Polysomnographic Effects of Adjuvant Ginkgo Biloba Therapy in Patients with Major Depression Medicated with Trimipramine[1]

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Sleep disturbance and cognitive impairment are frequent complaints of depressed patients under standard antidepressant medication. Therefore, additional therapies are required which specifically focus on the improvement of these deficits without exerting major side effects. Ginkgo biloba extract (EGb) has been shown to improve cognitive abilities in elderly subjects and in patients with disorders of the dementia spectrum. Animal studies surmise that EGb may reduce CRH activity, which is substantially related to depressive mood and behavior, predominantly cognition and sleep. An open non-randomized pilot study has been conducted to investigate the effects of ginkgo biloba extract (EGb Li 1370) on cognitive performance and sleep regulation in depressed inpatients. 16 patients were treated with a trimipramine (T)-monotherapy (200 mg) for six weeks. In eight of the 16 patients, an adjunct EGb therapy (240 mg/d) was applied for four weeks after a baseline week, the other eight patients remained on trimipramine monotherapy (200 mg) during the entire study. Polysomnography, cognitive psychomotor performance and psychopathology were assessed at baseline, after short-term and long-term adjunct EGb treatment, and after one week of ginkgo discontinuation (at the respective evaluation times in the eight patients on T-monotherapy). This report focuses on the results of EGb on sleep EEG pattern. EGb significantly improved sleep pattern by an increase of sleep efficiency and a reduction of awakenings. In addition, sleep stage 1 and REM-density were reduced, while stage 2 was increased. Non-REM sleep, predominantly slow wave sleep in the first sleep cycle, was significantly enhanced compared to trimipramine monotherapy. Discontinuation of EGb reversed most of these effects. Based on the animal data, these results suggest that EGb may improve sleep continuity and enhance Non-REM sleep due to a weakening of tonic CRH-activity. The compensation of the deficient Non-REM component in depression by the EGb application may provide a new additional treatment strategy, especially in the treatment of the depressive syndrome with sleep disturbance.

Introduction

Depressed mood, cognitive impairment and sleep disturbance are cardinal symptoms of major depression. Besides the specific psychopathology and cognitive impairment, distinct neurobiological symptoms have been described in major depression. The most robust neurobiological findings in depression are the neurophysiological alterations of sleep pattern [7,46,47] and the neuroendocrine dysregulation of the hypothalamus-pituitary-adrenal (HPA) axis due to an exaggerated secretion of corticotropin-releasing hormone (CRH) [21].

A disturbance of sleep continuity, decreased slow wave sleep, shortened REM latency and increase of the first REM episode length and of REM-density (rapid-eye movement during REM sleep) are well established polysomnographic findings reflecting the underlying neurobiological disturbance in severe depression [7,30,46,47]. The slow-wave sleep (SWS) deficit, which remains after antidepressant therapy even in remitted patients [54] has been suggested as reflecting a biological scar of depression probably being a vulnerability factor for relapse [29].

Mood, sleep and cognition are differently affected by various classes of antidepressants. While most of the traditional antidepressants, such as tri- and tetracyclics, improve sleep [9] and worsen cognitive performance due to their sedative properties [8,11], antidepressants of the second and third generation, e.g. selective serotonine reuptake inhibitors (SSRIs) do not detrimentally affect cognition [18]; however, most of them exert sleep disturbing effects, at least at the beginning of treatment [49,50]. A common disadvantage of all antidepressants, including also most of the newer ones, is the latency of onset of antidepressant action [38]. Even after the elevation of mood during antidepressant therapy, sleep disturbance and cognitive impairment may be remaining symptoms of depressed patients. In addition, both symptoms were predominantly observed in subjects with sub-threshold depression [23], which is frequently found in partially remitted patients and closely related to an increased risk for relapse [24].

Therefore, specific additional therapies providing a rapid and sustained improvement of both symptoms, sleep disturbance and cognitive impairment without major side effects are required.

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Preparations of extracts from ginkgo biloba leaves have been used therapeutically for centuries. Ginkgo biloba extracts (EGb) have been shown to improve cognitive abilities in healthy subjects [60] and patients with diseases of the dementia spectrum without exerting anticholinergic and serotonergic side effects [26, 28, 40]. Currently, EGb is predominantly used in the treatment of cognitive disorders of older age of the vascular, degenerative or mixed type [19, 26, 32].

EGb has thus far not been applied to patients with major depression. However, due to the observed beneficial effects of EGb, an additional improvement of cognitive dysfunction in depression may be expected.

An open pilot study has been conducted in order to evaluate the effects of an additional application of ginkgo biloba extract Li 1370 (EGb) for four weeks on cognitive performance in depressed patients who were on a constant standard medication of trimipramine.

No data on the effects of EGb on polysomnographic parameters are as yet available, either in healthy volunteers or in depressed patients.

Because there is a substantial amount of sleep research reporting a close relationship between cognitive performance and sleep, especially REM sleep (*Karni* et al 1994, *Smith* et al. 1996, *Kavanau* 1997, *Hemmeter* et al 1998) [17, 25, 27, 52], we were also interested in monitoring sleep in order to find out whether ginkgo biloba extract Li 1370 (EGb) is able to exert beneficial effects on polysomnographic sleep variables in depressed patients, thus testing for the neurobiological effects of EGb.

In this paper, we focus on the acute (one week) and long-term (four weeks) effects of the additional treatment with EGb on polysomnographic variables during a standardized antidepressant medication of trimipramine with constant dosage.

