Improved Sleep Continuity and Increased Slow Wave Sleep and REM Latency During Ziprasidone Treatment: A Randomized, Controlled, Crossover Trial of 12 Healthy Male Subjects

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Objective: Ziprasidone, an atypical antipsychotic, is a potent dopamine (D_2) and serotonin ($5\text{-}HT_{2A/C}$) receptor blocker, has agonistic properties at the $5\text{-}HT_{1A}$ receptor, and blocks serotonin and norepinephrine reuptake. These transmitter systems are closely related to the regulation of sleep.

Method: The aim of this double-blind, placebo-controlled, randomized, crossover study was to investigate the effects of ziprasidone on polysomnographic sleep structure and subjective sleep quality. Twelve healthy male subjects were randomly assigned to receive ziprasidone 40 mg or placebo for 2 sessions each composed of 2 consecutive nights (night 1, standard sleep conditions; night 2, acoustic stress) 5 days apart. Treatment was administered orally 2 hours before bedtime. The study was conducted from April 2004 to July 2004.

Results: Ziprasidone significantly increased total sleep time, sleep efficiency, percentage of sleep stage 2, and slow wave sleep; decreased the number of awakenings; and significantly affected tonic and phasic REM sleep parameters, i.e., it decreased percentage of REM and REM density and profoundly increased REM latency.

Conclusion: Ziprasidone's effects on the sleep profile are somehow opposite to what is known about sleep of depressed patients (e.g., disturbances of sleep continuity, a reduciton of slow wave sleep, and a disinhibition of REM sleep). Its REM sleep–suppressing properties resemble those of most, although not all, antidepressants and may be clinically relevant. The drug also demonstrates sleep-consolidating properties under both standard routine and acoustic stress conditions. These effects are most likely related to ziprasidone's $5\text{-}HT_{2C}$ antagonism, $5\text{-}HT_{1A}$ agonism, and serotonin and norepinephrine reuptake inhibition.

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Atypical antipsychotics have recently been shown to have beneficial effects in the treatment of affective disorders. In addition to their efficacy in the treatment of schizophrenia, quetiapine, olanzapine, risperidone, and ziprasidone demonstrated either as an add-on treatment to antidepressive medication or as antidepressant monotherapy potential[1–4] that might be related to their influence on sleep.

Both depression and schizophrenia are associated with sleep disturbance. Among the most frequently occurring and cumbersome symptoms of depression, sleep disturbance is found in up to 90% of the patients. Disturbed sleep, and especially rapid eye movement (REM) sleep, is considered by some authors to be a cornerstone of the pathophysiology of this disorder. Although not specific, sleep in depression is characterized by difficulties falling asleep, early morning awakenings, reduced sleep efficiency and slow wave sleep (SWS), and altered REM sleep (for review see Benca et al.[5] and Riemann et al.[6]). The alterations observed in REM sleep, i.e., increased percentage REM and REM density and shortened latency to the first REM phase, are considered to be more specific for depression. In patients suffering from schizophrenia, polysomnographic sleep studies documented a variety of parameters reflecting sleep disturbance in this patient group, including sleep fragmentation, reduced total sleep time (TST), and, more variably, reduced SWS, decreased

sleep efficiency, increased sleep latency, and shortened REM sleep–latency.[5,7–11] Although not distinguishing very precisely between negative symptomatology and depression, some studies show a relation between disturbed SWS and negative symptomatology in patients suffering from schizophrenia[12] with persisting negative symptomatology correlating with SWS deficit at follow-up.[13] The degree of SWS deficit appears to have a predictive value for the further development of the disease. Patients with more SWS show a more favorable outcome.[14] Additionally, shortened REM latency has been found to correlate with negative symptom severity while it was shown to be unrelated to the severity of depression.[15]

Despite these findings, only few studies have investigated the influence of atypical antipsychotics on sleep, and conflicting results have been presented. Clozapine appears to increase TST, sleep efficiency, percentage of stage 2 sleep, and REM density, while REM latency and percentage REM are unaffected.[16–19] The newer antipsychotic olanzapine shares the increase in TST and sleep efficiency and especially increases SWS in healthy subjects as well as in schizophrenic patients,[20,21] whereas REM sleep parameters were only inconsistently influenced, and only the higher dose demonstrated REM-suppressing effects. [20,21] The application of quetiapine, on the other hand, is associated with increases in TST, sleep efficiency, and percentage of sleep stage 2 and a reduction of percentage REM sleep, while SWS and REM latency remain unchanged.[22] Furthermore, risperidone shows no significant effects on these standard sleep parameters, including REM latency, with the exception of decreased REM percentage.[23] In contrast to the divergent effects of atypical antipsychotics on sleep, most antidepressants, but not all, exhibit a strong influence on REM sleep parameters, with an increase in REM latency and a decrease of percentage REM, which has been attributed to their impact on aminergic and cholinergic neurotransmission and has been hypothesized to be an important part of their mechanism of action.[24–27]

In addition to ziprasidone's usefulness in the treatment of schizophrenia with comparable improvement of cognitive symptoms in a head-to-head study with olanzapine; its superior effectiveness on cognitive symptoms after switching from risperidone, olanzapine, or conventional antipsychotics[28,29]; and its antidepressive potential as an add-on treatment, ziprasidone demonstrates sedating properties in agitated patients[30] and healthy subjects.[31] These effects are likely related to ziprasidone's influences on different neurotransmitter systems involved in the regulation of alertness and sleep, including serotonin and norepinephrine. Ziprasidone is a serotonin-2A (5-HT_{2A})/dopamine (D_2) antagonist and exhibits potent interaction with 5-HT_{2C}, 5-HT_{1D}, and 5-HT_{1A} receptors in human brain tissue.[32,33] Ziprasidone demonstrates antagonistic effects at the 5-HT_{2C} receptor and agonistic activity at the 5-HT_{1A} receptor.[32] Furthermore, inhibition of serotonin and norepinephrine reuptake has been described.[32,34–36] In addition to the possible importance of ziprasidone's effects on sleep parameters relevant to the treatment of depression, its influence on sleep may similarly be important for the treatment of schizophrenia.

