.8)	0.49, 0.62
Well balanced	3.6 (0.5)	3.7 (0.4)	3.6 (0.4)	0.61, ns
Exhaustion	2.5 (0.6)	2.5 (0.7)	2.8 (0.5)+	4.76, 0.05
Psychosom. compl.	1.6 (0.4)	1.3 (0.4)+	1.3 (0.3)+	4.13, 0.05
VIS-M				
Tiredness	47.8 (17.1)	50.3 (14.8)	48.1 (17.6)	0.21, 0.81
Sleep quality	46.1 (22.3)	49.9 (21.5)	59.1 (16.0)*	4.46, 0.05
Sleep latency	32.8 (24.9)	18.4 (14.4)	25.9 (34.1)	1.93, 0.17
n awake	2.9 (2.8)	2.4 (3.0)	1.6 (1.5)+	3.29, 0.053
Subj. sleep time	411.6 (59.3)	445.9 (43.3)*	451.4 (36.1)*	6.85, 0.005

Significance level of differences between quetiapine (25 mg or 100 mg) and placebo: #$p<0.01$, *$p<0.005$, **$p<0.001$

nergic receptors (Saller and Salama 1993; Richelson and Souder 2000). Usually the sedative and sleep-inducing effects of antipsychotics have been attributed to their antihistaminergic, antiadrenergic and anticholinergic properties (Gerlach and Peacock 1995). As quetiapine does not have relevant anticholinergic binding, this mechanism appears to be of little significance for the explanation of quetiapine's effects on sleep. Instead, its sleep-inducing properties might be related to its antihistaminergic and antiadrenergic activity. The strongly H_1-antihistaminergic drug promethazine decreases REM in healthy subjects and patients with schizophrenia (Brannen and Jewett 1969; Risberg et al. 1975) with a rapid adaptation of percentage REM to baseline values within a few days (Risberg et al. 1975). TST only increases in patients with schizophrenia (Brannen and Jewett 1969), while an enhancement of sleep stage 2 was observed in healthy subjects (Risberg et al. 1975). Some of the observed effects of quetiapine on sleep, such as the increased TST and transient reduction in REM sleep, therefore, might be related to its antihistaminergic activity.

Other mechanisms influencing quetiapine's effect on sleep might include its antidopaminergic and antiadrenergic properties. Dopamine plays an important role in the regulation of sleep/wake state (Rye and Jankovic 2002). The dopamine uptake system is one of the most important systems involved in the pharmacological control of EEG arousal. The in vivo potency for EEG arousal of dopamine-uptake inhibitors is significantly correlated with the binding affinities to the dopamine transporter (Nishino et al. 1998). Additionally, dopamine D_1 receptor antagonists have been shown to have sleep-inducing properties in rats (Fratta et al. 1987; Ongini et al. 1993; Gessa et al. 1995), whereas dopamine D_1 receptor agonists increase waking time (Trampus et al. 1993). Despite low affinity to the dopamine D_1 receptor, quetiapine is able to normalize the effects of a dopamine D_1 receptor agonist (SKF 38392) in a rodent parkinsonian model (Oh et al. 2002). Therefore, it is possible that the dopamine D_1 blocking qualities of quetiapine might be involved in its sleep-inducing properties.

Furthermore, the α_1 adrenergic receptor appears to have an important influence on wakefulness and sleep. α_1 receptor agonists induce wakefulness in a dose-related way (Pellejero et al. 1984). Prazosin, an α_1 adrenergic receptor antagonist, on the other hand, dose-dependently potentiates the sedating effects of additional drugs (Hilakivi and Leppavuori 1984). Hence, α_1-adrenergic antagonism may play a role in mediating quetiapine's sleep-inducing properties. However, α_1-adrenergic antagonists rather increase than decrease REM sleep (Hilakivi and Leppavuori 1984), as observed in our study.