Methods

Subjects

Eight patients (5 men, 3 women, age 44.8±8.5 years) with the diagnosis of a major depressive episode according to DSM-III-R (American Psychiatric Association, 1987) were consecutively enrolled in the study. To rule out any medical illness, clinical and laboratory investigations, including clinical chemistry, blood count, electroencephalogram, electrocardiogram and evaluation of endocrine status were performed. Possible intake of any hormone replacement therapy, such as thyroid hormones or estrogens, was carefully ruled out. Patients under treatment with long-acting benzodiazepine or fluoxetine medication could be included after a period of four weeks after cessation.

All patients were switched to a standard medication of 200 mg/d trimipramine at least one week before the start of the study. No other psychotropic medication was allowed during the entire study phase except chloralhydrate (500 to 1000 mg) for the treatment of sleep complaints, but not within two days prior and the day of polysomnographic recordings.

The results of the patients additionally treated with ginkgo biloba extract Li 1370 (EGb) were compared with a control group matched by gender and age (5 men, 3 women, age 49.5±9.7), which was selected from a previous study sample (Holsboer-Trachsler et al 1994).

Informed consent was signed by all patients after the purpose and the procedure of the study had been explained. The protocol had been approved by the local ethical committee.

Medication

Trimpramine is a well established atypical tricyclic antidepressant, which in addition to its affinity to noradrenergic and serotonergic receptors, also affects dopaminergic and histaminergic neurotransmission). The selection of trimipramine for the treatment of all patients is based on two considerations:

1. The substance is well known, safe and has sedative properties [3, 48], which is necessary for the treatment of agitated depressed states without the application of benzodiazepines.
2. Trimipramine is one of the rare antidepressants which do not exert major effects on sleep architecture, particularly it does not suppress REM sleep. Thus, variation of sleep pattern due to further stimulations can be studied well under constant trimipramine medication [16, 17, 55, 58, 59].

Ginkgo biloba extract Li 1370 (EGb) is a dried extract from ginkgo biloba leaves without the addition of concentrates, which is characterized by 22 – 27% ginkgo flavone glycosides, 5 – 7% terpenes including 2.8 – 3.4% ginkgolides A, B and C and 2.6 – 3.2% bilobalide and less than 5 ppm ginkgol acids. The intervals mentioned refer to differences in production and analyses of the substance. The selected dosage of 240 mg/d (2 x 120 mg EGb, morning and evening application) is based on the experience in previous studies in patients with milder forms of dementia, in which this dosage has proved to be well tolerated and efficient (See *Maurer* et al. 1997 [36]).

*Protocol (Fig. **1**)*

At the start of the study and during the first week, all patients were on a constant monotherapy with 200 mg/d trimipramine in order to obtain a stable baseline condition for the determination of the various neurobiological and neuropsychological investigations. These included measurements of polysomnography and cognitive psychomotor performance. From day 8 (begin of week 2) until day 35 (end of week 5), the patients of the experimental group received 240 mg/d EGb for four weeks, while therapy with 200 mg/d trimipramine had been kept constant until the end of the study (week 6).

In week 2, acute – and in week 5, long-term effects of additional EGb application on the psychometric, neuropsychological and polysomnographic parameters were assessed. After discontinuation of EGb at the end of week 5, all patients remained on a monotherapy of 200 mg trimipramine during week 6, in order to assess possible effects of EGb discontinuation.

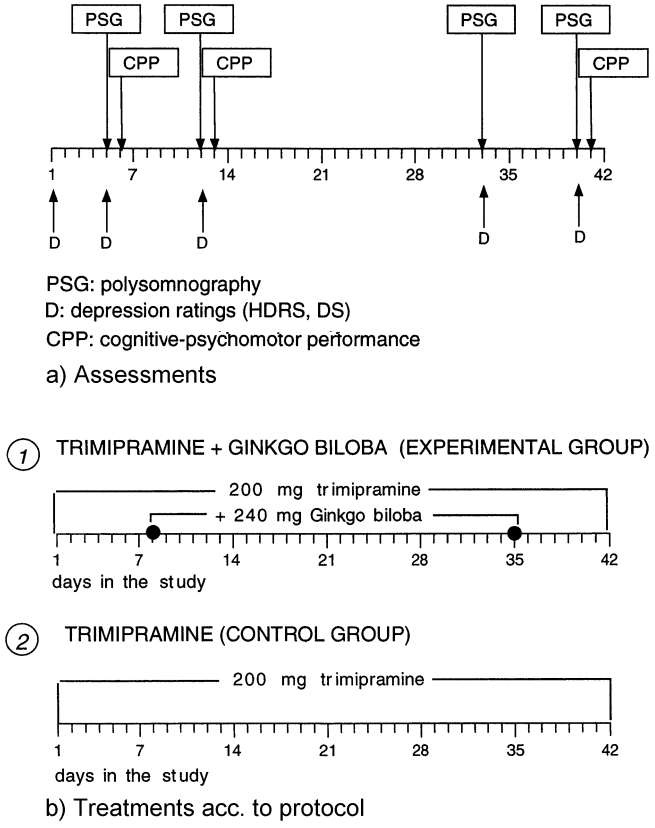

Fig. 1 Study design.

