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ORIGINAL PAPER

Controlled clinical, polysomnographic and psychometric studies on differences between sleep bruxers and controls and acute effects of clonazepam as compared with placebo

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Abstract The pathogenesis, pathophysiology, and pharmacotherapy of sleep bruxism (SB) are still not fully understood. We investigated symptomatology, objective and subjective sleep and awakening quality of middle-aged bruxers compared with controls and acute effects of clonazepam 1 mg compared with placebo by polysomnography and psychometry. Twenty-one drug-free bruxers spent 3 nights in the sleep lab, 21 age- and sex-matched controls 2 nights. Clinically, bruxers exhibited deteriorated PSQI, SAS, SDS and IRLSSG measures, polysomnographically impaired sleep maintenance, increased movement time, stage shift index, periodic leg movements (PLM) and arousals and psychometrically deteriorated subjective sleep and awakening quality, evening/morning well-being, drive, mood, drowsiness, attention variability, memory, and fine motor activity. As compared with placebo, clonazepam significantly decreased the SB index in all patients (mean: $-42 \pm 15\%$). Sleep efficiency, maintenance, latency, awakenings and nocturnal wake time, the stage shift index, S1, PLM, the arousal index, subjective sleep and awakening quality, and fine motor activity improved.

Keywords Sleep bruxers · Controls · Polysomnography · Psychometry · Clonazepam

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Introduction

Sleep bruxism (SB) was classified as a parasomnia (i.e. an undesirable physical phenomenon occurring during sleep) (306.8) in the first version of the International Classification of Sleep Disorders (ICSD-1), with stereotyped movements such as grinding or clenching of the teeth during sleep being the essential feature [5]. Interestingly, in the second edition (ICSD-2), SB is listed as a sleep-related movement disorder (780.58, G 47.64) [3]. On the other hand, in the International Classification of Diseases, 10th revision (ICD-10) by the WHO, teeth grinding appears in chapter F "Mental and Behavioral Disorders" under F45.8 "Other Somatoform Disorders" [96], which indicates that in the pathogenesis of SB, stress and psychosocial variables play a role. Macaluso et al. [52] and Kato et al. [38] suggested that SB is a sequel of microarousals during sleep (sudden brain and cardiac activation).

The prevalence of sleep bruxism is approximately 8% [25, 43, 63, 74] that of wake bruxism is around 20%. SB decreases with increasing age, with an incidence rate of 14% in children and 3% in the elders [41, 43].

In SB, a number of medical disciplines are involved, such as dental medicine (tooth destruction, temporomandibular dysfunction), neurology (Parkinson's disease, Meigs syndrome, oral tardive dyskinesia, olivopontocerebellar atrophy, cerebellar hemorrhage, cephalgia), somnology (irritation of the bed partner due to the grinding

sounds, periodic limb movements, apnea, REM behavior disorder) [8, 42], and psychiatry (anxiety, adjustment and affective disorder, dementia, mental retardation, tics). Psychosocial factors were reported by Glaros and Rao [26], Kristal [40], Harness and Peltier [28], Biondi and Picardi [10], Hartmann [29], and Kampe et al. [36], whereas Pierce et al. [68] found no relationship between diurnal stress and SB. Most authors, however, agree that SB patients have an anxious personality and are focused on successful performance [9, 10, 29, 36, 40, 53, 69]. A few neuropsychopharmacological agents, such as L-dopa, neuroleptics, amphetamines, selective serotonin re-uptake inhibitors, and substance abuse, such as cocaine, alcohol, smoking, may play a role in this context [39, 43].

Diagnostic procedures include clinical evaluation, ambulatory monitoring, sleep laboratory investigations and others [37, 42, 46, 47]. The clinical approach comprises the patient's history (reports of tooth grinding, jaw muscle tightness, discomfort, pain, etc.), orofacial examination, and tooth enamel or crown wear classification [33].

As is known for the therapy of sleep disorders in general [78], treatment of SB comprises psychological, somatic, and pharmacological strategies. Psychological approaches consist of explaining SB, sleep hygiene [78], relaxation strategies [26, 61, 67], hypnotherapy [16] and biofeedback [31, 76].

Orodental therapies, including mouth guards or stabilization bite splints, protect orofacial structures from damage, but are discussed controversially regarding SB-related EMG alterations: while Pierce and Gale [67] and Solberg et al. [90] described an improvement, Clark et al. [15] and Okeson [64] found an increase in muscle activity in 20% of hard splint users and 50% of soft splint users. Others reported no change [30, 51]. Splints may therefore be seen as "crutches" or "bumpers" preventing tissue damage rather than showing an effect on SB [18], which may be the reason for low compliance (fewer than 20% of patients use their splints after 1 year). Yustin et al. [97] and Ramfjord and Mich [72] suggested tooth equilibration for reduction of occlusal interference but its efficacy is controversial [14, 44, 65]. Dube et al. [19] found a significant reduction (41%) in the number of SB episodes per hour with both an occlusal splint and a palatal control device.

Drug treatment of SB is controversial as well [95] since dopaminergic, serotoninergic and adrenergic treatment strategies result in a suppression or exacerbation of SB. Studying the effects of two sympatholytic drugs—propranolol and clonidine—Huynh et al. [32] described a lack of significant effects of propranolol on sleep and SB, but a 61% reduction of SB by clonidine, with a prolongation of sleep stage S2 and a reduction of SREM. In our own pilot trial involving the dopamine agonist ropinirole, the benzodiazepine clonazepam and GABAhydroxybutyrate, clonazepam showed the most promising results [77]. Interestingly, clonazepam has been found effective as compared with placebo in the treatment of sleep-related movement disorders such as restless legs syndrome (RLS) and periodic limb movement disorder (PLMD) [83], thereby confirming earlier reports of Matthews [54], Oshtory and Vijayan [66], Coccagna and Lugaresi [17], Montagna et al. [59], and Ohanna et al. [62]. Finally, the pharmacology of clonazepam is characterized by anxiolytic, sleep-promoting, anti-convulsant, mood-stabilizing, and muscle-relaxant effects expected to be of benefit in nonorganic insomnia patients with anxiety and affective disorders. Thus, the aim of the present study was to investigate (1) clinical symptomatology as well as objective and subjective sleep and awakening quality of sleep bruxers as compared with age- and sex-matched normal controls and (2) the acute effect of clonazepam as compared with placebo utilizing polysomnography and psychometry.