Alternatively, further mechanisms might be involved in the sleep-inducing properties of quetiapine. In healthy subjects, GABA-A receptor agonists typically increase TST, shorten sleep latency, reduce the number of awakenings and prominently promote sleep stage 2, while sleep stage 1, slow wave sleep, and REM sleep might be decreased (Lancel 1999). Important aspects of this pattern, including a prominent increase in percentage sleep stage 2, have been found in our study after the administration of quetiapine. However, quetiapine itself has no relevant activity at the benzodiazepine binding site (Saller and Salama 1993). Therefore, indirect mechanisms would have to be involved. Recently, two other sleep-inducing atypical antipsychotics, olanzapine and clozapine, have been demonstrated to markedly increase the brain concentration of the neurosteroid and $GABA_A$ receptor agonist allopregnanolone, whereas risperidone and haloperidol do not have these properties (Marx et al. 2003). Data for the effect of quetiapine on allopregnanolone are not available yet. However, if quetiapine increased allopregnanolone some of the observed changes in sleep parameters could be related to such an influence on neurosteroids. Therefore, the sleep-improving properties of quetiapine, in addition to direct receptor binding, may be caused by other mechanisms such as a change in allopregnanolone brain concentration or, possibly, additional mechanisms like an influence on the expression of mRNA for subunits of receptors involved in the regulation of sleep and wakefulness (Tascedda et al. 1999).

Two subjects were withdrawn from our study due to symptomatic orthostatic hypotension after the first intake

of the 100 mg dose of quetiapine. They were both of Asian descent and of slim stature. To our knowledge no ethnic differences in the tolerability of quetiapine have been demonstrated and this symptomatology probably reflects α_1-antiadrenergic properties of quetiapine (Richelson and Souder 2000). The two cases of symptomatic hypotension in our study were associated with the 100 mg dose only. This dose relationship has been observed before and titration of the medication should be considered in patients and especially in studies including healthy subjects, who are possibly more sensitive to this side effect.

A further side-effect of quetiapine in this study was the occurrence of PLMs after the administration of the 100 mg dose. PLMs are unspecific but pathophysiologically related to the restless legs syndrome (RLS). Several pharmacologic agents, including neuroleptics and antidepressants such as tricyclics and selective serotonin-reuptake inhibitors, as well as lithium, antihistamines and metoclopramide, have been reported to induce or exacerbate restless legs syndrome (Trenkwalder et al. 2001). Of the newer atypical antipsychotics, olanzapine and risperidone have also been reported to induce RLS (Kraus et al. 1999; Wetter et al. 2002). After switching treatment from risperidone to quetiapine, RLS symptoms vanished and polysomnography demonstrated improved sleep and normal PLMS measurements (Wetter et al. 2002). Therefore, it might be that there are individual differences in the susceptibility of developing such side effects with specific drugs. RLS and PLMS have been related to different neurotransmitter systems, in particular D_2 receptors, as well as opioid receptors. The increase in PLMS in our study might be related to the antidopaminergic properties of quetiapine, but other mechanisms such as the antihistaminergic activity of the drug cannot be excluded. It remains to be clarified whether PLMS are also observed in patients with schizophrenia and whether this increase is seen only on initiation of treatment.

One limitation of this study is that the evaluation of the effects of quetiapine on sleep under acoustic stress always took place during N2. Adaptation to the sleep laboratory, known as first-night effect, is accompanied by an improvement of sleep quality (Agnew et al. 1966). In this study, it could be shown that acoustic stress during N2 was associated with marked disturbance of various sleep parameters under placebo. Therefore, the effects of quetiapine observed under acoustic stress can confidently be attributed to the drug. However, volunteers always received the drug under acoustic stress for the second time and adaptation to quetiapine might have had an influence on some parameters. Therefore, the pronounced effects of quetiapine on sleep measures during N2 under acoustic stress might express a combination of sleep-inducing carry-over effects from the first night as well as relatively increased effectiveness of the drug under external stress. The aspect most likely to be related to adaptation is the improvement in feeling refreshed in the morning after the second intake of quetiapine 100 mg. A parallel design for all combinations of conditions and treatment interventions would have been preferable to exclude possible carry-over effects; however, additional adaptation nights to the sleep laboratory would have been necessary, and due to limited resources such a design was not adopted. The main result of this study, i.e. strong sleep-inducing properties of quetiapine, remains unaffected by the chosen design.