Polysomnographic measurements

The first polysomnographic examination, including one adaptation night, took place at the end of the baseline week (day 5 of the study). Further sleep EEGs were registered after 5 days (day 12) and four weeks (day 33) of the additional EGb therapy and 5 days after termination of EGb (day 40) to assess effects of EGb discontinuation. All sleep EEGs were recorded between 11 p.m. and 7 a.m. by means of standard procedures – horizontal electrooculogram (EOG), sub-mental electromyogram (EMG), electroencephalogram (EEG, C3-A2; C4-A1; C3-C4) and electrocardiogram (ECG). The records were scored under blind conditions by two experienced raters according to standardized criteria [45]. The sleep parameters were analyzed according to the definitions in the standard program described by *Lauer* et al. 1991 [30].

Assessment of depressive symptomatology

Severity of depression was assessed at the days of sleep recordings with the 17-item version of the Hamilton rating scale for Depression (HDRS) [15]. In addition, self-ratings were completed by the patients on the Depression-Scale (DS) [61].

Data analysis

Statistical evaluation of the data was carried out by 1) descriptive statistics (median, mean and standard deviation) and 2) by the application of Mann Whitney U-tests used for the assessment of differences between sleep measures in the experimental group (four weeks of additional EGb to trimipramine monotherapy) and the control group (trimipramine monotherapy for six weeks).

This method was performed due to the small sample size and the lack of normal distribution of the used dependent sleep variables.

For the evaluation of the effects of the additional therapy with EGb, we decided to follow two approaches – first, the estimation of a global effect of EGb, and second, the evaluation of the effect of EGb withdrawal for one week.

For the analysis of the global effect of the additional EGb application compared to trimipramine monotherapy, summary measures were used according to *Matthews* et al. [35]. For both groups, baseline summary measures were computed by summing up the values for week 1 (baseline week) and week 6. In these periods both groups were treated only with trimipramine. A second summary measure was computed by adding the values of week 2 and week 5. In this period, the experimental group was exposed additionally to EGb, whereas the control group remained on the trimipramine monotherapy. In the next step, the differences between both summary measures [(week 2 + week 5) – (week 1 + week 6)] were computed. Experimental and control group were compared by using these differences in Mann Whitney U-tests as suggested by *Bortz* et al. 1990 [5] for the analysis of interaction effects. Test statistics and exact one sided *p*-values were calculated by the statistical program StatXact 4.01 (*Nikita* and *Patel* 1999).

The second approach represents the separate analysis of the withdrawal effect of EGb in week 6, well aware of the multiple comparison problem. However, due to the design of this study, which additionally allowed us to gain this information, we believe that this strategy is justified for additional support of the effects detected in the analysis of the global effect of the additional EGb treatment. The differences of the sleep variables between week 5 (last measurement of the patients in the experimental group under EGb, control group under monotherapy of trimipramine) and week 6 (all patients on monotherapy with trimipramine) were computed and analyzed by Mann-Whitney U-tests as described above, allowing an estimation of the interaction effect between the grouping variable and time of treatment [5]. The exact one-sided *p*-values were reported for U-values greater, less or equal than the observed test value. An alpha level of 0.05 is reported as significant, and of 0.10 as a trend.

Results

Ratings of depressive symptomatology and demographics

Both groups had improved HDRS-ratings from baseline to day 12 ($\cong$ one week of additional EGb treatment); trimipramine group: 25.00 ± 6.52 (day 5) vs. 17.50 ± 10.29 (day 12); EGb group: 23.50 ± 6.59 (day 5) vs. 17.37 ± 6.73 (day 12). In contrast to the trimipramine group, which improved continuously until the end of treatment (9.12 ± 10.23, day 35), the EGb treated patients did not improve further with their HDRS scores (19.87 ± 8,22, day 35). A comparable pattern emerged in DS self ratings (trimipramine: 23.6 ± 13.48 (day 5), 17.13 ± 16.82 (day 12), 14.75

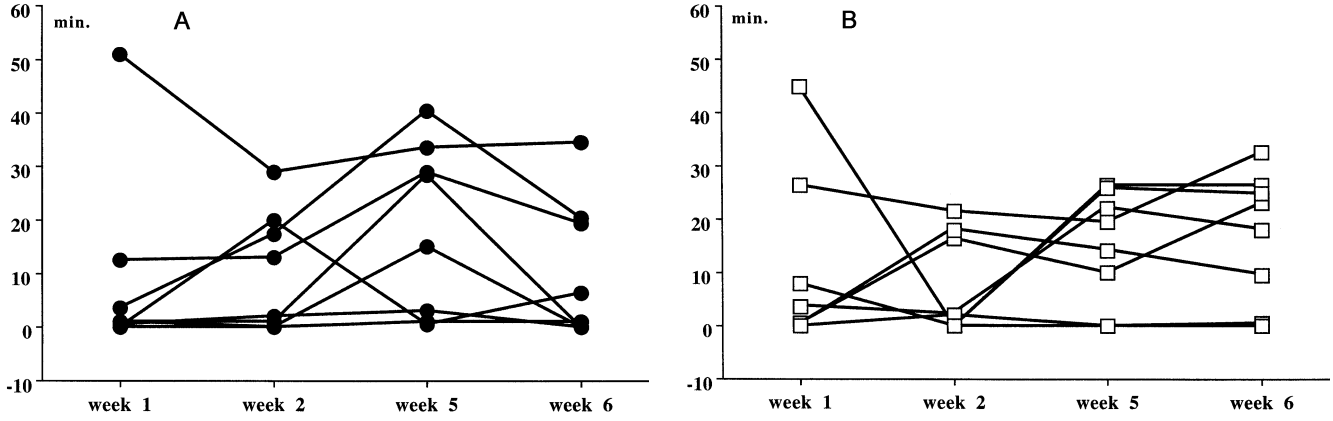

Fig. 2 **A.** Patients with major depression under trimipramine therapy additionally treated with EGb Li 1300 (week 2 – week 5), SWS 1st cycle. **B.** Patients with major depression under trimipramine monotherapy, SWS 1st cycle.