To the best of our knowledge, no information on the effects of ziprasidone on polysomnographic-registered sleep exists. On the background of the complex interaction of ziprasidone with the aminergic system, SWS-inducing and REM sleep–suppressing influences were hypothesized. Therefore, the aim of this study was to determine the effects of ziprasidone in comparison with placebo on polysomnographic and subjective sleep parameters in normal sleep and experimentally induced insomnia in a group of healthy male volunteers.

MATERIALS AND METHOD

Subjects

A total of 16 healthy male subjects (mean ± SD age = 26 ± 4.4 years; range, 20–35 years) were included in the study after clinical history, physical examination, electrocardiogram (ECG), and routine laboratory examinations (creatinine, urea, liver enzymes, blood cell count, and electrolytes) were recorded. Inclusion criteria were as follows: age 18 to 65 years and absence of clinically relevant health problems. Exclusion criteria were one of the following: sleep disorders, affective disorder, schizophrenia, delusions, epilepsy, obsessive-compulsive disorder, social phobia, alcohol or drug dependence, sensitivity to ziprasidone, cardiovascular disease (myocardial infarction, heart insufficiency, ECG-conduction abnormalities), concomitant psychotropic medication including melatonin, serious medical problems requiring treatment, cerebrovascular disease, liver disease, and any condition predisposing to arterial hypotension, e.g., dehydration, hypovolemia, or antihypertensive medication. Volunteers with a sleep apnea-hypopnea syndrome (apnea-hypopnea index of more than 10) or more than 10 periodic leg movements per hour during polysomnographic screening were also excluded. None of the subjects had undertaken long distance travel within the last 4 weeks before the study. Complete data sets were available for 12 subjects. Due to technical problems during 1 night for 2 subjects, withdrawal of consent for the acoustic stress condition (night 2) of another subject, and side effects under the treatment with ziprasidone in a further subject, the analysis was restricted to 12 subjects.

Study Design

This was a randomized, double-blind, crossover, placebo-controlled, single-center study, conducted from April 2004 to July 2004. Screening of volunteers usually preceded randomization by a maximum of 14 days. Each

subject was studied for a total of 5 nights. One polysomnographic screening night preceded the investigational nights by at least 3 days in order to exclude subjects with periodic leg movements or a sleep apnea syndrome. After inclusion, subjects were examined for 2 sessions, each 2 consecutive nights, separated by a 5-day washout period. 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 that sleep-improving properties of the drug in healthy good sleepers could be detected, as has been done in a similar manner in earlier studies.[22,37] Ziprasidone 40 mg was chosen as an intermediate test dose because of the known sedating effects in healthy subjects after the oral application of 5 to 20 mg[31] and the calming effects of 10 to 20 mg in agitated patients after intramuscular injection[30] on the one hand and higher doses of 80 to 160 mg for the treatment of psychosis[38] on the other hand. The same medication (ziprasidone 40 mg or placebo) was taken during night 1 and night 2 of each session in a randomized order between sessions 1 and 2. Medication was administered orally 2 hours before bedtime in order to reach sufficient blood concentrations to possibly influence sleep onset, since maximal ziprasidone levels are reached 4 to 5 hours after oral administration.[31] Additionally, the volunteers filled out standard morning sleep questionnaires[39,40] for all recorded nights.

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 300 Euro.

Application of Acoustic Stress

Application of acoustic stress during night 2 was undertaken the same way as described previously.[22] In brief, the study participants were exposed to acoustic stress during night 2 of each session. For generation of tones, the composition music software CUBASIS VST 3.0 (Steinberg, Hamburg, Germany) was used. During the 8-hour bedtime period, groups of staccato piano tones were played through speakers into each volunteer's room. The tones lasted for 4 to 5 seconds, occurred irregularly (every 30–90 seconds), 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 2 consecutive nights followed standard criteria[41,42] and included 2 electroencephalograms (EEGs), 2 electro-oculograms (EOGs), submental electromyogram (EMG), ECG, and EMGs of the anterior tibial muscles. During the screening night, air flow and thoracic and abdominal excursion, as well as peripheral oxygen saturation, were recorded in order to exclude relevant sleep-related breathing disorders or periodic movement in sleep. The subjects usually went to bed at 23:00. Time in bed was restricted to 8 hours. Sleep was recorded using the software Leonardo (MKE GmbH, Willroth, Germany).