In conclusion, low doses of quetiapine demonstrate sleep-inducing properties in healthy subjects that are paralleled by an increase in subjective sleep quality. The sleep-inducing properties were observed under standard sleep laboratory conditions and were more pronounced after a second intake of quetiapine under external stress conditions. Several mechanisms of action, including the antihistaminergic, antidopaminergic and antiadrenergic activity of quetiapine, might be involved in its sleep-inducing properties. Additionally, other mechanisms such as an increase in the neurosteroid allopregnanolone might be involved in the sleep-inducing action of quetiapine and, in particular, could explain the marked increase in sleep stage 2. The sleep-inducing properties of quetiapine and its underlying mechanisms might be an important aspect in its ability to counteract different aspects of psychopathology in schizophrenia and other disorders

Acknowledgement We thank AstraZeneca, Germany, for funding of the study and supply of quetiapine and placebo.

References

Adityanjee, Schulz SC (2002) Clinical use of quetiapine in disease states other than schizophrenia. J Clin Psychiatry 63:32–38

Agnew HW, Webb WB, Williams RL (1966) The first night effect: an EEG study of sleep. Psychophysiology 2:263–266

Bench CJ, Friston KJ, Brown RG, Scott LC, Frackowiak RS, Dolan RJ (1992) The anatomy of melancholia—focal abnormalities of cerebral blood flow in major depression. Psychol Med 22:607–615

Bilder RM, Goldman RS, Volavka J, Czobor P, Hoptman M, Sheitman B, Lindenmayer JP, Citrome L, McEvoy J, Kunz M, Chakos M, Cooper TB, Horowitz TL, Lieberman JA (2002) Neurocognitive effects of clozapine, olanzapine, risperidone, and haloperidol in patients with chronic schizophrenia or schizoaffective disorder. Am J Psychiatry 159:1018–1028

Brannen JO, Jewett RE (1969) Effects of selected phenothiazines on REM sleep in schizophrenics. Arch Gen Psychiatry 21:284–290

Caldwell DF, Domino EF (1967) Electroencephalographic and eye movement patterns during sleep in chronic schizophrenic patients. Electroencephalogr Clin Neurophysiol 22:414–420

Cluydts R, De Roeck J, Cosyns P, Lacante P (1995) Antagonizing the effects of experimentally induced sleep disturbance in healthy volunteers by lormetazepam and zolpidem. J Clin Psychopharmacol 15:132–137

Coleman RM (1982) Periodic movements in sleep (nocturnal myoclonus) and restless legs syndrome. In: Guilleminault C (ed) Sleeping and waking disorders: indications and techniques. Addison-Wesley, Menlo Park, Calif., pp 265–295

Cross EM, Chaffin WW (1982) Use of the binomial theorem in interpreting results of multiple tests of significance. Educ Psychol Manage 42:25–34

Fleiss JL (1999) The design and analysis of clinical experiments. Wiley, New York

Fratta W, Collu M, Martellotta MC, Pichiri M, Muntoni F, Gessa GL (1987) Stress-induced insomnia: opioid-dopamine interactions. Eur J Pharmacol 142:437–440