± 17.50 (day 35), EGb: 30.50 ± 9.72 (day 5), 24.75 ± 11.69 (day 12), 24.87 ± 12,20 (day 35). There was a significantly higher response rate based on reduction of 50% of HDRS baseline ratings in patients treated with trimipramine monotherapy (85.7% vs. 14.3% in patients with additional EGb, Chi-square 6.35, $p \leq .05$).

Due to the selection criteria, the groups were comparable in age and gender, however duration of illness was significantly longer in patients additionally treated with EGb (10.79 ± 8.38 years) than in the control group (3.35 ± 3.47 years; $Z = -2.14$, $p \leq .05$, U-test). In addition, there were descriptively more previous episodes in EGb-treated patients (4.00 ± 3.16) compared to patients treated only with trimipramine (2.85 ± 1.77; p = n. s., U-test).

Polysomnography

Global effects of the additional treatment with Gingko biloba (EGb)

Sleep continuity: Compared to the trimipramine monotherapy during the additional therapy with 240 mg EGb patients presented with a significantly better sleep efficiency due to significantly less awakenings and less wake time in minutes by trend, although sleep (SPT) was significantly prolonged in patients on trimipramine monotherapy (Table **1**).

Sleep architecture: Sleep stage 1 was reduced, and sleep stage 2 was increased by trend during the additional treatment with 240 mg/d EGb, but no significant interaction was detected for the slow-wave sleep stages 3 and 4 (Table **2**). In descriptive terms, slow-wave sleep (sleep stages 3 and 4) substantially increased during the additional therapy with EGb, showing a significant result for the augmentation of slow-wave sleep in the first sleep cycle in patients treated with EGb compared to patients with trimipramine monotherapy.

REM sleep: REM sleep was significantly increased in patients with trimipramine monotherapy compared to patients with additional EGb for four weeks (Table **3**). In addition, REM

Table 1 Parameters of sleep continuity under therapy with trimipramine or trimipramine and EGb Li 1300

	Week 1 mean ± SD (median)	Week 2 mean ± SD (median)	Week 5 mean ± SD (median)	Week 6 mean ± SD (median)
Total sleep time min.				
Trimipramine	428.18 ± 62.24 (450.25)	446.18 ± 42.66 (466.75)	460.12 ± 34.48 (472.25)	471.13 ± 14.53 (475.75)
Ginkgo	443.87 ± 31.30 (456.25)	442.56 ± 35.49 (444.25)	453.43 ± 19.03 (460.00)	455.37 ± 17.77 (463.75)
Sleep period time min.				
Trimipramine	453.68 ± 36.51 (468.50)	469.12 ± 18.04 (475.25)	472.37 ± 19.03 (480.75)	476.13 ± 12.29 (479.25)
Ginkgo	464.31 ± 18.96 (471.25)	446.31 ± 35.53 (451.25)	461.62 ± 15.92 (464.75)	462.50 ± 12.29 (464.25)
Sleep efficiency %				
Trimipramine	94.08 ± 10.60 (97.45)	94.27 ± 7.61 (97.70)	97.20 ± 4.91 (98.50)	97.20 ± 2.70 (99.30)
Ginkgo	95.53 ± 3.69 (96.45)	99.17 ± 1.32 (99.05)	98.23 ± 2.54 (99.10)	98.51 ± 4.18 (98.90)
Sleep onset latency (SOL)				
Trimipramine	19.37 ± 32.93 (8.00)	6.56 ± 3.08 (5.50)	4.31 ± 4.55 (2.75)	2.93 ± 1.74 (3.00)
Ginkgo	17.37 ± 20.14 (7.75)	18.68 ± 20.25 (9.50)	20.06 ± 14.80 (17.85)	17.37 ± 10.65 (11.75)
Awakenings (N)				
Trimipramine	18.75 ± 16.00 (15.50)	24.63 ± 16.73 (21.50)	11.00 ± 12.12 (7.50)	11.63 ± 13.36 (13.36)
Ginkgo	20.00 ± 11.10 (18.50)	15.12 ± 8.45 (15.00)	15.00 ± 10.47 (10.00)	14.25 ± 8.97 (13.50)
Wake min.				
Trimipramine	31.43 ± 48.44 (16.00)	26.81 ± 28.47 (15.50)	14.87 ± 20.53 (4.75)	8.00 ± 10.78 (4.75)
Ginkgo	24.87 ± 18.05 (18.50)	11.93 ± 6.95 (10.50)	13.25 ± 12.07 (9.25)	14.81 ± 14.49 (9.25)

