

## Insomnia in depression: Differences in objective and subjective sleep and awakening quality to normal controls and acute effects of trazodone

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### Abstract

Utilizing polysomnography (PSG) and psychometry, objective and subjective sleep and awakening quality was investigated in 11 drug-free patients (five females, six males) aged 35–75 years (mean age  $54.1 \pm 11.4$ ) suffering from nonorganic insomnia ( $F 51.0$ ) related to a depressive episode ( $F 32$ ) or recurrent depressive disorder ( $F 33$ ), as compared with 11 age- and sex-matched normal controls (five females, six males) aged 36–75 years (mean age  $53.0 \pm 13.5$ ). PSG demonstrated decreased sleep efficiency, total sleep time (TST), total sleep period (TSP) and sleep stage S2, as well as increased wakefulness during TSP, early morning awakening, sleep latency to S1, S2, S3 and sleep stage S1 in depressed patients. Subjective sleep quality and the total score of the Self-Assessment of Sleep and Awakening Quality Scale (SSA) were deteriorated as were morning and evening well being, drive, mood and fine motor activity right. Evening and morning blood pressure, the O<sub>2</sub> desaturation index and periodic leg movement (PLM) index were increased. In a subsequent acute, placebo-controlled cross-over design study, the acute effects of 100 mg of trazodone, a serotonin reuptake inhibitor with a sedative action due to 5-HT<sub>2</sub> and  $\alpha_1$  receptor blockade, were investigated in the patients. As compared with placebo, trazodone induced an increase in sleep efficiency (primary target variable), TST, TSP and SWS (S3 + S4), as well as a decrease in wakefulness during the TSP, early morning awakening and S2. There was no change in rapid eye movement (REM) sleep with the exception of an increase in the REM duration in minutes. Trazodone also caused an improvement in subjective sleep quality, affectivity, numerical memory and somatic complaints. All respiratory variables remained within normal limits. Critical flicker frequency and morning diastolic blood pressure were decreased. The present study demonstrated that depression induced significant changes in objective and subjective sleep and awakening quality, which were counteracted by 100 mg of trazodone, thus suggesting a key-lock principle in the treatment of depression. © 2001 Elsevier Science Inc. All rights reserved.

**Keywords:** Nonorganic insomnia; Depression; Controls; Polysomnography; Subjective sleep quality; Awakening quality; Trazodone

**Abbreviations:** AHI, apnea–hypopnea index; AI, apnea index; CFF, critical flicker frequency; DDA, descriptive data analysis; DSM, Diagnostic and Statistical Manual of Mental Disorders; EEG, electroencephalogram; EMG, electromyogram; EOG, electrooculogram; ICD, International Classification of Diseases; ICSD, International Classification of Sleep Disorders; LORETA, low-resolution brain electromagnetic tomography; PLM, periodic leg movement; PSG, polysomnogram; PSQI, Pittsburgh Sleep Quality Index; QLI, Quality of Life Index; REM, rapid eye movement; SSA, Self-Assessment of Sleep and Awakening Quality Scale; 5-HT, serotonin=5-hydroxytryptamine; S, sleep stage; SWS, slow-wave sleep; TIB, time in bed; TSP, total sleep period; TST, total sleep time; WHO, World Health Organization; SAS, Zung Anxiety Score; SDS, Zung Depression Score

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### 1. Introduction

The complaint of sleep disturbance has always been a defining feature of mood disorders. Epidemiological studies showed that insomnia was twice and up to three times as prevalent in depressed individuals as in nondepressed ones (Liljenberg et al., 1989; Livingston et al., 1990; Quera-Salva et al., 1991). In the World Health Organization (WHO) collaborative study on psychological problems in general health care, 5438 persons from different cultures were examined in primary care settings. Approximately half of the patients suffering from sleep disorders had a well-defined International Classification of Diseases (ICD)-10 diagnosis of mental disorders; 31.1% of them met the criteria for current depressive disorder (Üstün et al., 1996). This is in

line with the results of Schramm et al. (1995), who found that in general practice, affective disorders were the most common mental illness comorbid with chronic insomnia, as well as with our findings of 31% of affective disorders as a comorbid condition in our sleep outpatient clinic (Saletu et al., 1997a). Balan et al. (1998) evaluated psychiatrically 100 subjects referred to a sleep laboratory because of sleep complaints, mostly insomnia. Forty-three percent received axis-I DSM-III-R diagnoses (American Psychiatric Association, 1987); 8% was suffering from major depression, 5% from dysthymia and 9% from adjustment disorder with depressed mood. A new semistructured interview for sleep disorders was used to determine the prevalence of sleep complaints and insomnia in 1253 patients with major depressive disorders, both single episode and recurrent. Sleep complaints lasting at least 6–7 days/week were as follows: 33.7% of the patients had difficulties initiating sleep, 27% maintaining sleep, 37.5% showed a nonrestorative sleep, 30.3% early awakening and 11.1% excessive sleepiness. A strong association was found between the severity of depression and insomnia (Bobes et al., 1998).