Sleep was scored according to the standardized criteria of Rechtschaffen and Kales[42] in 30-second epochs by experienced sleep technologists and was reviewed by S.C. Standard calculated parameters included time in bed (TIB), sleep period time (SPT, time from sleep onset to final awakening), TST (SPT minus time spent awake), sleep efficiency (TST/TIB), percentage of sleep stage (stage 1, stage 2, SWS, REM sleep) of SPT, sleep latency to stage 1 and stage 2, REM latency (time from the first epoch of stage 2 until the first epoch of REM sleep), REM density (ratio of 3-second mini-epochs including at least 1 REM per REM epoch), and number of awakenings (at least 1 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.[43]

Subjects' Self-Ratings

Subjective sleep quality and daytime well-being were assessed daily, using standard visual analog scales and sleep questionnaires (Schlaffragebogen A [sleep questionnaire A; SF-A[39]], Visuelle Analogskala morgens [visual analog scale, morning; VIS-M[40]]). Both questionnaires were filled out shortly after awakening in the morning. The VIS-M consists of 2 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 included 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

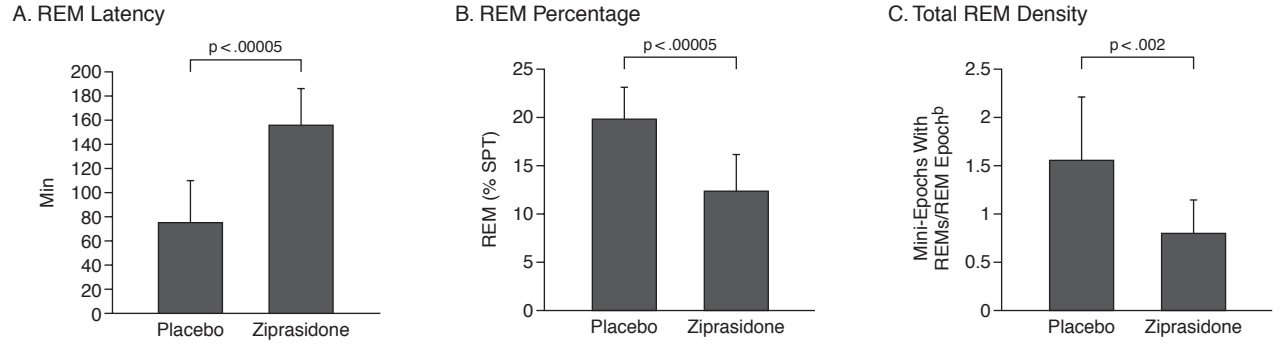
Results were expressed as mean ± SD. Analyses of variance (ANOVA) with repeated measures were used to evaluate the main effects of treatment (placebo, ziprasidone 40 mg) and intervention condition (undisturbed or acoustic stress) as well as interaction of treatment and intervention condition for each parameter. If the F values were significant, post hoc t tests were performed in order to determine statistical differences between the undisturbed and acoustic stress conditions in the placebo group and to compare the effects of 40 mg ziprasidone with placebo for both conditions separately, where applicable. Level of significance was set at $p < .05$. Significant

Table 1. Polysomnographic Sleep Parameters Measured in Healthy Male Subjects (N = 12) Taking Crossover Ziprasidone Treatment Under Stress and Undisturbed Conditions (ANOVA)

	Night 1 (standard sleep laboratory conditions)[a]		Night 2 (acoustic stress)[a]		Intervention Effect[b]		Treatment Effect[c]		Interaction[d]	
Sleep Parameter	Placebo	Ziprasidone, 40 mg	Placebo	Ziprasidone, 40 mg	F[e]	p	F[e]	p	F[e]	p
SPT, min	460.7 (23.5)	451.9 (23.7)	446.9 (44.3)	455.8 (15.7)	1.04	< .33	0.00	< .99	1.19	< .30
TST, min	433.7 (32.6)	439.2 (23.5)	392.6 (47.1)	429.4 (23.6)	11.97	< .01	7.45	< .02	2.95	< .11
Sleep efficiency (TST/TIB), %	90.4 (6.8)	91.5 (4.9)	81.8 (9.8)	89.4 (4.9)	12.18	< .01	7.31	< .05	3.03	< .11
Sleep stage 1 latency, min	14.0 (18.5)	21.8 (19.9)	17.9 (22.8)	19.5 (14.8)	0.05	< .83	0.77	< .40	0.79	< .39
Sleep stage 2 latency, min	16.9 (19.2)	26.9 (21.3)	33.0 (44.4)	24.5 (15.6)	1.64	< .23	0.01	< .91	1.59	< .23
SWS latency, min	14.0 (4.8)	13.9 (4.8)	51.3 (79.3)	23.3 (18.9)	4.1	< .07	1.6	< .23	1.33	< .27
REM latency, min	75.2 (26.0)	152.1 (75.3)	76.0 (59.2)	159.7 (55.4)	0.04	< .85	56.27	< .00005	0.05	< .83
Time awake, % SPT	6.0 (3.2)	2.8 (1.5)	12.2 (5.6)	5.8 (3.4)	14.54	< .005	32.91	< .0005	3.7	< .08
Sleep stage 1, % SPT	7.0 (3.8)	4.6 (3.0)	7.9 (2.2)	5.6 (2.3)	2.3	< .16	16.14	< .005	0.00	< .95
Sleep stage 2, % SPT	50.9 (4.4)	59.1 (6.1)	52.4 (7.5)	58.0 (5.6)	0.02	< .89	16.13	< .005	1.62	< .23
SWS, % SPT	16.0 (4.5)	22.3 (9.1)	8.4 (4.8)	17.3 (7.0)	18.0	< .002	19.45	< .002	2.70	< .13
REM, % SPT	20.2 (4.0)	11.2 (5.3)	19.1 (5.7)	13.3 (4.0)	0.17	< .69	45.1	< .00005	1.74	< .21
Total REM density[f]	1.4 (0.7)	0.6 (0.4)	1.7 (0.7)	0.9 (0.5)	4.45	< .06	17.69	< .002	0.06	< .81
REM density, period 1	1.1 (0.7)	0.9 (0.5)	1.4 (0.8)	0.8 (0.5)	0.43	< .52	5.06	< .05	1.21	< .30
No. of awakenings	29.1 (10.2)	16.4 (5.6)	41.0 (7.6)	24.9 (6.5)	22.43	< .001	46.23	< .00005	0.06	< .81
No. of PLMS	4.5 (10.6)	40.1 (69.2)	29.5 (46.3)	15.6 (26.4)	0.00	< .98	0.49	< .50	8.13	< .02