Table 2 Parameters of sleep architecture under therapy with trimipramine or trimipramine and EGb Li 1300

	week 1 mean ± SD (median)	week 2 mean ± SD (median)	week 5 mean ± SD (median)	week 6 mean ± SD (median)
Stage 1 min.				
Trimipramine	38.25 ± 15.10 (39.75)	38.43 ± 19.88 (37.25)	33.12 ± 19.96 (34.00)	32.89 ± 14.64 (32.75)
Ginkgo	44.25 ± 13.98 (51.75)	33.00 ± 13.29 (31.25)	30.68 ± 12.98 (28.50)	36.75 ± 11.60 (36.75)
Stage 2 min.				
Trimipramine	261.56 ± 64.16 (287.75)	253.50 ± 47.93 (265.00)	276.93 ± 42.33 (291.75)	305.06 ± 19.84 (310.75)
Ginkgo	280.18 ± 51.27 (271.50)	277.50 ± 34.82 (274.75)	279.18 ± 48.52 (283.25)	276.25 ± 33.58 (276.75)
Stage 3 min.				
Trimipramine	33.31 ± 25.07 (28.50)	37.37 ± 18.44 (40.50)	37.18 ± 16.15 (43.75)	32.06 ± 15.69 (32.75)
Ginkgo	14.12 ± 16.72 (3.50)	21.31 ± 14.89 (23.50)	21.18 ± 16.79 (19.75)	14.37 ± 14.58 (9.00)
Stage 4 min.				
Trimipramine	7.81 ± 12.42 (1.50)	11.93 ± 15.08 (6.00)	8.62 ± 11.33 (1.00)	4.75 ± 8.30 (1.75)
Ginkgo	3.62 ± 7.37 (0.00)	4.50 ± 8.20 (1.50)	21.06 ± 26.64 (6.50)	11.12 ± 14.25 (4.75)
Stage 4, 1st half min.				
Trimipramine	7.56 ± 12.00 (1.50)	9.50 ± 13.50 (5.00)	7.00 ± 10.07 (1.00)	4.75 ± 8.29 (0.00)
Ginkgo	3.62 ± 7.37 (0.00)	4.06 ± 8.14 (1.50)	16.18 ± 19.62 (6.50)	11.12 ± 14.25 (4.75)
Slow wave sleep (SWS) min.				
Trimipramine	41.12 ± 32.61 (37.00)	49.31 ± 27.29 (53.50)	45.81 ± 21.26 (46.00)	38.00 ± 22.22 (36.00)
Ginkgo	17.75 ± 21.90 (3.50)	25.81 ± 20.30 (25.25)	42.25 ± 37.39 (44.75)	25.50 ± 25.43 (25.40)
SWS, 1st half min.				
Trimipramine	37.43 ± 27.69 (34.50)	38.56 ± 21.77 (39.25)	36.00 ± 19.68 (40.30)	33.56 ± 24.78 (32.25)
Ginkgo	16.50 ± 20.66 (3.50)	22.25 ± 16.38 (24.50)	32.81 ± 26.18 (38.00)	24.18 ± 24.45 (22.25)

Table 3 Parameters of REM sleep under therapy with trimipramine or trimipramine and EGb Li 1300

	week 1 mean ± SD (median)	week 2 mean ± SD (median)	week 5 mean ± SD (median)	week 6 mean ± SD (median)
REM sleep min.				
Trimipramine	80.37 ± 20.19 (73.75)	100.06 ± 29.18 (103.25)	99.31 ± 19.00 (98.25)	90.56 ± 18.12 (91.50)
Ginkgo	96.37 ± 20.66 (95.00)	96.62 ± 15.63 (100.00)	95.68 ± 23.63 (93.25)	108.50 ± 33.75 (100.00)
REM sleep min.1st half				
Trimipramine	30.00 ± 27.69 (34.50)	42.69 ± 14.17 (40.25)	41.81 ± 13.43 (44.25)	40.06 ± 9.08 (41.00)
Ginkgo	96.37 ± 20.66 (95.00)	96.62 ± 15.63 (100.00)	95.68 ± 23.63 (93.25)	108.50 ± 33.75 (100.00)
REM sleep min.2nd half				
Trimipramine	41.38 ± 23.84 (39.75)	57.38 ± 21.48 (65.00)	57.50 ± 15.34 (61.25)	50.55 ± 18.29 (56.50)
Ginkgo	96.37 ± 20.66 (95.00)	96.62 ± 15.63 (100.00)	95.68 ± 23.63 (93.25)	108.50 ± 33.75 (100.00)
REM latency				
Trimipramine	106.25 ± 40.57 (80.75)	59.75 ± 27.77 (46.00)	86.25 ± 56.37 (81.94)	83.31 ± 45.90 (62.75)
Ginkgo	91.87 ± 44.57 (57.00)	80.50 ± 21.30 (58.75)	90.00 ± 14.30 (70.25)	73.68 ± 10.41 (54.40)
REM density				
Trimipramine	4.62 ± 1.16 (4.88)	4.90 ± 1.17 (5.38)	4.61 ± 1.53 (4.72)	4.50 ± 1.44 (4.09)
Ginkgo	4.57 ± 0.77 (4.44)	4.13 ± 0.66 (4.32)	3.95 ± 1.95 (4.18)	3.87 ± 1.84 (4.37)
REM density, 1st half				
Trimipramine	4.94 ± 1.51 (5.17)	5.01 ± 1.41 (5.18)	4.66 ± 1.75 (4.68)	4.41 ± 1.74 (3.84)
Ginkgo	4.72 ± 1.33 (5.24)	3.52 ± 1.42 (3.43)	3.97 ± 2.47 (3.57)	3.19 ± 1.69 (3.72)
REM density, 2nd half				
Trimipramine	3.67 ± 1.83 (4.13)	4.84 ± 1.12 (5.17)	4.57 ± 1.60 (4.77)	4.69 ± 1.23 (4.37)
Ginkgo	4.30 ± 0.98 (4.32)	4.42 ± 0.94 (4.49)	3.86 ± 1.83 (4.74)	4.32 ± 1.97 (4.95)
REM activity, 1st cycle				
Trimipramine	180.00 ± 127.14 (154.00)	168.62 ± 150.46 (119.50)	199.62 ± 122.56 (179.50)	207.12 ± 178.72 (190.50)
Ginkgo	251.37 ± 184.18 (250.50)	201.25 ± 177.38 (129.00)	209.75 ± 288.65 (111.50)	111.25 ± 122.52 (39.00)
REM activity, 2nd cycle				
Trimipramine	297.38 ± 230.59 (209.50)	253.87 ± 136.22 (225.00)	258.88 ± 122.87 (234.50)	213.75 ± 162.15 (190.50)
Ginkgo	183.50 ± 101.19 (174.50)	189.50 ± 104.42 (223.50)	148.50 ± 143.93 (145.00)	162.50 ± 136.10 (135.00)
REM activity, 3rd cycle				
Trimipramine	121.75 ± 82.95 (111.50)	329.50 ± 259.35 (220.50)	202.85 ± 118.05 (167.00)	198.14 ± 146.92 (157.00)
Ginkgo	267.50 ± 134.73 (267.50)	159.87 ± 171.55 (114.00)	199.50 ± 137.32 (218.50)	252.62 ± 178.57 (218.50)