Methods

Patients

Twenty-one drug-free middle-aged patients (11 females, 10 males, aged 45.1 ± 12.6 years) suffering from SB (ICD-10: F 45.8) recruited from the Department of Psychiatry and Psychotherapy and the Dental Department of the Medical University of Vienna and the Institute of Sleep Medicine of the Private General Hospital, Rudolfinerhaus, participated in the study. They were compared with 21 sex- and age-matched controls (Z00.6), aged 45.0 ± 12.7 years. The subjects underwent physical, dental, and psychiatric investigations, routine blood examinations, psychometric tests, and neurophysiological screening such as clinical EEG, EEG mapping during daytime and polysomnography at night. Patients fulfilled the inclusion criteria of SB according to the ICSD (306.8): (a) the patient has a complaint of tooth grinding or tooth clenching; (b) one or more of the following occurred: (1) abnormal wear of teeth (all patients had already received splints by their dentists), (2) sounds associated with bruxism, (3) jaw muscle discomfort; (c) polysomnography demonstrates both of the following: (1) jaw muscle activity during sleep; and (2) absence of associated epileptic activity.

As co-morbidity was high, patients demonstrated secondary bruxism rather than the primary form. The study was approved by the Ethics Committee of the Rudolfinerhaus and was performed in accordance with the rules and regulations for the conduct of clinical trials stated in the Declaration of Helsinki (1964), as amended by the World Medical Association General Assembly in Tokyo (1975),

Venice (1983), Hong Kong (1989), Somerset West (1996) and Edinburgh (2000). Informed consent was obtained. Although this was an acute trial with a low dose, patients were alerted to the sedative/muscle-relaxant effects due to the long half-life of clonazepam, specifically in the initial phase of chronic treatment.

Study design

In the single-blind, placebo-controlled, nonrandomized, cross-over study, patients were investigated for three consecutive nights: pre-drug night, placebo night and clonazepam 1 mg night (with both substances given orally at bedtime, 30 min prior to lights out). Due to the long half-life of clonazepam, placebo was given first. The clonazepam data of one patient were lost due to technical problems.

At the time of admission, the patients were required to have been free of psychopharmacological treatment for five times the half-life of the last given psychotropic drug with the potential of influencing the recordings.

The concomitant use of sedatives, propranolol, alpha-methyldopa, antidepressants, tranquilizers, antihistamines, amphetamine containing compounds, narcotic analgesics, anticholinergics or alcohol was prohibited 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 psychoactive medication was allowed. The patients were required not to nap during the day or evening for the duration of the study.

Drug information

Clonazepam, a 5-(0-chlorophenyl)-1,3-dihydro-7-nitro-2H-1,4-benzodiazepine-2-1(RO5-4023), is a potent benzodiazepine registered as an antiepileptic as early as in 1976. Like all benzodiazepines, in addition to its anticonvulsant properties, it also shows anxiolytic, muscle-relaxant and sleep-promoting effects, and thus is not only used as an anticonvulsant in partial or generalized epilepsy (including absence and myoclonus), infantile spasms, status epilepticus and Lennox-Gastaut syndrome [12], but also as a mood-stabilizer in panic disorder, social phobia and obsessive compulsive disorder and in insomnia/anxiety combinations. Clonazepam is the treatment of choice in REM sleep behavior disorder [86], is effective in controlling adult sleep terrors and injurious sleep walking [88], is a recognized treatment in RLS and PLMD [60, 83] and can be beneficial in controlling insomnia [35].

Clonazepam is rapidly absorbed, with a t_{max} of 1–4 h, and has a terminal elimination half-life of 19–42 h (mean 34 h) [11]. Due to the sedative and muscle-relaxant action of clonazepam, side-effects are relatively frequent in the initial phase of chronic treatment and include tiredness, sleepiness, slowed reaction time and respiratory depression, though clonazepam causes less respiratory depression than all the other benzodiazepines [89]. In panic disorder, 1–3 mg per day provides the best balance between benefit and tolerability [75].

In regard to the risk of dosage tolerance, Schenck and Mahowald [87] studied long-term nightly benzodiazepine treatment of injurious parasomnias and other disorders of disrupted nocturnal sleep in 170 adults, 136 of them receiving clonazepam for 3.5 ± 2.4 years. The authors found no significant difference between the initial and the final mean dose: 0.77 mg (±0.46) versus 0.10 mg (±0.96). They concluded that long-term nightly benzodiazepine treatment of injurious parasomnias and other disorders of disrupted nocturnal sleep resulted in sustained efficacy in most cases, with a low risk of dosage tolerance, adverse effects, or abuse. This is in agreement with the statement of Mendelson et al. [55] that in patients without a history of substance abuse, the dependence potential of the currently available hypnotics is minimal. If the drug has to be discontinued for any reason, tapering off is advised (50% reduction of the dose at 5-day intervals), as suggested by Steinberg and Soyka [91].