[a]Data are presented as mean (SD) for sleep parameters.
[b]Night 1 vs. night 2; ANOVA.
[c]Placebo vs. 40 mg ziprasidone; ANOVA.
[d]Interaction of treatment and intervention; ANOVA.
[e]df = 1,11.
[f]REM density = ratio of 3-second mini-epochs including at least 1 REM per REM epoch.
Abbreviations: ANOVA = analysis of variance, PLMS = periodic leg movements in sleep, REM = rapid eye movement, SPT = sleep period time, SWS = slow wave sleep, TIB = time in bed, TST = total sleep time.

Figure 1. Effect of Ziprasidone (40 mg) on REM Sleep Parameters[a]



[a]Data are mean ± SD of the averages of 2 nights for all subjects.
[b]Ratio of 3-second mini-epochs including at least 1 REM per REM epoch.
Abbreviation: SPT = sleep period time.

outcomes of ANOVA were α-adjusted and expressed as overall significance (p) using the Cross and Chaffin method.[44]

RESULTS

Of the 16 healthy male volunteers included in the trial, 1 subject was withdrawn from the study because of brief fainting with total recuperation most likely due to orthostatic hypotension after the first intake of 40 mg ziprasidone. One subject withdrew consent for participation during the first acoustic stress night when placebo had been administered. Additionally, technical problems during 1 night resulted in incomplete data for 2 subjects. Therefore, the analysis is based on 12 volunteers.

Polysomnographic Sleep Variables

Table 1 shows polysomnographic sleep variables for all conditions, as well as F and p values according to ANOVA. Ziprasidone significantly increased TST, sleep efficiency, REM latency, percentage sleep stage 2, and percentage SWS and significantly reduced percentage of

Table 2. Self-Ratings of Subjects (N = 12) Taking Crossover Treatment Under Stress and Undisturbed Conditions (ANOVA)

	Night 1 (standard sleep laboratory conditions)[a]		Night 2 (acoustic stress)[a]		Intervention Effect[b]		Treatment Effect[c]		Interaction[d]	
Sleep Variable	Placebo	Ziprasidone, 40 mg	Placebo	Ziprasidone, 40 mg	F[e]	p	F[e]	p	F[e]	p
SF-A item										
Sleep quality	3.7 (0.5)	3.9 (0.5)	2.0 (0.6)	2.5 (0.4)	64.2	< .00001	10.78	< .01	1.53	< .24
Feeling refreshed in the morning	3.4 (0.6)	3.0 (0.6)	2.8 (0.4)	3.0 (0.6)	6.11	< .05	2.63	< .13	15.07	< .005
Feeling well balanced in the evening	3.6 (0.7)	3.8 (0.5)	3.6 (0.3)	3.4 (0.5)	3.43	< .09	0.0	< .95	1.65	< .23
Feeling exhausted in the evening	2.8 (0.6)	2.7 (0.3)	2.3 (0.4)	2.3 (0.4)	12.5	< .005	0.47	< .51	0.16	< .70
Psychosomatic complaints during the sleep phase	1.5 (0.4)	1.2 (0.2)	2.0 (0.5)	1.7 (0.3)	27.45	< .0005	6.75	< .05	0.23	< .64
VIS-M item										
Feeling tired in the morning	45.3 (18.7)	54.8 (15.1)	56.8 (14.9)	49.9 (18.7)	0.46	< .51	0.13	< .73	5.7	< .05
Sleep quality	59.7 (16.0)	58.3 (17.0)	26.9 (13.1)	39.3 (15.6)	49.84	< .0001	1.12	< .31	2.72	< .13
Subjective sleep latency, min	25.8 (22.4)	24.6 (20.4)	40.0 (23.8)	31.3 (14.5)	7.1	< .05	1.42	< .26	0.74	< .41
No. of awakenings	1.4 (1.1)	0.9 (0.9)	5.0 (3.2)	4.0 (2.4)	18.30	< .005	6.91	< .05	0.65	< .44
Subjective sleep time, min	449.2 (27.9)	455.0 (27.5)	375.4 (76.0)	423.6 (34.4)	12.88	< .005	6.18	< .05	4.02	< .07

[a]Data are presented as mean (SD) for subjects' self-ratings.
[b]Night 1 vs. night 2; ANOVA.
[c]Placebo vs. 40 mg ziprasidone; ANOVA.
[d]Interaction of treatment and intervention; ANOVA.
[e]df = 1,11.
Abbreviations: ANOVA = analysis of variance; SF-A = sleep questionnaire A; VIS-M = visual analog scale, morning.

time awake, percentage sleep stage 1, number of awakenings, percentage REM, and REM density during the first REM period, as well as total REM density (Figure 1). The overall significance (11 out of 16 tests) was $p < .0001$. Furthermore, ANOVA showed significant effects for intervention (undisturbed vs. acoustic stress) on TST, sleep efficiency, percentage of time awake, percentage SWS, and number of awakenings and a trend for total REM density. The overall significance (5 out of 16 tests) was $p < .001$. Although there was no statistically significant increase in PLMS, 4 subjects who did not show PLMS under placebo demonstrated more than 5 PLMS per hour of TST under the treatment with ziprasidone.