Insomnia might not only be a symptom of depression, but also occur prior to and even presage the development of a full clinical syndrome (Dryman and Eaton, 1991; Breslau et al., 1996; Roberts et al., 2000). Perlis et al. (1997) assessed the sleep disturbance complaints in patients suffering from recurrent depression. They found that sleep progressively worsened prior to acute recurrence, i.e., the sleep disturbance not only predicts but also varies with the clinical state.

The sleep patterns of depressed patients have been studied extensively. Depressed patients were found to usually exhibit reduced sleep efficiency, prolonged sleep latency, frequent brief awakenings, an increase in light sleep, reduced slow-wave sleep (SWS), as well as rapid eye movement (REM) sleep abnormalities (Kupfer and Foster, 1972; Kupfer et al., 1978; Feinberg et al., 1982; Reynolds et al., 1983; Rush et al., 1982; Borbely et al., 1984; Dietzel et al., 1986; Thase et al., 1986). Changes in REM sleep, such as decreased REM latency, a prolonged first REM period, increased REM density and an increased amount of REM sleep, have been in focus of research and were thought to be rather specific to depression—particularly shortened REM latency (Akiskal et al., 1982; Reynolds and Kupfer, 1987; Rush et al., 1989). However, a meta-analysis of sleep and psychiatric disorders came to the conclusion that none of these REM sleep abnormalities was unique to depression (Benca et al., 1992).

REM sleep parameters were found to become increasingly abnormal with repetitive episodes of depression; a pronounced shortening of REM latency, an increase in the REM sleep percentage and higher numbers of REM periods and REM activity were observed at the time of recurrence (Kupfer et al., 1988, 1991). Moreover, depressed outpatients differed from depressed inpatients in having shortened REM latency at a somewhat lower percentage. Also the shift of REM activity to earlier in the night was of lower magnitude in the outpatient sample (Reynolds and Kupfer, 1987).

Although antidepressants are similar in their abilities to treat depression, many of them fail to treat preexisting insomnia, exacerbate insomnia or cause insomnia (Oberdorfer et al., 2000). Trazodone was found to be effective in treating insomnia associated with depression (Brooks et al., 1984; Wheatley, 1984; Fabre, 1990), as well as insomnia due to activating antidepressants (Jacobsen, 1990; Nierenberg et al., 1994). Trazodone hydrochloride is a triazolopyridine derivative possessing an antidepressant effect and possibly antianxiety activity. Pharmacologically, it blocks  $\alpha_1$  adrenergic receptors, presynaptic  $\alpha_2$  receptors and 5-HT<sub>2a/2c</sub> receptors. Its active metabolite, meta-chlorophenylpiperazine, is a direct 5-HT receptor agonist (Frazer, 1997). Its sedating effect seems to be related to 5-HT<sub>2a</sub> and  $\alpha_1$  receptor blockade (Delini-Stula, 1993; Ware et al., 1994). Some researchers found that a single nighttime dose of trazodone had the same hypnotic effect as a divided daily dosage regimen (Brooks et al., 1984), while others found that nighttime dosage was better than divided dosage as regards sleep latency, number of awakenings, sleep quality, dreaming and feeling on waking (Wheatley, 1984; Mashiko et al., 1999).

Neurophysiologically, the sedative effect of trazodone was already reported by us in 1982, utilizing pharmacoelectroencephalogram (EEG) analyses (Saletu, 1982, 1987). This was confirmed by Yamadera et al. (1998, 1999), who, in polysomnography (PSG) studies in normals, showed an increase in SWS and a decrease in S1 and S2.

Findings on the effect of trazodone on PSG variables in patients are ambiguous. Mouret et al. (1988) found an increase in total sleep time (TST), S2, S3 + S4 and REM latency, as well as a decrease in sleep latency and intrasleep awakening, while Van Bommel et al. (1992) noted only suppressed REM sleep and increased REM latency, which was also described in elderly nondepressed insomniac patients (Montgomery et al., 1983), as well as in normal healthy volunteers (Ware et al., 1994).

Thus, the aim of the present study was threefold: (1) to investigate objective and subjective sleep and awakening quality of 11 patients with nonorganic insomnia related to major depressive disorder; (2) to determine whether—like in other sleep disorders—also in insomnia related to depression, one adaptation night would be necessary, which may be of importance for insurance reimbursements; and (3) to measure the acute effect of trazodone, 100 mg, as compared to placebo on objective and subjective sleep and awakening quality of depressed patients.

## 2. Methods

### 2.1. Patients, inclusion and exclusion criteria

Eleven drug-free patients (five females, six males) aged 35–75 years (mean age  $54.1 \pm 11.4$  years) with the diagnosis of nonorganic insomnia ( $F$  51.0) related to a

depressive episode ( $F$  32) or recurrent depressive disorder ( $F$  33) were included in this study. Informed consent was obtained. Eleven matched normal subjects (five females, six males) aged 36–75 years (mean age  $53.0 \pm 13.5$  years) were studied as a control group ( $Z$  00.6).