Measures

Clinical evaluation

The following clinical rating scales were completed on admission of the patients: Pittsburgh Sleep Quality Index (PSQI) [13], Zung Self-Rating Scale for Depression (SDS) [98], Zung Self-Rating Scale for Anxiety (SAS) [99], Epworth Sleepiness Scale (ESS) [34], International Restless Legs Syndrome Study Group Rating Scale (IRLSSG) [94], and Quality of Life Index (QLI) according to Mezzich & Cohen [56, 81].

Objective sleep quality

Polysomnographic all-night recordings were obtained between approximately 10.30 pm (lights-out) and 6.00 am (buzzer or alarm clock). Data were recorded by means of a 20-channel polygraph (Jaeger Sleep Lab. 1000P) including 3 EEG channels (C4-A1, CZ-O2 and C3-A2) according to the 10/20 system, 2 electrooculogram (EOG) channels (left/right), submental myogram (EMG) and tibialis anterior electromyogram from both legs (EMG), nasal and oral airflow, movement of the chest and abdomen, snoring, transcutaneous oxygen saturation, and pulse rate (CRITICARE Pulse Oxymeter 504), as previously described [80,

84, 85]. For evaluation of SB, the jaw masseter, temporalis, and digastric muscles were recorded as well (Fig. 1), were analyzed according to the suggested research criteria of Lavigne et al. [46] and plotted together with the sleep profile and PLM measures over the 7.5 h time in bed.

Respiratory events such as apneas (more than 10 s without nasal or oral flow 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_2 values and average low oxygen saturation were determined automatically by means of SleepLab 1000P software.

PLM parameters were scored visually based on the recommendation of the ASDA Atlas Task Force [7] with the following criteria: (1) an EMG burst length between 0.5 and 5.0 s; (2) a movement amplitude >25% of a calibration movement; (3) an interval of 5–90 s between movements; (4) a minimum number of 4 consecutive movements required for a group of movements to be scored as PLM. PLM indices were subdivided into PLM/h of time in bed (PLM/h TIB), PLM/h of sleep (PLM/h TST), PLM-arousals/h of sleep, PLM/h of REM (PLM/h REM), PLM/h of NON-REM (PLM/h NREM), PLM/h of wake time (PLM/hW).

Arousals were subjected to a computer-assisted classification based on EEG and EMG recordings according to