Additionally, ANOVA revealed significant interactions of treatment (placebo or ziprasidone 40 mg) with intervention condition (undisturbed vs. acoustic stress) only for PLMS. The overall significance (1 out of 16 tests) was $p > .5$.

Subjects' Self-Ratings

The results for the subjective sleep variables, including F and p values according to ANOVA, are presented in Table 2. Ziprasidone significantly reduced number of awakenings and increased subjective sleep time (VIS-M) and significantly increased sleep quality and reduced psychosomatic complaints (SF-A). The overall significance (4 out of 10 tests) was $p < .005$. Furthermore, significant main effects for intervention condition (undisturbed vs. acoustic stress) were detected for the VIS-M items sleep quality, subjective sleep latency, number of awakenings, and subjective sleep time and the SF-A items sleep quality, feeling refreshed in the morning, exhaustion in the evening, and psychosomatic complaints. The overall significance (8 out of 10 tests) was $p < .00005$. Significant interactions of treatment (placebo or ziprasidone 40 mg) and intervention condition (undisturbed vs. acoustic stress) were found for the items feeling tired in the morning and feeling refreshed in the morning. The overall significance demonstrated only a trend (2 out of 10 tests); $p < .09$. Subsequent t tests revealed that subjects felt less refreshed under ziprasidone treatment after night 1. No significant drug influence was observed during night 2. A trend toward more tiredness after night 1 ziprasidone treatment, with no significant effect after night 2, was found.

DISCUSSION

In healthy subjects, an intermediate dose of ziprasidone resulted in a marked suppression of REM sleep characterized by a reduction in percentage REM, an approximately doubled REM latency, and a decrease in REM density. Furthermore, ziprasidone demonstrated sleep-consolidating properties including an increase of sleep depth and continuity, which was expressed by an increase in TST, sleep efficiency, and percentage SWS and a reduction in number of awakenings. These features were found independent of condition under which the influence of ziprasidone on sleep was studied and were paralleled by subjective assessments.

Earlier studies investigating the effects of atypical antipsychotics on polysomnographically registered sleep found only partially similar results. Clozapine, olanzapine, and quetiapine demonstrated an increase in TST and sleep efficiency in a variety of studies including healthy subjects and patients suffering from schizophrenia.[16–22,45,46] The influence of these drugs on SWS is more diverse. Clozapine either reduced SWS or left it unchanged[16–19,45]; likewise quetiapine left SWS uninfluenced,[22] whereas olanzapine was repeatedly demonstrated to increase SWS.[20,21,46] Risperidone, however, has only little effect on these sleep parameters,[23,47] and only healthy subjects and depressed patients, but not patients suffering from schizophrenia, demonstrated a reduction of percentage REM while REM latency was unaffected. Percentage REM and REM latency are also unaffected by clozapine,[16–19] although one study on a small group of schizophrenic patients reported an increase of REM percentage.[45] However, REM density was consistently reported to be increased by clozapine.[16–18] Olanzapine leaves percentage REM and REM latency mainly unchanged, although a higher dose in healthy subjects appears to reduce percentage REM and increase REM latency.[20] The only study reporting REM density demonstrated an increase of this measure in a group of schizophrenic patients treated with olanzapine.[21] Quetiapine dose-dependently reduces percentage REM in healthy subjects but leaves REM latency and REM density unaffected.[22]

The sleep profile exhibited under ziprasidone, therefore, appears to demonstrate some unique features in that it profoundly suppresses REM sleep, including tonic and phasic aspects of this sleep stage, and demonstrates a marked increase in SWS in addition to rather general sleep-consolidating aspects known from the other atypical antipsychotics. These effects on the sleep profile are somehow opposite to what is known about sleep of depressed patients. Sleep in depression is characterized by disturbances of sleep continuity, a reduction of SWS, and a disinhibition of REM sleep, with a shortening of REM latency, increased REM density, and percentage REM.[5,6] The effects on REM sleep observed under the treatment with ziprasidone are best known from antidepressants. Most of the effective antidepressant agents suppress REM sleep, including an increase in REM latency and a decrease in REM percentage[6,24–27,48]; however, there are antidepressants that do not affect REM sleep or even increase it, like bupropion, trimipramine, nefazodone, or mirtazapine.[6,49] Additionally, an increase of SWS is not uniformly seen with antidepressants.

Although the issue of REM suppression and antidepressant response awaits further critical assessment,[26] suppression of REM sleep may be related to the antidepressive action of some antidepressants and possibly other drugs, since nonpharmacologic REM sleep deprivation as a sole treatment intervention has been demonstrated to generate a marked amelioration of depressive symptomatology.[50] According to the reciprocal interaction model of non-REM/REM sleep regulation, REM sleep is suppressed by an increased aminergic activity.[51,52] The increase in REM latency and reduction of percentage REM observed under the treatment with ziprasidone are possibly related to its ability to inhibit reuptake of serotonin and norepinephrine.[32,36] Ziprasidone's affinity for the reuptake sites is similar to that of the antidepressants imipramine and amitriptyline, 2 drugs that produce comparable changes in REM latency and percentage REM in depressed patients and healthy subjects.[53–56] These findings might be relevant for ziprasidone's clinical usefulness in the treatment of depressive symptomatology.