### 2.1.1. Inclusion criteria

They called for patients of either sex, aged 18–75 years, satisfying the ICD-10 diagnostic criteria (World Health Organisation, 1992) of nonorganic insomnia related to a depressive episode or recurrent depressive disorder. Clinically, these patients had difficulties falling asleep, maintaining sleep or a poor quality of sleep. The complaint of sleep disturbance occurred at least three times a week for at least 1 month. There was preoccupation with the sleeplessness and excessive concern over its consequences at night and during the day. The unsatisfactory quality of sleep either caused marked distress or interfered with social and occupational functioning. According to a polydiagnostic approach, the patients were also required to meet the criteria of the DSM-IV (American Psychiatric Association, 1994) diagnosis of nonorganic insomnia related to major depressive disorder and the International Classification of Sleep Disorders (ICSD) (American Sleep Disorders Association, 1997) diagnosis of sleep disorder associated with mood disorder.

In patients, the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989) on admission was  $13.2 \pm 4.1$  (normals:  $2.7 \pm 1.7$ ), the Quality of Life Index (QLI) (Mezzich and Cohen, 1996; Mezzich et al., 2000)  $6.0 \pm 1.4$  (normals:  $8.5 \pm 0.6$ ), the Zung Depression Score (SDS) (Zung, 1965)  $52.1 \pm 10.0$  (normals:  $25.4 \pm 2.6$ ), the Zung Anxiety Score (SAS) (Zung, 1976)  $47.7 \pm 9.0$  (normals:  $25.4 \pm 2.6$ ).

### 2.1.2. Exclusion criteria

The following groups of people were excluded from the study: pregnant or lactating women; women in the child-

bearing period who were not applying adequate contraceptive methods, patients with insomnia secondary to other conditions, e.g., nocturia, pain, etc.; patients with a history of drug abuse or habituation including alcohol; patients with a history of trazodone hypersensitivity; patients with any significant medical disorder; patients requiring psychoactive medication or any other drug, which might interfere with the study assessments; patients who worked at night and patients with narrow angle glaucoma.

The study was performed in accordance with the rules and regulations for the conduct of clinical trials, stated in the declaration of Helsinki, as revised by the World Medical Assembly in Somerset West (World Medical Assembly, 1996).

### 2.2. Study design

In the single-blind, placebo-controlled cross-over study, the patients were investigated for three nights:

1. Adaptation night (**A**)
2. Baseline/placebo night (**P**)
3. Trazodone, 100 mg, at night (**T**).

The decision to choose a dosage of 100 mg was based on a meta-analysis on sleep studies in both normal volunteers and patients (Oberndorfer et al., 2000).

At the time of admission, the patients were required to have been free of psychopharmacological treatment for five times the half-life of the psychopharmacological agent given last. The concomitant use of sedatives, propranolol,  $\alpha$ -methyl dopa, other antidepressants, tranquilizers, antihistamines, amphetamine-containing compounds, narcotic analgesics, anticholinergics or alcohol was prohibited during the study. Aspirin or acetaminophen could be taken, but the patients were instructed to refrain from doing so after

Table 1

Insomnia ( $F$  51.0) in depression ( $F$  32,  $F$  33): differences to normal controls (C) and acute effects of 100 mg of trazodone (T) and placebo (P) after an adaptation night (A)

Variable	Sleep initiation and maintenance				Internight differences Wilcoxon	Intergroup differences $U$ test
	Controls (md, $n=11$ ) C	Patients (md, $n=11$ ) A P T				
Latency to S1 (min)↓	5	22	24	21		P:C**
Latency to S2 (min)↓	10	43	44	27		P:C**
Latency to S3 (min)↓	32	64	66	77		P:C*
Latency to S4 (min)↓	85	88	123	84		
Latency to REM (min)↓	105	112	113	95		
Wake within TSP (min)↓	17	109	58	33	A:P**	
Wake before buzzer (min)↓	0	3	12	0	A:P* P:T*	P:C**
Awakenings (N)↓	5	9	11	4	P:T*	P:C**
TSP (min)↑	440	421	392	428	A:P* P:T*	P:C**
TST (min)↑	409	309	342	375	P:T*	P:C**
Sleep efficiency (%)↑	92	69	77	84	P:T*	P:C**

(↑↓) Direction of improvement.

\*  $P < .05$ .

\*\*  $P < .01$ .

1700 h during the study. In addition, meals, coffee, tea, Coca-Cola or other caffeine-containing beverages were to be avoided within 8 h of retiring. No other medication was allowed after the study treatment had been taken at bed-time. The patients were required not to nap during the day or evening for the duration of the study.

### 2.3. Evaluation of objective sleep quality

Polysomnographic all-night recordings were obtained between approximately 2230 (lights out) and 0600 h (buzzer or alarm clock). Thus, time in bed (TIB) was fixed with 7.5 h. Data were recorded by means of a 16-channel polygraph (Jaeger Sleep Lab. 1000P) including three EEG channels (C4-A1, CZ-O2 and C3-A2) according to the 10/20 system, two electrooculogram (EOG) channels (left/right), submental electromyogram (EMG) and tibialis anterior EMG from both legs, nasal and oral airflow, movement of the chest and abdomen, snoring, transcutaneous oxygen saturation and pulse rate (CRITICARE pulse oxymeter 504).