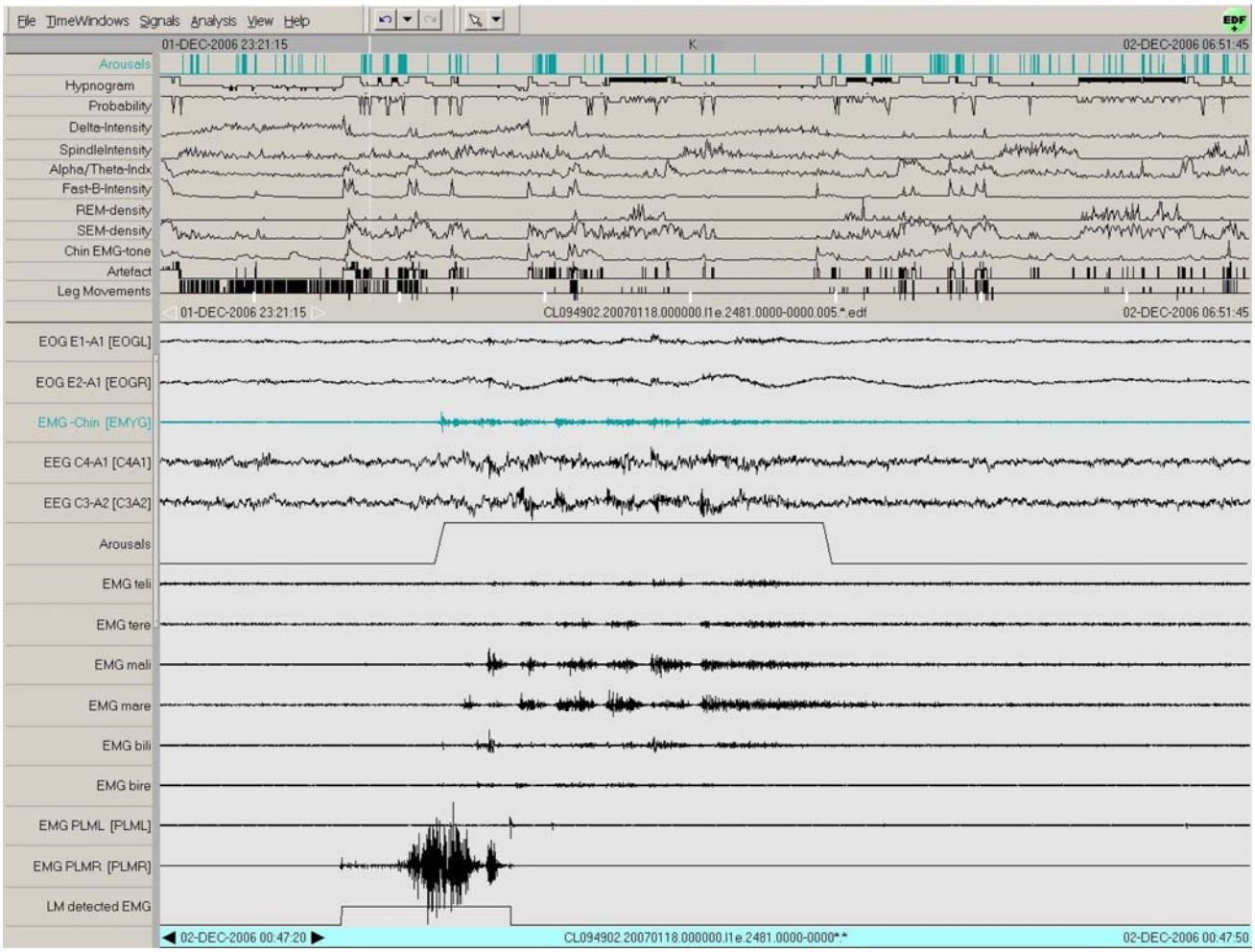

Fig. 1 Example of a 30-s polysomnogram demonstrating one sleep bruxism episode between 00:47:20 and 00:47:50. The 15 polygraphic traces in the *lower part* of the figure demonstrate from the top to the bottom: the left and right electrooculogram (EOG), the submental electromyogram (EMG), the right (C4) and left (C3) central and vertex (CZ) electroencephalogram (EEG), the arousal classification, the left and right temporalis, masseter and biventer muscles, the left and right periodic leg movement (PLM) recordings from the respective anterior tibial muscle and finally the LM detected EMG. In the upper part of the figure the following complex all-night measures are shown: arousals, hypnogram, probability, delta intensity, spindle intensity, alpha/theta index, fast beta intensity, REM density, SEM density, chin EMG tone, artefact and leg movements. Note the relationship between the periodic leg movement, the central arousal and sleep bruxism motor activity

the following rules: minimum frequency change required: 2.5 Hz; minimum frequency level 6 Hz; required amplitude increase 30%; minimal duration 3 s; maximal duration 15 s; EMG ratio for REM 2.0. Subsequently, arousals were visually scored based on the EEG arousal scoring rules published by the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association [4]. For sleep staging, 30-s epochs were scored according to Rechtschaffen and Kales criteria [73], utilizing the automatic sleep classification system Somnolyzer® including standardized quality control by sleep experts [6].

Total sleep time (TST) is the amount of actual sleep time in the total sleep period (TSP). TSP is the period 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 arousals to wakefulness during TST. The frequency of awakenings is the number of awakenings within the total sleep period and the awakening index is the number of awakenings within the TSP per hour of sleep. The frequency of stage shifts is the number of stage shifts within the total sleep period, while the stage shift index is the number of stage shifts within the TSP per hour of sleep. Latencies to different sleep stages are given in minutes and cover the time from lights-out to the first occurrence of a certain sleep stage. REM latency is defined as the time from sleep onset to the first occurrence of stage REM, SWS latency as the time from sleep onset to the first of occurrence of stage 3 or 4. Sleep onset latency is the time from lights-out to the first occurrence of three consecutive epochs of stage 1 or the first occurrence of stage 2. The sleep efficiency index is the proportion of sleep in the recorded period, and it is calculated by dividing TST by the total time in bed (TIB) multiplied by 100.

Subjective sleep and awakening quality/side effects

After awakening, the subjects completed the Self-Assessment of Sleep and Awakening Quality Scale (SSA) [79, 82] consisting of 3 subscales (sleep quality, awakening quality and somatic complaints based on 7, 8 and 5 questions, respectively; questions 8–20 also address treatment side effects). A 100 mm Visual-Analog Scale (VAS) for RLS symptomatology was completed as well. The VAS consisted of a line of 100 mm, on which the patient had to mark his present condition, distinguishing between "no symptoms at all" (left end) and "most severe symptoms" (right end).

Thymopsychic variables (according to Stransky [92], the thymopsyche is the part of our psyche concerned with mood, drive and affect) included subjective well-being in the evening and morning, based on the Von Zerssen Bf-S Scale [93], as well as drive, mood, affectivity and drowsiness in the morning, measured by means of 100 mm VAS.

Objective awakening quality (psychometry)

Morning noopsychic performance tests (according to Stransky [92], the noopsyche involves intellectual and mnestic performance) included the Alphabetical Cancellation Test (Alphabetischer Durchstreichtest = AD) [27] for quantification of attention (AD/total score), concentration (AD/E%; errors in percentage of the total score) and attention variability (AD/SV; difference between extreme scores), the Numerical Memory Test as well as the Fine Motor Activity Test (right and left hand) [27] for evaluation of changes in psychomotor activity and drive. Reaction time, reaction time variability (ms), and errors of omission and commission were determined by the Viennese computer-assisted reaction time apparatus.

Psychophysiological investigations

These included muscular strength of the right and left hand as well as of the right and left index finger and thumb evaluated by means of a vigorimeter (kp/cm^2) [23]. As clonazepam is a benzodiazepine with muscle-relaxant properties, the measures were included for safety evaluations. Evening and morning pulse rates as well as systolic and diastolic blood pressure were also recorded.

Biometric planning and statistics

The sample size was calculated to be 20 based on a previous bruxism study [77], with the standard deviation of the bruxism index at 5.2, a clinically relevant difference between clonazepam and placebo at 3, $\alpha = 0.05$ and $\beta = 0.20$.

Statistical analysis was based on the concept of descriptive data analysis (DDA), as proposed by Abt [1] and Ferber et al. [22] for controlled clinical trials, which allows one confirmatory statement on a pre-selected variable based on previous findings [77]. The pre-selected null hypothesis was that there were no differences between clonazepam 1 mg and placebo in terms of the primary target variable—the bruxism index (bruxism episodes/h of sleep) (maximum error probability $\alpha = 0.05$). All other effects were tested descriptively.

Due to the nature of the variables under study, non-parametric statistical analyses were applied. The Wilcoxon signed ranks test was used for within-group comparisons; differences between bruxism patients and normal controls were calculated based on the Mann–Whitney U test.

The null hypotheses were there are no differences between clonazepam and placebo nights and no differences between bruxism patients and controls (error probability = 0.05).