latency was significantly shortened in patients with trimipramine monotherapy, but not in patients with additional EGb (Table **3**). A significant reduction was observed for REM density in patients with additional EGb treatment, which was also evident by trend in the second half of the night (Table **3**).

This result is supported by a significant suppression of REM activity in the third sleep cycle in these patients (Table **3**).

Sleep cycles: The first sleep cycle was longer by trend, and duration of Non-REM sleep was significantly increased in patients with additional EGb compared to patients on trimipramine monotherapy. The duration of REM sleep within the cycles did not significantly differ between both groups during the treatment (Table **4**).

Effects of EGb discontinuation

No changes of sleep continuity parameters were found after discontinuation of EGb, whereas wakefulness in minutes was reduced by trend under constant trimipramine monotherapy. In addition, SOL was, in descriptive terms, markedly reduced compared to patients with additional EGb (Table **1**). Sleep stage 2 slightly decreased by trend after the discontinuation of EGb, whereas in patients with trimipramine, a further increase was observed (Table **2**). A significant interaction effect for REM latency, which was reduced after the discontinuation of EGb, but not in patients with trimipramine monotherapy, was found (Table **3**). In addition, the duration of the first sleep cycle, predominately the length of the first non-REM period, was reduced after the withdrawal of EGb compared to patients on trimipramine monotherapy, and SWS in the first sleep cycle was reduced by trend. In contrast, the length of the REM period in the second sleep cycle was increased after EGb withdrawal and reduced in patients on trimipramine monotherapy within this period (Table **4**).

Discussion

The main result of this study is a substantial effect of ginkgo biloba extract Li 1370 (EGb) on the sleep pattern reflected by a beneficial effect on sleep efficiency and an augmentation of non-REM sleep, predominantly slow-wave sleep in the first sleep cycle during a four week additional therapy to a trimipramine basis medication.

The efficacy of EGb concerning the augmentation of non-REM sleep is supported by the fact that after discontinuation of EGb the length of the first sleep cycle is significantly decreased due to a significant reduction of non-REM sleep and a reduction by trend of SWS to a level comparable with that prior to the additional EGb therapy. The observed reduction of sleep stage 1 and the increase of sleep stage 2 by trend under EGb therapy both additionally support this finding.

The second result is that REM density, the phasic component of REM sleep, is significantly reduced during the additional therapy with EGb. In addition, the increase of REM sleep and the shortening of REM latency in the control group were not observed in patients additionally treated with EGb. These findings were stressed by the significant interaction effect for REM latency, which is markedly shortened after EGb withdrawal.

Furthermore, the additional application of EGb exerted beneficial effects on sleep continuity, reflected by an increase of

Table 4 Parameters of sleep cycles under therapy with trimipramine or trimipramine and EGb Li 1300