Respiratory events such as apneas (more than 10 s without nasal or oral flow, measured by thermistors in regard to temperature-induced conduction changes, and cessation or cancellation of movements of chest and abdomen), hypopneas (more than 50% reduction in the respiratory amplitude for at least 10 s), snoring events, desaturation events (reduction of the start oxygen saturation value by 4%), minimum O<sub>2</sub> values and average low oxygen saturation were determined automatically by means of SleepLab 1000P software.

Periodic leg movement (PLM) parameters were as follows:

- (i) the number of seconds to be used to compute the baseline (nonmovement) was 120;
- (ii) EMG ratio for leg movement: there must be an increase of 3.0 times the local baseline for the event to be scored as PLM;
- (iii) The movement must be at least 1 s and not longer than 20 s;
- (iv) There must be a minimum interval of 4 s and maximum interval of 90 s between movements to regard them as periodic;
- (v) A minimum number of five consecutive movements are required for a group of movements to be scored as PLM.

For sleep staging, 30-s epochs were visually scored according to the criteria of Rechtschaffen and Kales (1968). TST is the amount of actual sleep time in the total sleep period (TSP). TSP is the period of time measured from sleep onset until the final awakening. In addition to TST, TSP includes wake time (wake/TSP) and movement time. The number of awakenings refers to arousal to wakefulness during TST. The sleep efficiency index is the

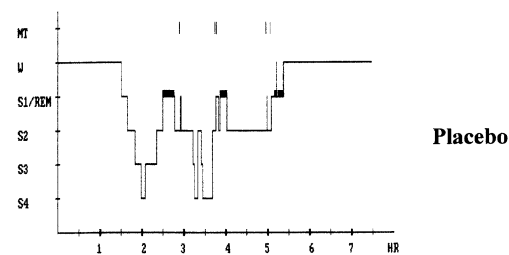
proportion of sleep in the recorded period and is calculated by dividing TST by the total TIB (fixed in our study) multiplied by 100.

### 2.4. Subjective sleep and awakening quality

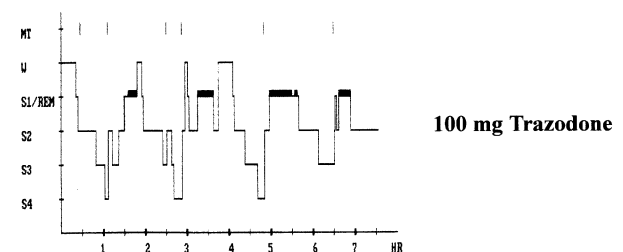
After the morning toilet, the patients completed the Self-Assessment of Sleep and Awakening Quality Scale (SSA) (Saletu et al., 1987). Thymopsychic variables included subjective well-being in the evening and morning, based on the Von Zerssen Bf-S Scale (Von Zerssen et al., 1970), as well as drive, mood, affectivity and drowsiness in the morning, measured by means of 100-mm visual-analog scales.

## Nonorganic Insomnia/Depression

**J.B. F 51.0  
F 33.01**



**J.B. F 51.0  
F 33.01**



**H.S. Z 00.6**

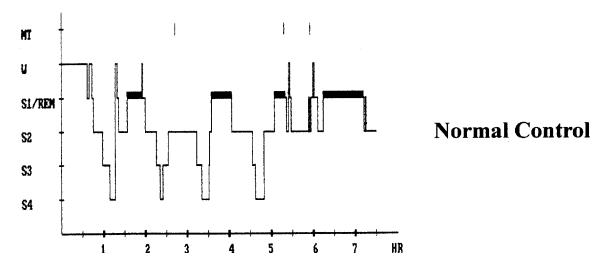


Fig. 1. Sleep print of a 50-year-old male patient with nonorganic insomnia related to recurrent depressive episodes after placebo and 100 mg of trazodone as compared with an age- and sex-matched normal control. Time is shown in the abscissa; sleep stages are shown in the ordinate. While under placebo, the patient demonstrated both early and late insomnia, 100 mg of trazodone normalized the sleep profile.

### 2.5. Objective awakening quality (psychometry)

Noopsyche tests included the Grünberger Alphabetical Cancellation Test for quantification of attention (total score), concentration (errors in percentage of the total score) and attention variability (difference between extreme scores) (Grünberger, 1977), the Numerical Memory Test (Grünberger, 1977), as well as the Grünberger Fine Motor Activity Test (right and left hands) for evaluation of changes in psychomotor activity and drive (Grünberger, 1977). Reaction time, reaction time variability (ms) and errors of omission and commission were determined by the computer-assisted reaction time apparatus.

### 2.6. Psychophysiological investigations

These included the critical flicker frequency (CFF; descending threshold) after awakening, muscular strength of the right and left hands, as well as of the right and left index fingers and thumbs evaluated by means of a vigorimeter (kp/cm<sup>2</sup>) (Fünfgeld, 1966). The evening and morning pulse rate, as well as systolic and diastolic blood pressure were also recorded.

### 2.7. Biometric planning and evaluation

The sample size was based on the meta-analysis study on sleep in psychiatric disorders by Benca et al. (1992).