Results

Clinical findings

Diagnostic evaluation (ICD-10) based on clinical and sleep laboratory investigations demonstrated high comorbidity. Out of 21 sleep bruxers, 17 were suffering from movement disorders: 9 from restless legs syndrome (G25.8) and 8 from periodic leg movements during sleep (G25.3). Nonorganic sleep disorders (F51) were observed in 19 patients: 18 showed nonorganic insomnia, 1 nonorganic hypersomnia and 4 nightmares. Organic sleep disorders were observed in seven cases: sleep apnea in one patient and primary snoring in six patients.

Sleep bruxism showed also a high comorbidity with psychiatric disorders such as neurotic, stress-related, and somatoform disorders (F40-F48) in 15 patients and affective disorders (F30-F39) in 6 patients. Within the F4 group, adjustment disorders (F43.2) were by far the leading diagnostic group (*n*: 10).

Self-ratings of the patients on admission demonstrated an increased Pittsburgh Sleep Quality Index (PSQI) of 10.5 ± 4.2 as compared with normal controls (3.0 ± 1.8), which reflects a disorder of sleep initiation and maintenance (DIMS) in the last 4 weeks. The Zung Self-Rating Scale for Depression (SDS) showed a mean value of 40.9 ± 9.9, suggesting a slight depressive syndrome as compared with controls (27 ± 4.1). The Zung Self-Rating Scale for Anxiety (SAS) yielded a mean value of 35.8 ± 7.5, suggesting a slight anxiety syndrome as compared with controls (24.9 ± 3.8). The Epworth Sleepiness Scale (ESS) demonstrated a mean value of 8.8 ± 6.8, suggesting only marginally increased daytime sleepiness as compared with controls (5.9 ± 2.2). The mean value of the International Restless Legs Syndrome Study Group rating scale was 6.3 ± 7.8, suggesting a slight increase in restless legs symptomatology as compared with controls (0). Finally, the Quality of Life Index according to Mezzich and Cohen was slightly deteriorated with 7.2 ± 1.3 as compared with controls (8.2 ± 0.9).

Polysomnographic findings

Confirmatory statistics—bruxism index

Confirmatory statistics on the target variable, the bruxism index, demonstrated a significant ($P < 0.01$, Wilcoxon) improvement from 7.2 ± 4.9/h of sleep under placebo to 4.2 ± 2.6 under 1 mg clonazepam (Fig. 2). The overall percentage improvement after acute administration of 1 mg clonazepam was 41.7 ± 14.8% as compared with placebo (calculated on individual change values).

Descriptive statistics

Objective sleep quality—sleep initiation and maintenance

As compared with normal controls, sleep bruxers showed no significant difference in sleep initiation but significantly deteriorated sleep maintenance, i.e. total sleep period and total sleep time (Table 1). Sleep efficiency was nonsignificantly reduced to 83% as compared with 89% in controls.

Acute administration of 1 mg clonazepam induced a significant improvement in almost all sleep initiation and maintenance variables and a significant increase in sleep efficiency to 93% (Table 1).

Objective sleep quality—sleep architecture

As compared with normal controls, SB patients demonstrated a significantly increased movement time and an increased stage shift index but apart from that no significant differences in S1, S2, S3 + 4 and SREM% (Table 2). Acute administration of 1 mg clonazepam resulted in a significant reduction of the stage shift index and S1% (Table 2).

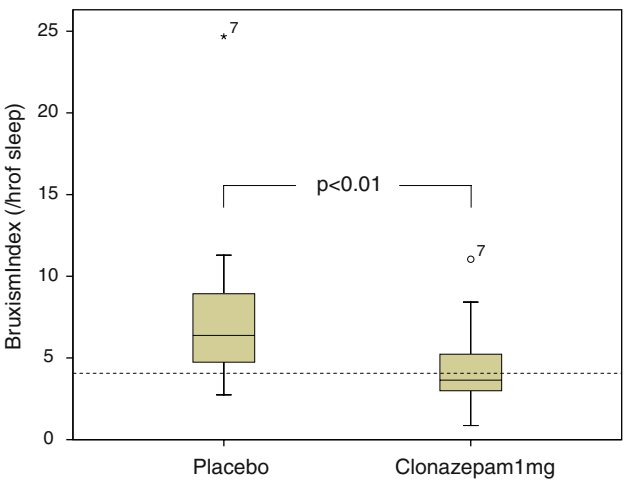

Fig. 2 Improvement of the sleep bruxism index after acute bedtime administration of 1 mg clonazepam as compared with placebo ($P < 0.01$, Wilcoxon, *n*: 20) and normal values

Table 1 Sleep initiation and maintenance in sleep bruxers (n:21) as compared with controls (n:21) and acute effects of 1 mg clonazepam (n:20)

Variables	Controls (C)	Sleep bruxers (SB)	
		Placebo (P)	Drug (D)
Latency to S1 (min) ↓	14.5 ± 19.3	15.8 ± 18.4	7.9 ± 6.7*
Latency to S2 (min) ↓	21.6 ± 22.0	22.3 ± 23.3	13.8 ± 16.0*
Latency to S3 (min) ↓	40.7 ± 31.1	45.1 ± 30.2	37.2 ± 30.8
Latency to S4 (min) ↓	61.4 ± 52.9	46.7 ± 29.4	41.8 ± 31.3
Latency to REM (min) ↓	93.2 ± 33.5	113.0 ± 70.0	95.3 ± 47.5
Lights out to sleep onset ↓	15.6 ± 19.5	16.8 ± 17.9	9.7 ± 8.2*
Lights out to 10 min. continuous sleep ↓	17.6 ± 21.6	24.7 ± 26.2	14.1 ± 17.8**
Wake within TSP (min) ↓	35.7 ± 34.7	51.1 ± 52.9	18.6 ± 22.2**
Wake after final awakening (min) ↓	3.5 ± 5.1	3.5 ± 11.3	0.6 ± 1.1
Awakenings (n) ↓	16.0 ± 9.4	13.0 ± 6.2	8.4 ± 5.3**
Awakening index (n/h of sleep) ↓	2.3 ± 1.4	2.4 ± 1.3	1.2 ± 0.8**
Wake after sleep onset (min) ↓	38.0 ± 38.8	54.0 ± 61.0	17.7 ± 19.1**
Total sleep period (TSP) (min) ↑	457.9 ± 34.0$^{\diamond\diamond}$	427.7 ± 28.9	442.2 ± 10.3**
Total sleep time (TST) (min) ↑	420.4 ± 42.1$^{\diamond\diamond}$	372.0 ± 71.3	419.1 ± 22.6**
Sleep efficiency (%) ↑	88.7 ± 8.3	83.3 ± 15.9	93.0 ± 5.0**