	Week 1 mean ± SD (median)	Week 2 mean ± SD (median)	Week 5 mean ± SD (median)	Week 6 mean ± SD (median)
Duration of 1st cycle				
Trimipramine	108.31 ± 36.71 (108.50)	74.06 ± 31.99 (70.75)	109.43 ± 64.88 (78.25)	114.50 ± 43.08 (104.75)
Ginkgo	103.50 ± 43.63 (90.75)	92.50 ± 27.35 (84.25)	94.68 ± 18.80 (86.75)	77.81 ± 18.37 (75.00)
Duration of 2nd cycle				
Trimipramine	116.87 ± 59.16 (103.50)	112.25 ± 23.43 (112.25)	125.31 ± 34.36 (110.50)	114.93 ± 30.36 (109.00)
Ginkgo	101.06 ± 17.24 (102.50)	132.37 ± 31.57 (126.25)	114.68 ± 36.42 (127.00)	125.75 ± 23.29 (128.00)
Duration of NonREM, 1st cycle				
Trimipramine	86.87 ± 29.63 (80.75)	53.18 ± 27.80 (46.00)	81.93 ± 57.17 (47.25)	83.31 ± 45.89 (62.75)
Ginkgo	74.50 ± 33.72 (57.00)	61.81 ± 16.84 (58.75)	69.93 ± 8.84 (70.25)	56.31 ± 14.76 (54.50)
Duration of NonREM, 2nd cycle				
Trimipramine	78.75 ± 50.98 (75.00)	76.18 ± 20.47 (80.00)	88.37 ± 24.48 (78.00)	89.21 ± 37.42 (78.75)
Ginkgo	76.31 ± 16.03 (73.50)	101.56 ± 28.92 (103.50)	89.31 ± 28.63 (95.75)	94.12 ± 19.45 (92.75)
Duration of REM, 1st cycle				
Trimipramine	21.44 ± 13.74 (24.25)	20.88 ± 14.94 (21.00)	27.50 ± 12.32 (28.00)	31.19 ± 12.78 (35.00)
Ginkgo	29.00 ± 13.29 (29.25)	30.69 ± 16.50 (27.00)	24.75 ± 19.89 (23.75)	21.50 ± 13.97 (18.75)
Duration of REM, 2nd cycle				
Trimipramine	38.13 ± 27.36 (33.50)	36.06 ± 14.14 (36.50)	36.94 ± 12.24 (37.25)	26.25 ± 11.17 (26.75)
Ginkgo	24.75 ± 6.28 (25.75)	30.81 ± 13.11 (34.50)	25.38 ± 16.83 (28.50)	31.63 ± 15.73 (30.50)
SWS, 1st cycle				
Trimipramine	16.12 ± 19.97 (5.75)	7.50 ± 9.38 (2.00)	14.68 ± 10.59 (16.75)	16.87 ± 12.24 (20.50)
Ginkgo	8.75 ± 17.56 (1.00)	10.31 ± 11.15 (7.50)	18.93 ± 16.08 (21.75)	10.31 ± 13.00 (3.75)
SWS, 2nd cycle				
Trimipramine	17.75 ± 19.93 (9.25)	27.25 ± 19.94 (25.75)	19.63 ± 10.84 (21.25)	16.69 ± 17.12 (12.00)
Ginkgo	6.81 ± 13.90 (1.00)	10.94 ± 11.12 (6.50)	11.81 ± 13.56 (4.50)	11.88 ± 15.13 (6.50)

Table 5 Interaction effects of type of therapy (trimipramine or trimipramine and EGb Li 1300) at different times of measurement on polysomnographic parameters

	Mann Whitney U-test,			
	Global effect		Withdrawal effect	
	U	p	U	p
Sleep continuity				
Total sleep time (TST)	39.00	.253	22.50	.170
Sleep period time (SPT)	49.00	.039	24.50	.230
Sleep efficiency (SEI)	12.00	.019	24.00	.221
Sleep onset latency (SOL)	30.00	.439	42.50	.143
Awakenings (N)	52.50	.015	28.00	.349
Waketime	47.00	.065	46.50	.069
REM sleep				
REM sleep	48.00	.052	44.00	.112
REM sleep 1st half	39.00	.253	42.00	.164
REM sleep 2nd half	47.00	.065	39.20	.228
REM latency	15.50	.044	11.50	.015
REM density	48.00	.052	34.00	.417
REM density, 1st half	34.00	.417	31.00	.480
REM density, 2nd half	45.00	.097	38.00	.287
REM activity, 1st cycle	30.00	.439	25.00	.253
REM activity, 2nd cycle	33.00	.480	36.00	.361
REM activity, 3rd cycle	55.00	.007	40.00	.221
Sleep architecture				
Stage 1	47.50	.056	36.00	.350
Stage 2	17.00	.065	17.00	.065
Stage 3	31.00	.458	32.00	.520
Stage 4	31.00	.469	29.00	.398
Stage 4, 1st half	38.00	.276	35.50	.365
Slow wave sleep (SWS)	26.00	.287	28.50	.370
SWS, 1st half	25.00	.253	26.50	.296
Sleep cycles				
Duration of 1st cycle	18.00	.080	15.00	.042
Duration of 2nd cycle	24.00	.221	36.00	.361
Duration of NonREM, 1st cycle	15.50	.044	11.50	.015
Duration of NonREM, 2nd cycle	22.50	.171	30.00	.439
Duration of REM, 1st cycle	28.00	.361	25.00	.253
Duration of REM, 2nd cycle	37.00	.313	48.00	.049
SWS, 1st cycle	14.00	.031	17.50	.068
SWS, 2nd cycle	32.50	.491	40.00	.214

sleep efficiency due to reduced awakenings, although sleep period time was reduced and sleep-onset latency prolonged compared to trimipramine monotherapy.

These results suggest that the additional application of EGb is able to improve sleep in depressed patients under trimipramine treatment by an augmentation of non-REM sleep associated with a better sleep efficiency and an inhibitory effect on REM sleep, which may be secondary to the enhancement of non-REM sleep.

Neither group showed any major differences concerning sleep disturbance at baseline, although patients in the control group descriptively present with more SWS, but in contrast to the EGb-treated patients, the control group did not show any marked variation of SWS between the evaluation times.

The findings for patients on trimipramine monotherapy showing an improvement of sleep continuity, a shortening of sleep latency and an augmentation of REM sleep are in line with previous findings on the polysomnographic effects of trimipramine [55,58,59].

No data on the effects of EGb on sleep EEG pattern have yet been reported. Therefore, these findings are the first results showing that ginkgo biloba affects central nervous activity during sleep.