The primary target variable was sleep efficiency (%). An improvement by 1 S.D. (4%) from our normative database for subjects aged between 40 and 60 years (Saletu et al., 1991) was considered as clinically relevant.

Statistical analysis was based on the concept of descriptive data analysis (DDA) as proposed by Abt (1988) for controlled clinical trials. The predetermined null hypothesis for the confirmatory statement was: There is no difference between trazodone and placebo in regard to sleep efficiency (maximum error probability  $\alpha = .05$ ). Normal distribution was tested by means of the one-sample Kolmogorov–Smirnov Test. In case of a violation of the assumption of normal distribution, a Wilcoxon test was used for within-group comparisons and a Mann–Whitney *U* test for intergroup comparison. All other effects were tested descriptively.

## 3. Results

### 3.1. Objective sleep quality

#### 3.1.1. Sleep initiation and maintenance

Major depression patients showed a first-night effect in regard to wakefulness within TSP, which was significantly longer in the first night than in the second night, while wake time before the buzzer was shorter and TSP was significantly longer (Table 1).

As compared with normal controls, insomniac depressive patients showed a significantly lower sleep efficiency (77% vs. 92%,  $P < .01$ ), further, a significantly longer sleep latency to S1, S2 and S3, a higher number of awakenings and shorter TST and TSP, as well as more early morning awakening (Table 1).

Acute treatment with trazodone, 100 mg, resulted in a significant increase in sleep efficiency from 77% to 84% ( $P < .05$ ), a significant improvement in TST, TSP, the

Table 2

Insomnia ( $F 51.0$ ) in depression ( $F 32$ ,  $F 33$ ): differences to normal controls (C) and acute effects of 100 mg of trazodone (T) and placebo (P) after an adaptation night (A)

Variable	Sleep architecture					
	Controls (md, $n = 11$ )	Patients (md, $n = 11$ )			Internight differences Wilcoxon	Intergroup differences <i>U</i> test
		A	P	T		
Sleep stage	1 (%)	7	12	13	8	P:C**
	1 (min)	27	35	39	33	P:C*
Sleep stage	2 (%)	57	43	52	45	A:P* P:T*
	2 (min)	235	125	164	167	A:P*
Sleep stage	3 (%)	9	12	8	15	A:P** P:T**
	3 (min)	40	33	30	51	P:T**
Sleep stage	4 (%)	2	13	10	8	A:P*
	4 (min)	11	43	27	31	
Sleep stage	3+4 (%)	16	26	20	29	A:P* P:T**
	3+4 (min)	68	79	62	115	A:P* P:T**
Sleep stage	REM (%)	20	18	17	19	
	REM (min)	78	55	51	72	P:T*
Movement time	(min)	2	1	1	2	
REM latency	(min)	68	71	55	68	
Stage shifts	( <i>n</i> )	53	61	61	56	

\*  $P < .05$ .

\*\*  $P < .01$ .

Table 3

Insomnia ( $F$  51.0) in depression ( $F$  32,  $F$  33): differences to normal controls (C) and acute effects of 100 mg of trazodone (T) and placebo (P) after an adaptation night (A)

Variable	Respiratory variables and PLMs				Internight differences Wilcoxon
	Normal range	Patients (md, $n = 11$ )			
		A	P	T	
Apneas (total number)		1	1.5	0	P:T*
A index (number/hours of sleep)	0–5	0.16	0.33	0.00	P:T**
Apneas + hypopneas (total number)		3	6	2	
AH index (number/hours of sleep)	0–10	0.48	1.32	0.32	P:T*
Desaturations (total number)		15	33	21	
D index (number/hours of sleep)	0–5	3.8	5.7	3.4	
Minimum O <sub>2</sub> (%)		86	86	85	
Average low O <sub>2</sub> (%)	≥ 90	91	91	90	P:T*
Snoring events (total number)		38	30	110	P:T*
S index (number/hours of sleep)	0–20	9.7	5.6	16.7	
PLMs (total number)		98	145	80	
PLM index (number/hours of sleep)	0–5	21.2	21.2	12.6	

\*  $P < .05$ .

\*\*  $P < .01$ .

number of awakenings and early morning awakening (Table 1). Fig. 1 demonstrates the sleep profiles of a patient with both early and late insomnia under placebo and a significant normalization after 100 mg of trazodone. The postdrug profile became very much the sleep profile of the normal age- and sex-matched control.

### 3.1.2. Sleep architecture

From the adaptation night to the baseline night, sleep stage S2 significantly increased while S3, S4 and SWS (S3 + S4) significantly deteriorated in depressed patients (Table 2).

As compared with normal controls, depressed patients showed significantly more light sleep S1, as measured in both minutes and percent of the TST, and further less S2, measured in minutes. SWS (S3 + S4), REM duration and

percentage, movement time and stage shifts showed no significant differences between patients and controls. REM latency was below 65 min, but the difference to controls did not reach the level of significance (Table 2).