The decrease of REM density found under ziprasidone differs from the increase found under both the atypical antipsychotics clozapine and olanzapine[16–18,21] and some antidepressants.[57–59] However, not all studies have found an increase in REM density under antidepressants,[60] and there are also reports of a short lived decrease in REM density after a small dose of imipramine given to healthy subjects.[61] The physiology of REM saccades, the equivalent of REM density, is not very well understood, but 5-HT_{1A} agonism has been related to a decrease in REM density.[62,63] Therefore, one of the mechanisms by which ziprasidone may have influenced REM density could be its agonistic activity on this receptor.[32] Furthermore, REM density appears to be negatively correlated with SWS pressure.[64] The increase of SWS under ziprasidone may have contributed to the decrease in REM density.

The increase in SWS observed under ziprasidone is comparable to that found under treatment with olanzapine.[20] According to the results of Sharpley et al.[20] and earlier studies, this increase in SWS is most likely mediated through the antagonism of 5-HT_{2C} receptors[20,65,66] and may be relevant for the treatment of schizophrenia, since patients with more SWS show a more favorable outcome.[14]

The effects of ziprasidone on sleep presented in this study demonstrate the influence of the drug on sleep of healthy subjects under a routine condition and within a model of insomnia. Further studies should evaluate the influence of different doses and duration of the drug on sleep in patients. Patient groups to be studied should include those suffering from schizophrenia and major depression. One goal of these investigations should be to evaluate the clinical significance of a possible increase in sleep depth and the suppression of REM sleep.

In conclusion, a small dose of the atypical antipsychotic ziprasidone profoundly influences sleep in healthy subjects under routine and acoustic stress conditions. It markedly suppresses REM sleep and consolidates sleep depth and continuity. These effects on the sleep profile are somehow opposite to what is known about sleep of depressed patients. The REM sleep–suppressing properties

of ziprasidone resemble the influence of the majority of, although not all, antidepressants on sleep and may be clinically relevant. These effects are most likely related to the drug's 5-HT_{2C} antagonism, 5-HT_{1A} agonism, and reuptake blockade of serotonin and norepinephrine. Further studies should investigate the relevance of ziprasidone's influence on sleep in patients suffering from schizophrenia and depression.

Drug names: bupropion (Wellbutrin and others), clozapine (Clozaril, FazaClo, and others), imipramine (Tofranil and others), mirtazapine (Remeron and others), nefazodone (Serzone and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), trimipramine (Surmontil), ziprasidone (Geodon).