Gerlach J, Peacock L (1995) New antipsychotics: the present status. Int Clin Psychopharmacol 10:39–48
Gessa GL, Pani L, Fadda P, Fratta W (1995) Sleep deprivation in the rat: an animal model of mania. Eur Neuropsychopharmacol 5:89–93
Gillin JC, van Kammen DP, Post R, Bunney WE (1977) Effects of prolonged administration of pimozide on sleep-EEG patterns in psychiatric patients. Commun Psychopharmacol 1:225–232
Görtelmeyer R (1981) Schlaffragebogen SF-A and SF-B. In: (CIPS) CIPS (ed) Internationale Skalen für Psychiatrie. Beltz, Weinheim
Hamner MB, Deitsch SE, Brodrick PS, Ulmer HG, Lorberbaum JP (2003) Quetiapine treatment in patients with posttraumatic stress disorder: an open trial of adjunctive therapy. J Clin Psychopharmacol 23:15–20
Hilakivi I, Leppavuori A (1984) Effects of methoxamine, and alpha-1 adrenoceptor agonist, and prazosin, an alpha-1 antagonist, on the stages of the sleep-waking cycle in the cat. Acta Physiol Scand 120:363–372
Hinze Selch D, Mullington J, Orth A, Lauer CJ, Pollmacher T (1997) Effects of clozapine on sleep: a longitudinal study. Biol Psychiatry 42:260–266
Kaplan J, Dawson S, Vaughan T, Green R, Wyatt RJ (1974) Effect of prolonged chlorpromazine administration on the sleep of chronic schizophrenics. Arch Gen Psychiatry 31:62–66
Keshavan MS, Reynolds CF, Miewald JM, Montrose DM (1996) A longitudinal study of EEG sleep in schizophrenia. Psychiatry Res 59:203–211
Keshavan MS, Reynolds CF, Miewald MJ, Montrose DM, Sweeney JA, Vasko RC, Kupfer DJ (1998) Delta sleep deficits in schizophrenia: evidence from automated analyses of sleep data. Arch Gen Psychiatry 55:443–448
Kraus T, Schuld A, Pollmacher T (1999) Periodic leg movements in sleep and restless legs syndrome probably caused by olanzapine. J Clin Psychopharmacol 19:478–479
Lancel M (1999) Role of GABAA receptors in the regulation of sleep: initial sleep responses to peripherally administered modulators and agonists. Sleep 22:33–42
Lauer CJ, Schreiber W, Pollmacher T, Holsboer F, Krieg JC (1997) Sleep in schizophrenia: a polysomnographic study on drug-naive patients. Neuropsychopharmacology 16:51–60
Lee JH, Woo JI, Meltzer HY (2001) Effects of clozapine on sleep measures and sleep-associated changes in growth hormone and cortisol in patients with schizophrenia. Psychiatry Res 103:157–166
Linden M, Thiels C (2001) Epidemiology of prescriptions for neuroleptic drugs: tranquilizers rather than antipsychotics. Pharmacopsychiatry 34:150–154
Maixner S, Tandon R, Eiser A, Taylor S, DeQuardo JR, Shipley J (1998) Effects of antipsychotic treatment on polysomnographic measures in schizophrenia: a replication and extension. Am J Psychiatry 155:1600–1602
Marx CE, VanDoren MJ, Duncan GE, Lieberman JA, Leslie Morrow A (2003) Olanzapine and clozapine increase the GABAergic neuroactive steroid allopregnanolone in rodents. Neuropsychopharmacology 28:1–13
Nemeroff CB, Kinkead B, Goldstein J (2002) Quetiapine: preclinical studies, pharmacokinetics, drug interactions, and dosing. J Clin Psychiatry 63:5–11
Nishino S, Mao J, Sampathkumaran R, Shelton J, Mignot E (1998) Increased dopaminergic transmission mediates the wake-promoting effects of CNS stimulants. Sleep Res Online 1:49–61
Oh JD, Bibbiani F, Chase TN (2002) Quetiapine attenuates levodopa-induced motor complications in rodent and primate parkinsonian models. Exp Neurol 177:557–564