Trazodone, 100 mg, caused a significant increase in both duration and percentage of S3 + S4 as compared with placebo, as well as a significant increase in S2% (Table 2). It lengthened REM latency up to the normal value and significantly prolonged REM sleep in minutes.

### 3.1.3. Respiratory variables and PLMs

Respiratory variables of our insomniac depressed patients were all within normal limits, while the PLM index was increased (Table 3). Acute administration of 100 mg of trazodone caused a significant decrease in the total number of apneas, the apnea index (AI), the apnea–hypopnea index

Table 4

Insomnia ( $F$  51.0) in depression ( $F$  32,  $F$  33): differences to normal controls (C) and acute effects of 100 mg trazodone (T) and placebo (P) after an adaptation night (A)

Variable	Subjective sleep/awakening quality and thymopsychic measures				Internight differences Wilcoxon	Intergroup differences $U$ test
	Controls (md, $n = 11$ )	Patients (md, $n = 11$ )				
	C	A	P	T		
Sleep quality (score)↓	10	17	16.5	14	P:T*	P:C**
Awakening quality (score)↓	14	18	20	20		
Somatic complaints (score)↓	7	7	5.5	6	A:P** P:T*	
SSA (score)↓	29	41	43.5	39		P:C*
Well being, evening (score)↓	7	34	27.5	30		P:C**
Well being, morning (score)↓	13	39	28.5	27	A:P*	P:C**
Drive (mm)↓	19	55	68.5	75		P:C*
Mood (mm)↑	81	55.5	48	49		P:C*
Affectivity (mm)↑	74	71.5	51.5	51	P:T*	
Drowsiness (mm)↓	31	57	68	70		

(↑↓) Direction of improvement.

\*  $P < .05$ .

\*\*  $P < .01$ .

Table 5

Insomnia ( $F$  51.0) in depression ( $F$  32,  $F$  33): differences to normal controls (C) and acute effects of 100 mg of trazodone (T) and placebo (P) after an adaptation night (A)

Variable	Noopsychic measures					Internight differences Wilcoxon	Intergroup differences $U$ test
	Controls (md, $n=11$ )		Patients (md, $n=11$ )				
	C		A	P	T		
Attention (score)†	448		543	539	479	A:P**	
Concentration (% errors)↓	3.6		6.4	5.6	3.8		
Attention variability (score)↓	16		16	16.5	14		
Numerical memory ( $n$ )†	5		3	4	5	A:P* P:T*	
Fine motor activity, right†	40		36	37	35		P:C*
Fine motor activity, left†	30		24	26.5	27		
Fine motor activity, right + left†	76		58	64	62		
Reaction time (RT) (ms)↓	494		610	533	561		
RT variability (ms)↓	119		152	139	119		
RT errors/commission ( $n$ )↓	2		6	6	2		
RT errors/omission ( $n$ )↓	0		0	0	0		

(†↓) Direction of improvement.

\*  $P < .05$ .

\*\*  $P < .01$ .

(AHI) and the average low oxygen saturation, with a significant increase in snoring events (Table 3). It also caused a decrease in PLMs, but this drop did not reach the level of significance.

### 3.2. Subjective sleep/awakening quality and thymopsychic measures

Somatic complaints and morning well-being scores showed a significant first-night effect (Table 4). In comparison with controls, insomniac depressed patients showed a significantly deteriorated subjective sleep quality and total SSA score (Table 4). Morning and evening well-being, as well as morning drive and mood, were also significantly deteriorated.

Acute trazodone use caused a significant improvement in subjective sleep quality and a significant though slight deterioration of affectivity and somatic complaints (Table 4).

### 3.3. Objective awakening quality/noopsychic measures

From the adaptation night to the baseline night, numerical memory improved, while the attention score deteriorated (Table 5).

As compared with controls, depressed patients showed a significantly deteriorated fine motor activity of the right hand (Table 5). Acute use of 100 mg of trazodone caused a mild but significant improvement of patients' numerical memory (Table 5).

Table 6

Insomnia ( $F$  51.0) in depression ( $F$  32,  $F$  33): differences to normal controls (C) and acute effects of 100 mg of trazodone (T) and placebo (P) after an adaptation night (A)

Variable	Psychophysiological measures					Internight differences Wilcoxon	Intergroup differences $U$ test
	Controls (md, $n=11$ )		Patients (md, $n=11$ )				
	C		A	P	T		
CFF (Hz)			42.7	42.5	41.5	P:T**	
Vigorimeter (right finger)	0.52		0.46	0.48	0.43		
Vigorimeter (left finger)	0.47		0.44	0.48	0.50		
Vigorimeter (right hand)	0.67		0.62	0.60	0.58		
Vigorimeter (left hand)	0.66		0.56	0.63	0.54		
Systolic RR, evening (mmHg)	110		120	128	120		P:C*
Diastolic RR, evening (mmHg)	75		75	83	80		P:C*
Pulse rate, evening (bpm)	72		67	67	72		
Systolic RR, morning (mmHg)	105		123	120	125		P:C*
Diastolic RR, morning (mmHg)	70		80	80	75	P:T*	P:C**
Pulse rate, morning (bpm)	72		64	66	72		

\*  $P < .05$ .