REFERENCES

1. Tohen M, Vieta E, Calabrese J, et al. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. Arch Gen Psychiatry 2003;60:1079–1088
2. Calabrese JR, Macfadden W, McCoy R, et al. Double-blind, placebo-controlled study of quetiapine in bipolar depression. Presented at the 157th annual meeting of the American Psychiatric Association; May 1–6, 2004; New York, NY
3. Papakostas GI, Petersen TJ, Nierenberg AA, et al. Ziprasidone augmentation of selective serotonin reuptake inhibitors (SSRIs) for SSRI-resistant major depressive disorder. J Clin Psychiatry 2004;65:217–221
4. Barbee JG, Conrad EJ, Jamhour NJ. The effectiveness of olanzapine, risperidone, quetiapine, and ziprasidone as augmentation agents in treatment-resistant major depressive disorder. J Clin Psychiatry 2004;65: 975–981
5. Benca RM, Obermeyer WH, Thisted RA, et al. Sleep and psychiatric disorders: a meta-analysis. Arch Gen Psychiatry 1992;49:651–668
6. Riemann D, Berger M, Voderholzer U. Sleep and depression: results from psychobiological studies: an overview. Biol Psychol 2001;57: 67–103
7. Caldwell DF, Domino EF. Electroencephalographic and eye movement patterns during sleep in chronic schizophrenic patients. Electroencephalogr Clin Neurophysiol 1967;22:414–420
8. Zarcone VP, Benson KL, Berger PA. Abnormal rapid eye movement latencies in schizophrenia. Arch Gen Psychiatry 1987;44:45–48
9. Kempenaers C, Kerkhofs M, Linkowski P, et al. Sleep EEG variables in young schizophrenic and depressive patients. Biol Psychiatry 1988; 24:833–838
10. Lauer CJ, Schreiber W, Pollmacher T, et al. Sleep in schizophrenia: a polysomnographic study on drug-naive patients. Neuropsychopharmacology 1997;16:51–60
11. Keshavan MS, Reynolds CF III, Miewald MJ, et al. Delta sleep deficits in schizophrenia: evidence from automated analyses of sleep data. Arch Gen Psychiatry 1998;55:443–448
12. Ganguli R, Reynolds CF III, Kupfer DJ. Electroencephalographic sleep in young, never-medicated schizophrenics: a comparison with delusional and nondelusional depressives and with healthy controls. Arch Gen Psychiatry 1987;44:36–44
13. Tandon R, DeQuardo JR, Taylor SF, et al. Phasic and enduring negative symptoms in schizophrenia: biological markers and relationship to outcome [Erratum in Schizophr Res 2001;51:185]. Schizophr Res 2000;45: 191–201
14. Keshaven MS, Reynolds CF III, Miewald J, et al. Slow-wave sleep deficits and outcome in schizophrenia and schizoaffective disorder. Acta Psychiatr Scand 1995;91:289–292
15. Tandon R, Shipley JE, Taylor S, et al. Electroencephalographic sleep abnormalities in schizophrenia: relationship to positive/negative symptoms and prior neuroleptic treatment. Arch Gen Psychiatry 1992;49: 185–194
16. Touyz SW, Beumont PJ, Saayman GS, et al. A psychophysiological investigation of the short-term effects of clozapine upon sleep parameters of normal young adults. Biol Psychiatry 1977;12:801–822
17. Hinze Selch D, Mullington J, Orth A, et al. Effects of clozapine on sleep: a longitudinal study. Biol Psychiatry 1997;42:260–266
18. Wetter TC, Lauer CJ, Gillich G, et al. The electroencephalographic sleep pattern in schizophrenic patients treated with clozapine or classical antipsychotic drugs. J Psychiatr Res 1996;30:411–419
19. Lee JH, Woo JI, Meltzer HY. Effects of clozapine on sleep measures and sleep-associated changes in growth hormone and cortisol in patients with schizophrenia. Psychiatry Res 2001;103:157–166
20. Sharpley AL, Vassallo CM, Cowen PJ. Olanzapine increases slow-wave sleep: evidence for blockade of central 5-HT(2C) receptors in vivo. Biol Psychiatry 2000;47:468–470
21. Salin-Pascual RJ, Herrera-Estrella M, Galicia-Polo L, et al. Olanzapine acute administration in schizophrenic patients increases delta sleep and sleep efficiency. Biol Psychiatry 1999;46:141–143
22. Cohrs S, Rodenbeck A, Guan Z, et al. Sleep-promoting properties of quetiapine in healthy subjects. Psychopharmacology (Berl) 2004; 174:421–429
23. Sharpley AL, Bhagwagar Z, Hafizi S, et al. Risperidone augmentation decreases rapid eye movement sleep and decreases wake in treatment-resistant depressed patients. J Clin Psychiatry 2003;64:192–196
24. Sharpley AL, Cowen PJ. Effect of pharmacologic treatments on the sleep of depressed patients. Biol Psychiatry 1995;37:85–98
25. Rijnbeek B, de Visser SJ, Franson KL, et al. REM sleep effects as a biomarker for the effects of antidepressants in healthy volunteers. J Psychopharmacol 2003;17:196–203
26. Winokur A, Gary KA, Rodner S, et al. Depression, sleep physiology, and antidepressant drugs. Depress Anxiety 2001;14:19–28
27. Gursky JT, Krahn LE. The effects of antidepressants on sleep: a review. Harv Rev Psychiatry 2000;8:298–306
28. Harvey PD. Ziprasidone and cognition: the evolving story. J Clin Psychiatry 2003;64(suppl 19):33–39
29. Harvey PD, Meltzer H, Simpson GM, et al. Improvement in cognitive function following a switch to ziprasidone from conventional antipsychotics, olanzapine, or risperidone in outpatients with schizophrenia. Schizophr Res 2004;66:101–113
30. Daniel DG, Potkin SG, Reeves KR, et al. Intramuscular (IM) ziprasidone 20 mg is effective in reducing acute agitation associated with psychosis: a double-blind, randomized trial. Psychopharmacology (Berl) 2001;155: 128–134
31. Miceli JJ, Wilner KD, Hansen RA, et al. Single- and multiple-dose pharmacokinetics of ziprasidone under non-fasting conditions in healthy male volunteers. Br J Clin Pharmacol 2000;49(suppl 1):5s–13s
32. Seeger TF, Seymour PA, Schmidt AW, et al. Ziprasidone (CP-88,059): a new antipsychotic with combined dopamine and serotonin receptor antagonist activity. J Pharmacol Exp Ther 1995;275:101–113
33. Stahl SM, Shayegan DK. The psychopharmacology of ziprasidone: receptor-binding properties and real-world psychiatric practice. J Clin Psychiatry 2003;64(suppl 19):6–12
34. Tatsumi M, Jansen K, Blakely RD, et al. Pharmacological profile of neuroleptics at human monoamine transporters. Eur J Pharmacol 1999;368:277–283
35. Caley CF, Cooper CK. Ziprasidone: the fifth atypical antipsychotic. Ann Pharmacother 2002;36:839–851
36. Schmidt AW, Lebel LA, Howard HR Jr, et al. Ziprasidone: a novel antipsychotic agent with a unique human receptor binding profile. Eur J Pharmacol 2001;425:197–201
37. Cluydts R, De Roeck J, Cosyns P, et al. Antagonizing the effects of experimentally induced sleep disturbance in healthy volunteers by lormetazepam and zolpidem. J Clin Psychopharmacol 1995;15:132–137
38. Kane JM. Oral ziprasidone in the treatment of schizophrenia: a review of short-term trials. J Clin Psychiatry 2003;64(suppl 19):19–25
39. Görtelmeyer R. Schlaffragebogen SF-A and SF-B [in German]. In: Collegium Internationale Psychiatriae Scalarum (CIPS), ed. Internationale Skalen für Psychiatrie. Weinheim, Germany: Beltz; 1981
40. Ott H, Oswald I, Fichte K, et al. Visuelle Analogskalen zur Erfassung von Schlalfqualität [in German]. In: Collegium Internationale Psychiatriae Scalarum (CIPS), ed. Internationale Skalen für Psychiatrie. Weinheim, Germany: Beltz; 1986
41. Penzel T, Hajak G, Hoffmann RM, et al. Empfehlungen zur Durchführung und Auswertung polygraphischer Ableitungen im diagnostischen Schlaflabor [in German]. EEG-EMG-Z ELEK ELEKT 1993;24:65–70
42. Rechtschaffen A, Kales A. A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects. Washington, DC: United States Government Printing Office; 1968.