The augmentation of non-REM sleep, predominately SWS in the first sleep cycle accompanied by a reduction of REM density is in line with the mechanisms of sleep regulation described in the neurophysiological two process model by *Borbély* [4], which stresses an inverse relationship between REM density and non-REM intensity, expressed by non-REM slow-wave activity (SWA).

The descriptive increase of non-REM sleep in the second sleep cycle accompanied by a reduction of REM-density already after short-term application of EGb may indicate the early initiation of the non-REM augmentation on the basis of this inverse relationship between SWS and REM density.

In addition, the results observed after discontinuation of the additional four week therapy with EGb were characterized by a shortening of REM latency and the length of the first sleep cycle due to a reduction of non-REM sleep, predominantly a reduction of SWS. This may indicate that REM sleep advances as a consequence of the weakening of process S, the homeostatic sleep component of the two process model [4].

The combined neurophysiological/neuroendocrine two-model process of sleep regulation [14,57], which extends the two process model of *Borbély* [4] provides an additional explanation for the observed effects of EGb on sleep EEG. Within the theoretical frame of this model, CRH is related to process C, and GHRH represents process S, reflecting the major neuropeptides responsible for the regulation of non-REM and REM sleep. The ratio of GHRH / CRH has been shown to determine the strength of process S to a major extent in morning recovery sleep [51]. Therefore, strengthening process S can be achieved by increasing GHRH or reducing CRH activity.

Neuroendocrine data from animal studies on the effects of ginkgo biloba on CRH support the latter view, although no data on the effects of ginkgo biloba on GHRH activity have yet been published.

Reduced basal [2] and stress-stimulated [44] corticosterone levels have been found in rats after long-term ginkgo biloba application. One explanation for these results is provided by the finding that EGb is able to reduce corticosterone secretion in rats by affecting peripheral type benzodiazepine receptors (PBR) in the adrenal gland, which are involved in the transport of cholesterol from intracellular stores to the inner mitochondria, the rate-determining step in steroid biosynthesis [2]. The reduction of corticosterone via PBR was not accompanied by a concomitant increase of ACTH suggesting a central inhibitory action of EGb on the HPA-axis. The reduced CRH and AVP gene expression associated with lower peripheral corticosterone secretion, which has been detected recently in EGb treated rats, may reflect this central inhibitory effect [34]. According to these

findings, EGb is able to reduce HPA axis tone by a central and peripheral mode of action.

Based on the extended two-process model of sleep regulation, these results indicate that the ratio of GHRH/CRH may be increased under EGb therapy due to a reduction of CRH secretion. Thus, process S is strengthened, which is reflected by the observed increase of the non-REM component and SWS after EGb application in this study.

The hypothesis that ginkgo biloba exerts its action by a weakening of the circadian component of the extended two-process model due to a reduction of CRH secretion is further supported by the observed REM density decrease, even after short-term treatment with EGb.

Furthermore, the endocrine hypothesis also provides an explanation of the beneficial effects on sleep continuity, predominantly the reduction of awakenings, as nocturnal application of CRH evoked a disturbance of sleep continuity reflected by an increase of awakenings and a decrease of sleep efficiency in rats and volunteers [13,14,20].

The fact that – in spite of the beneficial effects on sleep architecture – no additional effects of EGb in terms of psychometric measures could be detected may be related to the finding that the reduction of stress-induced corticosterone secretion in animal depression models clearly differed from effects of anxiolytics and antidepressants in these models, suggesting a stress-adaptive effect of EGb, but no distinct antidepressant or anxiolytic properties [42,44]. In addition, the longer duration of illness and the greater number of previous episodes of depression may explain the poor response in terms of depression ratings in this group.

The design of this study (e.g. not randomized, non-blind conditions) and the small number of patients does not allow a definitive estimation of the observed effects of EGb on sleep. However, the variation of polysomnographic measures, predominately non-REM sleep, under EGb application and after cessation, which was not found in the control group, fits well with what is known from previous animal studies involving the effects of EGb on endocrine sleep-related activity. Therefore, these first results of EGb on sleep EEG of this study provide a scientific and a clinical implication, suggesting that 1) central nervous activity during sleep is affected by EGb, probably due to direct peripheral and central effects of EGb on HPA-axis activity (scientific implication) and 2) even in less responsive patients (according to psychometric assessment), an additional improvement of the underlying neurobiological disturbance, which is reflected by the observed promotion of non-REM sleep, predominantly the SWS increase, can be achieved (clinical implication).

Sleep disturbance, predominantly reduced SWS, and dysregulation of the HPA axis in depressed patients have been related to a neurobiological scar associated with an increased vulnerability for relapse [29,55,62]. This is especially true for a subgroup of depressed patients who do not show complete remission, but remain in a sub-threshold depression state [24], which is predominantly characterized by sleep disturbance and cognitive impairment [23].

In addition, a disturbed sleep profile and a dysregulation of the HPA axis have also been found in healthy first-degree relatives of depressed patients suggesting a higher risk for the development of depressive illness (*Lauer* et al. 1998). In this context, the non-REM and SWS-increasing properties of an additional gingko biloba therapy – especially due to the lack of side effects – may also be of prophylactic value.

The benefit of these preliminary findings of additional therapy with EGb on sleep EEG in depressed patients cannot be definitely estimated to date, although they may open a way to the development of new strategies of acute, long-term and prophylactic antidepressant treatment.

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