\*\*  $P < .01$ .

### 3.4. Psychophysiological measures

There was no significant first-night effect in psychophysiological measures (Table 6). Evening and morning blood pressure were significantly higher in depressed patients than in normals (Table 6). Trazodone significantly reduced the CFF as compared with placebo and also significantly decreased morning diastolic blood pressure (Table 6).

## 4. Discussion

### 4.1. Sleep initiation and maintenance

The polysomnographic investigations in depressed insomniac patients demonstrated a disturbed sleep initiation and maintenance characterized by prolonged sleep latency, as well as by a decreased sleep efficiency, TSP and TST, and an increased number of nocturnal awakenings. This confirmed previous PSG findings of sleep disturbances in depressed patients (Gillin et al., 1979; Reynolds and Kupfer, 1987; Rush et al., 1989). There was also a deterioration of subjective sleep quality in our depressed patients as compared with controls, which is in line with the fact that sleep disturbance is one of the main complaints of depressed patients (Ford and Kamerow, 1989). Acute administration of 100 mg of trazodone at night resulted in a subjective and objective improvement of sleep quality, as indicated by the patients' rating of sleep quality and PSG sleep maintenance variables. However, trazodone showed no effect on sleep latency. Nierenberg et al. (1994) found that trazodone 50 mg at night improved patients' sleep duration and their total PSQI scores and caused an improvement in early morning awakening in patients with antidepressant-associated insomnia. The authors also described a trend towards an improvement in subjective sleep latency, but no significant difference in difficulty falling asleep between patients treated with trazodone and placebo. Mouret et al. (1988) also noted an increase in the total duration of sleep and a decrease in nocturnal awakenings, but also a shortened sleep latency in the first night of administration of 100 mg of trazodone to depressed patients. On the other hand, Muratorio et al. (1974) reported that a single 50-mg dose of trazodone had no detectable effect on sleep, while repeated administration of 300–600 mg increased TST and decreased the number and duration of awakenings. However, Van Bommel et al. (1992) found that trazodone, 300–400 mg, in divided doses after 5 weeks had no significant effect on any indicator of sleep continuity.

### 4.2. Sleep architecture

In regard to sleep architecture, our depressed patients showed increased S1 and decreased S2 sleep as compared to normal controls, while there was no significant intergroup

difference between depressed patients and normal controls regarding SWS (S3 + S4). Depressed patients usually exhibit an increase in light sleep and a decrease in deep sleep (Coble et al., 1976; Hawkins and Mendels, 1966; Ansseau et al., 1984). REM latency tended to be shorter in depressed insomniacs than in normal controls. Shortened REM latency was considered the "psychobiologic marker" for primary depression (Kupfer, 1976). Borbely et al. (1984) hypothesized that a reduction of the generation of SWS in depression (which especially occurred in the first third of the night) was the reason for the advance of REM sleep. In our study, acute oral administration of trazodone, 100 mg, caused a significant increase in SWS, which confirmed previous findings of Yamadera et al. (1998, 1999) in normals and of Mouret et al. (1988) in depressed patients, as well as a normalization of REM latency and had an ambiguous effect on S1 and S2. Trazodone was found to increase SWS and produce a negative rebound on withdrawal in elderly poor sleepers (Montgomery et al., 1983), as well as in healthy young adults (Ware and Pittard, 1990). The prolongation of SWS seems to be related to the effect of trazodone on 5-HT<sub>2A/2c</sub> receptors, which play a critical role in the regulation of SWS (Sharpley and Cowen, 1995).

Like ours, all available PSG studies on the effect of trazodone in depressed patients found that it increased REM latency (Montgomery et al., 1983; Mouret et al., 1988; Van Bommel et al., 1992; Ware et al., 1994). While we observed a prolongation of REM sleep time but no change in REM%, some studies noted no effect for trazodone on REM sleep (Mouret et al., 1988; Scharf and Sachais, 1990) and others found that trazodone did suppress REM sleep (Montgomery et al., 1983; Van Bommel et al., 1992; Ware et al., 1994).

### 4.3. Respiration and PLMs

Regarding respiratory variables, our patients were within normal limits with the exception of a marginal increase in the desaturation index. Trazodone did not deteriorate these variables. On the contrary, it decreased the number of apneas, the AI and the AHI. The PLM index was increased at baseline and improved under trazodone, 100 mg. We consider these findings of interest, as drug treatment may improve certain aspects of sleep disorders while others deteriorate, and different substances of the same psychopharmacological class may have different effects on sleep. It is well known that certain drugs may improve nonorganic insomnia, while at the same time deteriorate snoring and sleep-related breathing disorders or a restless legs syndrome (Mendelson et al., 1981; Cirignotta et al., 1988; Ferry, 1993; Robinson and Zwillich, 2000; Ware et al., 1984; Paik et al., 1989; Bakshi, 1996).