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43. Coleman RM. Periodic movements in sleep (nocturnal myoclonus) and restless legs syndrome. In: Guilleminault C, ed. Sleeping and Waking Disorders: Indications and Techniques. Menlo Park, Calif: Addison-Wesley; 1982:265–295
44. Cross EM, Chaffin WW. Use of the binomial theorem in interpreting results of multiple tests of significance. Educ Psychol Meas 1982;42: 25–34
45. Rüther E, Davis L, Papousek M, et al. Pharmakologische Beeinflussung zentraler serotonerger Mechanismen am Menschen und Auswirkungen auf den Schlaf [in German]. Arzneimittelforschung 1976;26:1071–1073
46. Sharpley AL, Vassallo CM, Pooley EC, et al. Allelic variation in the 5-HT2C receptor (HT2RC) and the increase in slow wave sleep produced by olanzapine [letter]. Psychopharmacology (Berl) 2001;153: 271–272
47. Yamashita H, Morinobu S, Yamawaki S, et al. Effect of risperidone on sleep in schizophrenia: a comparison with haloperidol. Psychiatry Res 2002;109:137–142
48. van Bemmel AL. The link between sleep and depression: the effects of antidepressants on EEG sleep. J Psychosom Res 1997;42:555–564
49. Aslan S, Isik E, Cosar B. The effects of mirtazapine on sleep: a placebo controlled, double-blind study in young healthy volunteers. Sleep 2002; 25:677–679
50. Vogel GW, Thurmond A, Gibbons P, et al. REM sleep reduction effects on depression syndromes. Arch Gen Psychiatry 1975;32:765–777
51. Hobson JA, McCarley RW, Wyzinski PW. Sleep cycle oscillation: reciprocal discharge of two brainstem neuronal groups. Science 1975;189: 55–58
52. Hobson JA, Pace-Schott EF, Stickgold R. Dreaming and the brain: toward a cognitive neuroscience of conscious states [Erratum in Behav Brain Sci 2001;24:575]. Behav Brain Sci 2000;23:793–842
53. Kupfer DJ, Foster FG, Reich L, et al. EEG sleep changes as predictors in depression. Am J Psychiatry 1976;133:622–626
54. Riemann D, Velthaus S, Laubenthal S, et al. REM-suppressing effects of amitriptyline and amitriptyline-N-oxide after acute medication in healthy volunteers: results of two uncontrolled pilot trials. Pharmacopsychiatry 1990;23:253–258
55. Kupfer DJ, Coble P, Kane J, et al. Imipramine and EEG sleep in children with depressive symptoms. Psychopharmacology (Berl) 1979;60: 117–123
56. Yamadera H, Nakamura S, Suzuki H, et al. Effects of trazodone hydrochloride and imipramine on polysomnography in healthy subjects. Psychiatry Clin Neurosci 1998;52:439–443
57. Armitage R, Emslie G, Rintelmann J. The effect of fluoxetine on sleep EEG in childhood depression: a preliminary report. Neuropsychopharmacology 1997;17:241–245
58. Reynolds CF III, Buysse DJ, Brunner DP, et al. Maintenance nortriptyline effects on electroencephalographic sleep in elderly patients with recurrent major depression: double-blind, placebo- and plasma-level-controlled evaluation. Biol Psychiatry 1997;42:560–567
59. Trivedi MH, Rush AJ, Armitage R, et al. Effects of fluoxetine on the polysomnogram in outpatients with major depression. Neuropsychopharmacology 1999;20:447–459
60. Feige B, Voderholzer U, Riemann D, et al. Fluoxetine and sleep EEG: effects of a single dose, subchronic treatment, and discontinuation in healthy subjects. Neuropsychopharmacology 2002;26:246–258
61. Okuma T, Hata N, Fujii S. Differential effects of chlorpromazine, imipramine, nitrazepam and amobarbital on REM sleep and REM density in man. Folia Psychiatr Neurol Jpn 1975;29:25–37
62. Gillin JC, Jernajczyk W, Valladares-Neto DC, et al. Inhibition of REM sleep by ipsapirone, a 5HT1A agonist, in normal volunteers. Psychopharmacology (Berl) 1994;116:433–436
63. Gillin JC, Sohn JW, Stahl SM, et al. Ipsapirone, a 5-HT1A agonist, suppresses REM sleep equally in unmedicated depressed patients and normal controls. Neuropsychopharmacology 1996;15:109–115
64. De Gennaro L, Ferrara M, Bertini M. The relationship between frequency of rapid eye movements in REM sleep and SWS rebound. J Sleep Res 2000;9:155–159
65. Paiva T, Arriaga F, Wauquier A, et al. Effects of ritanserin on sleep disturbances of dysthymic patients. Psychopharmacology (Berl) 1988; 96:395–399
66. Sharpley AL, Elliott JM, Attenburrow MJ, et al. Slow wave sleep in humans: role of 5-HT2A and 5-HT2C receptors. Neuropharmacology 1994;33:467–471