↑↓ Direction of improvement
$^{\diamond}$ $P < 0.05$, $^{\diamond\diamond}P < 0.01$ (P vs. C, Mann–Whitney U test); * $P < 0.05$, ** $P < 0.01$ (P vs. D, Wilcoxon signed ranks test)

Table 2 Sleep architecture in sleep bruxers (n:21) as compared with controls (n:21) and acute effects of 1 mg clonazepam (n:20)

Variables	Controls (C)	Sleep bruxers (SB)	
		Placebo (P)	Drug (D)
Sleep stage 1 (%)	9.0 ± 4.2	7.5 ± 3.6	4.3 ± 3.1**
Sleep stage 2 (%)	52.0 ± 11.2	55.0 ± 9.0	57.3 ± 7.7
Sleep stage 3 (%)	9.9 ± 3.9$^{\diamond}$	7.1 ± 3.8	9.0 ± 5.3**
Sleep stage 4 (%)	6.3 ± 6.6$^{\diamond}$	11.2 ± 8.3	9.9 ± 7.4
Sleep stage 3 + 4 (%)	16.3 ± 7.3	18.3 ± 8.8	19.0 ± 7.9
Sleep stage REM (%)	22.8 ± 6.8	19.3 ± 6.4	19.4 ± 5.5
Movement time (min)	1.8 ± 1.3$^{\diamond\diamond}$	4.5 ± 3.2	4.4 ± 1.9
Sleep onset to SWS	25.1 ± 24.4	29.0 ± 22.9	27.5 ± 27.3
Rem latency (min)	77.6 ± 24.4	97.7 ± 63.2	85.6 ± 48.8
Stage shifts (n)	126.6 ± 22.7	127.2 ± 33.0	121.8 ± 30.6
Stage shift index (n/h of sleep)	18.3 ± 4.3$^{\diamond}$	21.0 ± 5.1	17.5 ± 4.4**

$^{\diamond}$ $P < 0.05$, $^{\diamond\diamond}P < 0.01$ (P vs. C, Mann–Whitney U test); * $P < 0.05$, ** $P < 0.01$ (P vs. D, Wilcoxon signed ranks test)

Objective sleep quality—respiration and periodic leg movements

The respiratory indices such as the apnea index (AI), apnea–hypopnea index (AHI) and desaturation index (DI) were within normal limits in all recordings (Table 3).

Periodic leg movements during the total time in bed (TIB) were significantly elevated in bruxers as compared with controls and decreased nonsignificantly under clonazepam (Table 3). The PLM index during wake time was increased in bruxers as compared with controls and was decreased significantly under clonazepam. The PLM indices per TIB and TST were significantly elevated in SB patients as compared with controls, but did not change under clonazepam 1 mg. Arousals were reduced in bruxers as compared with controls. Clonazepam induced a further decrease in the arousal index (Table 3).

Subjective sleep and awakening quality/side effects and thymopsyche

As compared with normal controls, in the SSA, SB patients demonstrated a significantly deteriorated subjective sleep and awakening quality and total score, with subjective sleep quality improving significantly under the acute dose of 1 mg clonazepam (Table 4).

Regarding the thymopsyche, well-being in the evening and morning was significantly deteriorated in SB patients as compared with controls, as were drive, mood, and wakefulness in the morning (Table 4). Under acute

Table 3 Respiratory variables, periodic leg movements (PLM) and arousals in sleep bruxers (*n*:21) as compared with controls (*n*:21) and acute effects of 1 mg clonazepam (*n*:20)

Variables	Controls (C)	Sleep Bruxers (SB)	
		Placebo (P)	Drug (D)
Apnea index (*n*/h of sleep)	0.6 ± 1.2	0.6 ± 1.1	0.5 ± 0.4
Apnea–hypopnea index (*n*/h of sleep)	1.7 ± 2.5	2.0 ± 2.5	2.2 ± 1.9
Desaturation index (*n*/h of sleep)	1.7 ± 3.5	1.2 ± 1.7	1.3 ± 1.3
Periodic leg movements (total *n*/TIB)	36.6 ± 28.6$^{\diamond\diamond}$	129.1 ± 127.8	117.7 ± 147.6
Periodic leg movements (total *n*/TST)	13.2 ± 12.3	55.7 ± 62.2	77.4 ± 120.8
Periodic leg movements (total *n*/wake)	21.9 ± 20.7	64.0 ± 86.5	37.4 ± 65.2**
PLM index—TIB (*n*/h of TIB)	4.6 ± 3.4$^{\diamond\diamond}$	16.5 ± 17.0	15.7 ± 19.7
PLM index—TST (*n*/h of TST)	1.8 ± 1.6$^{\diamond}$	10.6 ± 13.6	11.2 ± 17.2
PLM index—wake (*n*/h of wake)	28.3 ± 21.0	44.3 ± 30.3	61.3 ± 58.4
Arousals—total (*n*)	157.9 ± 43.7$^{\diamond\diamond}$	116.8 ± 54.4	106.8 ± 46.2
Arousal index (*n*/h of sleep)	22.8 ± 6.7$^{\diamond}$	19.2 ± 8.7	15.3 ± 6.7*
Arousals with PLM	1.2 ± 3.2	5.2 ± 7.0	8.2 ± 16.6
Other arousals	110.4 ± 36.2$^{\diamond\diamond}$	77.1 ± 39.3	67.4 ± 32.3