### 4.4. Subjective sleep and awakening quality

While in our depressed patients subjective sleep quality was deteriorated, as discussed before, concerning awaken-



ing quality, they showed no difference when compared with normal controls. At the same time, the patients' total SSA score was worse than that of the controls. Trazodone caused a mild but nonsignificant improvement in the total SSA score and had no effect on awakening quality. Moreover, it did not affect well-being in the evening or in the morning. Moon and Davey (1988) found that trazodone, 150 mg hs, improved sleep quality but worsened the ease of awakening in the morning and the feelings on and after awakening during the first 15 days. After day 16, the latter two variables also began to improve. Blacker et al. (1988) also observed the initial worsening regarding the ease of awakening and feelings after awakening. However, they also noted an improvement after day 7. Trazodone, 100 mg, was found to minimally increase the somatic complaints of our patients, which may be due to  $\alpha_1$  adrenergic effects. Anyhow, continuous use of trazodone for 3 weeks was found to decrease somatic findings among depressed patients (Klieser and Lehmann, 1988).

Utilizing 100-mm visual-analog scales, we found drive and mood scales deteriorated in patients, while affectivity and drowsiness were not different from controls. Acute use of 100 mg of trazodone caused a mild but significant deterioration of affectivity.

#### 4.5. Objective awakening quality

Regarding noopsyche measures, our patients did not differ from controls except for a deteriorated right-hand fine motor activity. Trazodone, 100 mg, did not affect these noopsyche measures except for a mild improvement of numerical memory. No deterioration in cognitive functions was observed in normal geriatric subjects when assessed 4 h after acute administration of 100 mg of trazodone (Branconnier and Cole, 1981). Meanwhile, Newton (1981) found that continuous treatment with trazodone caused some behavior changes, including indecision, loss of interest, poor memory, difficulty in concentration, forgetfulness and confusion. Our patients showed a decrease in CFF, but no change of muscular strength on trazodone, 100 mg. The critical flicker fusion threshold was described to decrease after the first dose of trazodone, 150 mg, with performance improving very gradually thereafter (Moon and Davey, 1988). When comparing the self-rated adverse clinical effects of trazodone and fluoxetine, a high frequency of muscle weakness was found with trazodone, which had not been anticipated (Fisher et al., 1993). On assessing morning and evening blood pressure and pulse rate, we noted that 100 mg of trazodone lowered only the morning diastolic blood pressure. Acute use of 100 mg of trazodone had no effect on erect or supine pulse rate and systolic or diastolic blood pressure in a normal geriatric population (Branconnier and Cole, 1981), while continuous use tended to produce a significant decrease in pulse rate and blood pressure (Cole et al.,

1981; Perry et al., 1989). Due to its  $\alpha_1$  adrenergic blockade, trazodone is also liable to produce postural hypotension (Silvestrini, 1988), which is also the reason why a retard formulation avoiding steep blood level peaks was developed. Indeed, in a recent field study with such a retard formulation, we found only slight side effects (Saletu et al., in preparation).

## 5. Conclusion

From our results, we may conclude that patients with nonorganic insomnia due to depressive episodes or recurrent depressive disorder exhibit a significant deterioration in objective and subjective sleep and awakening quality as compared with normal controls. Moreover, they also show a first-night effect, just like patients suffering from other sleep disorders such as nonorganic insomnia due to generalized anxiety disorder (Saletu et al., 1996), panic disorder (Saletu-Zyhlarz et al., 2000a), dysthymia (Saletu-Zyhlarz et al., 2001) or organic sleep disorders such as restless legs syndrome (Saletu et al., 2000b,c), periodic limb movement disorder (Saletu et al., 2001), snoring and sleep-related breathing disorders (Saletu et al., 1998).

In regard to the psychopharmacological aspects of the study, we can conclude that trazodone possesses a good hypnotic effect in patients with nonorganic insomnia related to depressive episodes and recurrent depression, as it improved subjective and objective sleep quality and other sleep measures already after a single dose. This is also in line with our recent findings on the acute effects of trazodone in nonorganic insomnia related to dysthymia (Saletu-Zyhlarz et al., 2001). Trazodone has been proven to be as effective as other antidepressants and superior to them in improving sleep disturbances (Mann et al., 1981; Davis and Vogel, 1981; Weisler et al., 1994; Cunningham et al., 1994; Kallepalli et al., 1997). Since the mood-elevating effect of nearly all available antidepressants usually does not become apparent before 10–14 days, a rapid improvement in sleep patterns at the onset of treatment can be psychologically beneficial, particularly in regard to the patient's future compliance. Most important seems to us the fact that the changes in sleep variables induced by trazodone were opposite to the differences between untreated depressed patients and age- and sex-matched normal controls. This supports a key-lock principle in the diagnosis and treatment of nonorganic sleep disorders, as recently described by us for nonorganic insomnia due to generalized anxiety disorder (Saletu et al., 1997b; Saletu-Zyhlarz et al., 1997), panic disorder (Saletu-Zyhlarz et al., 2000a) and dysthymia (Saletu-Zyhlarz et al., 2001). Moreover, such a key-lock principle was also demonstrated utilizing EEG mapping and EEG tomography by low-resolution brain electromagnetic tomography (LORETA) (Saletu, 1997, 2000; Saletu et al., 1997b, 2000a; Saletu-Zyhlarz et al., 1997, 2000b).

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