Ongini E, Bonizzoni E, Ferri N, Milani S, Trampus M (1993) Differential effects of dopamine D-1 and D-2 receptor antagonist antipsychotics on sleep-wake patterns in the rat. J Pharmacol Exp Ther 266:726–731
Ott H, Oswald I, Fichte K, Sastre-Y-Hernandez M (1986) Visuelle Analogskalen zur Erfassung von Schlalfqualität. In: (CIPS) CIPS (ed) Internationale Skalen für Psychiatrie. Beltz, Weinheim
Pellejero T, Monti JM, Baglietto J, Jantos H, Pazos S, Cichevski V, Hawkins M (1984) Effects of methoxamine and alpha-adrenoceptor antagonists, prazosin and yohimbine, on the sleep-wake cycle of the rat. Sleep 7:365–372
Penzel T, Hajak G, Hoffmann RM, Lund R, Podszus T, Pollmaecher T, Schaefer T, Schulz H, Sonnenschein W, Spieweg I (1993) Empfehlungen zur Durchführung und Auswertung polygraphischer Ableitungen im diagnostischen Schlaflabor. Z EEG-EMG 24:65–70
Rechtschaffen A, Kales A (1968) A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. United States Government Printing Office
Richelson E, Souder T (2000) Binding of antipsychotic drugs to human brain receptors focus on newer generation compounds. Life Sci 68:29–39
Risberg AM, Risberg J, Ingvar DH (1975) Effects of promethazine on nocturnal sleep in normal man. Psychopharmacologia 43:279–284
Rye DB, Jankovic J (2002) Emerging views of dopamine in modulating sleep/wake state from an unlikely source: PD. Neurology 58:341–346
Salin Pascual RJ, Herrera Estrella M, Galicia Polo L, Laurrabaquio MR (1999) Olanzapine acute administration in schizophrenic patients increases delta sleep and sleep efficiency. Biol Psychiatry 46:141–143
Saller CF, Salama AI (1993) Seroquel: biochemical profile of a potential atypical antipsychotic. Psychopharmacology 112:285–292
Sharpley AL, Vassallo CM, Cowen PJ (2000) Olanzapine increases slow-wave sleep: evidence for blockade of central 5-HT(2C) receptors in vivo. Biol Psychiatry 47:468–470
Sharpley AL, Bhagwagar Z, Hafizi S, Whale WR, Gijsman HJ, Cowen PJ (2003) Risperidone augmentation decreases rapid eye movement sleep and decreases wake in treatment-resistant depressed patients. J Clin Psychiatry 64:192–196
Tascedda F, Lovati E, Blom JM, Muzzioli P, Brunello N, Racagni G, Riva MA (1999) Regulation of ionotropic glutamate receptors in the rat brain in response to the atypical antipsychotic seroquel (quetiapine fumarate). Neuropsychopharmacology 21:211–217
Taylor SF, Tandon R, Shipley JE, Eiser AS (1991) Effect of neuroleptic treatment on polysomnographic measures in schizophrenia. Biol Psychiatry 30:904–912
Touyz SW, Beumont PJ, Saayman GS, Zabow T (1977) A psychophysiological investigation of the short-term effects of clozapine upon sleep parameters of normal young adults. Biol Psychiatry 12:801–822
Trampus M, Ferri N, Adami M, Ongini E (1993) The dopamine D_1 receptor agonists, A68930 and SKF 38393, induce arousal and suppress REM sleep in the rat. Eur J Pharmacol 235:83–87
Trenkwalder C, Wetter TC, Stiasny K, Clarenbach P (2001) Restless-legs-Syndrom und "periodic limb movements in sleep". Nervenarzt 72:425–436
Wetter TC, Lauer CJ, Gillich G, Pollmacher T (1996) The electroencephalographic sleep pattern in schizophrenic patients treated with clozapine or classical antipsychotic drugs. J Psychiatr Res 30:411–419
Wetter TC, Brunner J, Bronisch T (2002) Restless legs syndrome probably induced by risperidone treatment. Pharmacopsychiatry 35:109–111
Zarcone VP, Benson KL, Berger PA (1987) Abnormal rapid eye movement latencies in schizophrenia. Arch Gen Psychiatry 44:45–48