$^{\diamond}$ $P < 0.05$, $^{\diamond\diamond}P < 0.01$ (P vs. C, Mann–Whitney U test); * $P < 0.05$, ** $P < 0.01$ (P vs. D, Wilcoxon signed ranks test)

Table 4 Subjective sleep/awakening quality and thymopsychic measures in sleep bruxers (*n*:21) as compared with controls (*n*:21) and acute effects of 1 mg clonazepam (*n*:20)

Variables	Controls (C)	Sleep Bruxers (SB)	
		Placebo (P)	Drug (D)
Sleep quality (score) ↓	10.7 ± 3.1$^{\diamond\diamond}$	14.7 ± 4.0	10.4 ± 3.8**
Awakening quality (score) ↓	10.3 ± 2.5$^{\diamond\diamond}$	18.0 ± 3.9	17.1 ± 4.1
Somatic complaints (score) ↓	5.3 ± 0.6	6.0 ± 1.4	6.2 ± 1.6
SSA-total (score) ↓	26.3 ± 4.8$^{\diamond\diamond}$	38.6 ± 6.9	33.7 ± 8.0**
Well-being evening (score) ↓	9.1 ± 7.3$^{\diamond}$	16.3 ± 11.5	13.2 ± 7.8
Well-being morning (score) ↓	6.5 ± 6.4$^{\diamond\diamond}$	19.1 ± 10.6	14.5 ± 9.7
Drive (mm) ↓	21.5 ± 15.9$^{\diamond\diamond}$	56.4 ± 24.1	48.3 ± 27.6
Mood (mm) ↑	78.2 ± 11.8$^{\diamond}$	67.7 ± 17.3	67.8 ± 17.0
Affectivity (mm) ↑	77.8 ± 13.5	70.1 ± 19.3	71.3 ± 20.1
Drowsiness (mm) ↓	21.6 ± 14.5$^{\diamond\diamond}$	62.5 ± 23.7	57.6 ± 24.9

↑↓ Direction of improvement
$^{\diamond}$ $P < 0.05$, $^{\diamond\diamond}P < 0.01$ (P vs. C, Mann–Whitney U test); * $P < 0.05$, ** $P < 0.01$ (P vs. D, Wilcoxon signed ranks test)

administration of 1 mg clonazepam, there were no significant thymopsychic changes as compared with placebo.

Objective awakening quality and noopsyche

As compared with normal controls, sleep bruxers showed a significant deterioration in attention variability, numerical memory, and fine motor activity (Table 5). There were no changes after clonazepam as compared with placebo, with the exception of a significant improvement of fine motor activity (Table 5).

Psychophysiological measures

Psychophysiological measures, such as pulse rate, systolic and diastolic blood pressure, did not show any statistically significant differences between sleep bruxers and controls, with the exception of the pulse rate in evening and morning, which was decreased in patients. Clonazepam did not influence any psychophysiological measures as compared with placebo.

Discussion

Our sleep laboratory study demonstrated that a group of middle-aged sleep bruxers indeed showed significant aberrations from the norm about some subjective and objective sleep and awakening quality measures, which improved significantly by acute oral administration of clonazepam. The target variable (sleep bruxism index) improved by 1/3 as compared with pre-treatment values. Based on descriptive data analysis with one confirmatory statement according to Abt [1] and Ferber et al. [22], the

Table 5 Noopsychic performance in the morning in sleep bruxers (n:21) as compared with controls (n:21) and acute effects of 1 mg clonazepam (n:20)

↑↓ Direction of improvement
$^{\diamond}$ $P < 0.05$, $^{\diamond\diamond}P < 0.01$ (P vs. C, Mann–Whitney U test); * $P < 0.05$, ** $P < 0.01$ (P vs. D, Wilcoxon signed ranks test)

Variables	Controls (C)	Sleep Bruxers (SB)	
		Placebo (P)	Drug (D)
Attention (score) ↑	550.7 ± 123.9	524.1 ± 105.8	511.8 ± 103.0
Concentration (% errors) ↓	3.4 ± 2.4	4.0 ± 3.0	4.5 ± 2.9
Attention variability (score) ↓	12.1 ± 3.4$^{\diamond\diamond}$	16.4 ± 4.4	15.3 ± 4.3
Numerical memory (n) ↑	6.9 ± 1.3$^{\diamond\diamond}$	4.9 ± 2.0	4.6 ± 1.9
Fine motor activity RI ↑	47.2 ± 10.9$^{\diamond\diamond}$	39.2 ± 7.7	42.3 ± 8.0*
Fine motor activity LE ↑	36.8 ± 9.8	35.0 ± 6.9	34.2 ± 8.7*
Fine motor activity RI + LE ↑	84.0 ± 20.1	74.2 ± 12.5	76.4 ± 14.6*

improvement was found to be both clinically and statistically relevant. Intriguingly, most bruxers also exhibited a nocturnal movement disorder such as RLS or PLMD, which is interesting in the light of the recent change in the ICSD-2 categorization of bruxism from parasomnia to nocturnal movement disorder. On the other hand, our clinical data make it understandable that in the ICD-10, sleep bruxism is listed in the chapter of mental disorders (F45.8), as 9 out of 10 patients showed psychiatric comorbidity such as adjustment disorders, anxiety or affective disorders. Clonazepam was chosen because of its benzodiazepine-inherent pharmacological properties, i.e. anxiolytic, sleep-promoting, muscle-relaxant and anticonvulsant effects. Concerning the latter, it is conceivable that the drug exerts its therapeutic action also by its anti-arousal properties as Lobbezoo and Naeije [49] and Lavigne et al. [45] pointed out that bruxism may be triggered by central arousals. Finally yet importantly, clonazepam was found effective in nocturnal movement disorders such as RLS and PLMD in doses of 1 mg [83].

Our baseline clinical evaluations demonstrated that SB is indeed a disorder at the crossroads of dental medicine, somnology, psychiatry, and neurology. As revealed by the PSQI, SB patients suffer from a disorder of initiating and maintaining sleep, which results in a slight increase in daytime sleepiness (seen in the ESS) and a deterioration of quality of life (QLI). The slightly elevated depression and anxiety scores may be partly due to comorbidities including affective and anxiety disorders, which, however, in clinical psychiatry settings, generally reveal much higher SAS and SDS scores. Nevertheless, the increased anxiety and depression scores do speak for the decision to place SB in the F4 chapter on "Neurotic, Stress-Related and Somatoform Disorders". On the other hand, the IRLSSG score—although only mildly elevated in SB patients—substantiates the clinically diagnosed movement disorder. Interestingly, another F4 chapter disorder with a comorbid nocturnal movement disorder is somatoform pain disorder (F45.4), which revealed RLS in 71% of the patients suffering from continuous pain [2]. It is noteworthy that in our studies, untreated RLS and PLMD patients also showed slightly elevated SAS and SDS scores, which at the neurophysiological level were accompanied by EEG maps resembling those found in depression and anxiety [80].

The subjective sleep disorder of SB patients was objectified by polysomnography, which—apart from an increased bruxism index—showed a decreased total sleep period and total sleep time, an increased stage shift index, movement time, periodic leg movements and PLM indices as well as a decreased arousal index. The latter is not easily understood, as one would expect an increased arousal index in the patients. However, in clinical/dental practices, teeth clenching is sometimes actively induced during daytime in order to reduce sleep problems at night, thus also decreasing arousals, which are further reduced by anticonvulsants. After acute administration of 1 mg clonazepam as compared with placebo, a statistically significant decrease in the bruxism index as well as an improvement of subjective and objective sleep quality were observed. Periodic leg movements improved as well, which confirms our previous studies in RLS and PLMD patients with the same compound [83].

The decrease in the bruxism index is in as much of clinical interest as up to now pharmacological interventions have been inconclusive. With L-dopa Lobbezoo et al. [50] showed a modest (approximately 30%) but significant reduction in SB-related motor activity. On the other hand, Micheli et al. [57] reported increased tooth-grinding in schizophrenics treated with the antidopaminergic haloperidol. Later, controlled studies with the modest DA agonist bromocriptine did not show any effects in SB [48]. In a recent controlled study with 120 mg propranolol, Huynh et al. [32] did not find a significant effect on SB. The role of serotonin in the pathophysiology of SB is also unclear. SSRIs, such as fluoxetine, sertraline, fluvoxamine, and paroxetine, have been associated with tooth clenching or tooth grinding [20, 24, 70]. In contrast, tryptophan, a 5HT precursor, and the classical modest serotonin reuptake inhibitors, such as amitryptiline or its metabolites, neither exacerbated nor attenuated SB [21, 58, 71]. Recently,

Huynh et al. [32] described that 0.3 mg clonidine, an alpha-2 receptor agonist that causes central sympathetic nervous system depression, reduced the average sleep bruxism index, and burst index by 61 and 73%, respectively. While these results support the role of sympathetic activity in the pathophysiology of SB, as advocated by Lobbezoo and Naeije [49], the decrease in morning blood pressure in 19% of the patients requires further research on the safety of clonidine in SB. A further problem with clonidine is the suppression of REM sleep in 14 out of 16 patients. In contrast, in our present study, clonazepam left sleep stages unchanged, except for a decrease in S1 and the stage shift index. As one would expect from an anticonvulsant, the arousal index during sleep was decreased. The PLM index during wake was decreased as well.

As far as subjective sleep and awakening quality in the present study is concerned, SB patients demonstrated a significant deterioration as compared with controls, which was normalized after acute administration of 1 mg clonazepam. Well-being in the evening and morning, drive, mood, and wakefulness were also significantly deteriorated in SB as compared with controls, with the amelioration after 1 mg clonazepam not reaching the level of statistical significance.

In morning noopsychic performance, we observed a decrement in sleep bruxers, which reached the level of statistical significance in attention variability, numerical memory, and fine motor activity of the right hand. Acute clonazepam 1 mg resulted in an improvement of psychomotor activity as compared with placebo. Psychophysiological variables showed a decreased pulse rate in SB, but no changes after clonazepam.

Our psychometric findings speak for a good tolerability of acutely administered clonazepam in sleep bruxers, which, however, has to be proved in long-term trials as well. As with all benzodiazepines, patients have to be alerted to habituation phenomena and a certain risk of dependence. However, the dependence risk is rather small, as was pointed out by Schenck and Mahowald [87]. Clonazepam has now been on the market for three decades and has been prescribed as anticonvulsant and thymoprophylactic agent and used in RLS and PLMD since the late 1970s and 1980s [17, 54, 59, 62, 66, 83]. The present patient sample may indeed be regarded as a suitable target group of clonazepam as sleep bruxers demonstrate a high comorbidity with both nocturnal movement disorders and nonorganic insomnia associated with mental disorders. However, this postulation has to be proved in double-blind, placebo-controlled, randomized cross-over and parallel-group studies involving clinical, psychometric, polysomnographic, and dental evaluation methods.

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